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Pharmacotherapy

principles & practice

MARIE A. CHISHOLM-BURNS

BARBARA G. WELLS

TERRY L. SCHWINGHAMMER

PATRICK M. MALONE

JILL M. KOLESAR

JOHN C. ROTSCHAFER

JOSEPH T. DIPIRO



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Pharmacotherapy Principles & Practice

Editors

Marie A. Chisholm-Burns, PharmD, FCCP, FASHP

Professor and Head
Department of Pharmacy Practice and Science
The University of Arizona College of Pharmacy
Tucson, Arizona

Barbara G. Wells, PharmD, FASHP, FCCP, BCPP

Professor and Dean
Executive Director, Research Institute of Pharmaceutical Sciences
School of Pharmacy
The University of Mississippi
University, Mississippi

Terry L. Schwinghammer, PharmD, FCCP, FASHP, BCPS

Professor and Chair
Department of Clinical Pharmacy
West Virginia University
School of Pharmacy
Morgantown, West Virginia

Patrick M. Malone, PharmD, FASHP

Professor and Assistant Dean, Internal Affairs
School of Pharmacy
University of Findlay
Findlay, Ohio

Jill M. Kolesar, PharmD, BCPS, FCCP

Associate Professor
University of Wisconsin School of Pharmacy
Faculty Supervisor
Analytical Instrumentation Laboratory
Madison, Wisconsin

John C. Rotschafer, PharmD, FCCP

Professor
Department of Experimental and Clinical Pharmacology
College of Pharmacy
University of Minnesota
Minneapolis, Minnesota

Joseph T. DiPiro, PharmD, FCCP

Professor and Executive Dean
South Carolina College of Pharmacy
University of South Carolina, Columbia
Medical University of South Carolina
Charleston, South Carolina

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CONTRIBUTORS

Val R. Adams, PharmD
Associate Professor
University of Kentucky
Oncology Clinical Specialist
Markey Cancer Center
Lexington, Kentucky
Chapter 87: Lung Cancer

Ronda L. Akins, PharmD
Assistant Professor–Infectious Diseases
University of Louisiana at Monroe
College of Pharmacy
Monroe, Louisiana
Chapter 71: Infective Endocarditis

Kari Alperovitz-Bichell, MD, MPH
Assistant Professor
Family Medicine
University of Maryland School of Medicine
University of Maryland Medical System
Baltimore, Maryland
Chapter 44: Pregnancy and Lactation: Therapeutic Considerations

J. V. Anandan, PharmD
Adjunct Associate Professor of Pharmacy
Eugene Applebaum College of Pharmacy and Health Sciences
Wayne State University
Pharmacy Specialist
Henry Ford Hospital
Detroit, Michigan
Chapter 75: Parasitic Diseases

Justin M. Balko, PharmD
Graduate Student
University of Kentucky
Pharmacist
UK Chandler Medical Center
Lexington, Kentucky
Chapter 87: Lung Cancer

Tawny L. Bettinger, PharmD
Assistant Professor
University of Texas at Austin
College of Pharmacy
Austin, Texas
Chapter 37: Generalized Anxiety Disorder, Panic Disorder, and Social Anxiety Disorder

Marianne Billeter, PharmD, BCPS
Clinical Pharmacy Specialist
Infectious Diseases
Ochsner Clinic Foundation
New Orleans, Louisiana
Chapter 83: Vaccines and Toxoids

Angela Ann Boggs, PharmD
Clinical Pharmacist
University of Maryland
Baltimore, Maryland
Chapter 35: Major Depressive Disorder

Sheila R. Botts, PharmD, BCPP
Assistant Professor
University of Kentucky College of Pharmacy
Clinical Pharmacy Specialist
Psychiatry
Lexington Veterans Affairs Medical Center
Lexington, Kentucky
Chapter 37: Generalized Anxiety Disorder, Panic Disorder, and Social Anxiety Disorder

Bradley A. Boucher, PharmD, FCCP, FCCM
Professor of Pharmacy
Department of Pharmacy
University of Tennessee Health Science Center
Clinical Pharmacist
Regional Medical Center at Memphis
Memphis, Tennessee
Chapter 10: Hypovolemic Shock

Toya M. Bowles, PharmD, BCPP
Senior Medical Science Manager
Organon USA
Hallandale Beach, Florida
Chapter 32: Alzheimer's Disease

Gretchen M. Brophy, PharmD, BCPS, FCCP, FCCM
Associate Professor of Pharmacy and Neurosurgery
Clinical Specialist
Neuroscience Intensive Care Unit
Virginia Commonwealth University
Medical College of Virginia Campus
Richmond, Virginia
Chapter 28: Status Epilepticus

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Kirk J. Brower, MD
Associate Professor of Psychiatry
University of Michigan Medical School
Executive Director
Chelsea Arbor Addiction Treatment Center
Ann Arbor, Michigan
Chapter 33: Substance-Related Disorders

Susan P. Bruce, PharmD, BCPS
Associate Professor of Pharmacy Practice
Albany College of Pharmacy
Clinical Pharmacist
The Center for Rheumatology
Albany, New York
Chapter 54: Rheumatoid Arthritis

Dianne Brundage, PharmD, FCCP, BCPS, BCOP
Oncology Clinical Pharmacy Specialist
Methodist Hospital/Park Nicollet Health Services
Minneapolis, Minnesota
Chapter 85: Cancer Chemotherapy and Treatment

Imad F. Btaiche, BS, PharmD, BCNSP
Clinical Associate Professor of Pharmacy
Department of Clinical Sciences
University of Michigan College of Pharmacy
Clinical Pharmacist
University of Michigan Hospitals and Health Centers
Ann Arbor, Michigan
Chapter 97: Parenteral Nutrition

R. Todd Burkhardt, PharmD
Research Fellow
Cardiovascular Pharmacotherapy
Experimental and Clinical Pharmacology Department
University of Minnesota
Minneapolis, Minnesota
Chapter 2: Hypertension

Jill S. Burkiewicz, PharmD, BCPS
Associate Professor and Director
Primary Care Residency Program
Midwestern University Chicago College of Pharmacy
Clinical Pharmacist
Mercy Family Health Center–Chicago
Chicago, Illinois
Chapter 57: Musculoskeletal Disorders

Karim Anton Calis, PharmD, MPH, BCPS, BCNSP, FASHP, FCCP
Professor
Virginia Commonwealth University
Clinical Professor
University of Maryland and Shenandoah University
Clinical Specialist, Endocrinology and Women's Health
Director, Drug Information Service, NIH Clinical Center
National Institutes of Health
Bethesda, Maryland
Chapter 42: Adrenal Gland Disorders
Chapter 43: Pituitary Gland Disorders

Diane M. Cappelletty, PharmD
Associate Professor of Pharmacy Practice
The University of Toledo
Adjunct Assistant Professor
Department of Medicine
Medical University of Ohio
Toledo, Ohio
Chapter 68: Lower Respiratory Tract Infections

Marshall E. Cates, PharmD, BCPP, FASHP
Professor of Pharmacy Practice
Samford University McWhorter School of Pharmacy
Clinical Pharmacist
Department of Psychiatry and Behavorial Neurobiology
University of Alabama at Birmingham
Birmingham, Alabama
Chapter 35: Major Depressive Disorder

Larisa H. Cavallari, PharmD
Assistant Professor
Department of Pharmacy Practice
University of Illinois at Chicago College of Pharmacy
Chicago, Illinois
Chapter 4: Ischemic Heart Disease

Juliana Chan, PharmD
Clinical Assistant Professor
Department of Pharmacy Practice
College of Pharmacy
Department of Medicine
Sections of Digestive Diseases and Nutrition
Section of Hepatology
University of Illinois at Chicago
Chicago, Illinois
Chapter 21: Viral Hepatitis

Judy T. Chen, PharmD, BCPS
Assistant Professor of Pharmacy Practice
Purdue University
School of Pharmacy and Pharmaceutical Sciences
Pharmacotherapist
Tippecanoe Community Health Clinic
West Lafayette, Indiana
Chapter 42: Adrenal Gland Disorders
Chapter 43: Pituitary Gland Disorders

Marie A. Chisholm-Burns, PharmD, FCCP, FASHP
Professor and Head
Department of Pharmacy Practice and Science
The University of Arizona College of Pharmacy
Tucson, Arizona
Chapter 14: Gastroesophageal Reflux Disease

Kevin W. Cleveland, PharmD
Clinical Assistant Professor
College of Pharmacy
Idaho State University
Pocatello, Idaho
Chapter 39: Attention-Deficit Hyperactivity Disorder

Christopher L. Cook, PharmD, PhD
Clinical Assistant Professor
University of Georgia College of Pharmacy
Athens, Georgia
Chapter 40: Diabetes Mellitus

Amanda H. Corbett, PharmD, BCPS
Clinical Assistant Professor
School of Pharmacy
University of North Carolina
Clinical Pharmacist
University of North Carolina Health Care
Infectious Disease Clinic
Chapel Hill, North Carolina
Chapter 84: Human Immunodeficiency Virus Infection

Brian L. Crabtree, PharmD, BCPP
Associate Professor of Pharmacy Practice
Clinical Associate Professor of Psychiatry,
University of Mississippi School of Pharmacy
University of Mississippi Medical Center
School of Medicine
Psychopharmacologist
Mississippi State Hospital
Whitfield, Mississippi
Chapter 36: Bipolar Disorder

Nicole S. Culhane, PharmD, BCPS
Associate Professor
Pharmacy Practice
Wilkes University
Nesbitt College of Pharmacy and Nursing
Clinical Pharmacist Faculty
Wyoming Valley Family Practice Residency
Wilkes-Barre, Pennsylvania
Chapter 47: Hormone Replacement Therapy in Menopause

Clarence E. Curry, Jr., PharmD
Associate Professor
School of Pharmacy
CPNAHS
Howard University
Clinical Pharmacist
Ambulatory Care
Howard University Hospital Clinics
Washington, DC
Chapter 18: Constipation, Diarrhea, and Irritable Bowel Syndrome

Devra K. Dang, PharmD
Assistant Clinical Professor
University of Connecticut School of Pharmacy
Clinical Faculty
St. Francis Hospital/UCONN Primary Care Center
at Burgdorf Health Center
Instructor
Department of Medicine
University of Connecticut School of Medicine
Hartford, Connecticut
Chapter 42: Adrenal Gland Disorders
Chapter 43: Pituitary Gland Disorders

Simon de Denus, BPharm, MSc
Assistant Professor
Faculty of Pharmacy
University of Montreal Pharmacy Department
Fellow in Cardiovascular Research
Montreal Heart Institute
Montreal
Quebec, Canada
Chapter 5: Acute Coronary Syndromes

John W. Devlin, PharmD, BCPS, FCCM
Associate Professor
Northeastern University School of Pharmacy
Clinical Pharmacist
Medical Intensive Care Unit
Tufts-New England Medical Center
Boston, Massachusetts
Chapter 15: Peptic Ulcer Disease

Robert J. DiDomenico, PharmD
Clinical Associate Professor
Department of Pharmacy Practice
University of Illinois
Cardiovascular Clinical Pharmacist
University of Illinois Medical Center at Chicago
Chicago, Illinois
Chapter 4: Ischemic Heart Disease

Joseph T. DiPiro, PharmD, FCCP
Professor and Executive Dean
South Carolina College of Pharmacy
University of South Carolina
Columbia
Medical University of South Carolina
Charleston, South Carolina
Chapter 74: Intraabdominal Infections

John M. Dopp, PharmD
Assistant Professor
University of Wisconsin-Madison School of Medicine
Clinical Pharmacist
University of Wisconsin Sleep Disorders Center
Madison, Wisconsin
Chapter 38: Sleep Disorders

Julie Dumond, PharmD
University of North Carolina–Chapel Hill
School of Pharmacy
Chapel Hill, North Carolina
Chapter 84: Human Immunodeficiency Virus Infection

Megan J. Ehret, PharmD
Assistant Professor
University of Connecticut
School of Pharmacy
Storrs, Connecticut
Chapter 32: Alzheimer's Disease

Benjamin J. Epstein, PharmD, BCPS
Clinical Assistant Professor
Departments of Pharmacy Practice and Internal Medicine
Colleges of Pharmacy and Medicine
University of Florida
Gainesville, Florida
Chapter 55: Osteoarthritis

John Erramouspe, PharmD, MS
Professor
Idaho State University College of Pharmacy
Pocatello, Idaho
Chapter 39: Attention-Deficit Hyperactivity Disorder

Edward Faught, MD
Professor of Neurology
University of Alabama School of Medicine
Director
University of Alabama at Birmingham Epilepsy Center
Birmingham, Alabama
Chapter 27: Epilepsy

Martha J. Faulkner, BSN, MSW, MSN, LISW, CNP
Nurse Practitioner
University of New Mexico
Albuquerque, New Mexico
Chapter 36: Bipolar Disorder

Christopher A. Fausel, PharmD, BCOP
Adjunct Associate Professor of Medicine
Indiana University Cancer Center
Indianapolis, Indiana
Chapter 90: Malignant Lymphomas

Jacqueline Maus Feldman, MD
Patrick H. Linton Professor
University of Alabama School of Medicine
Director
Division of Public Psychiatry
Community Psychiatry Program
Birmingham, Alabama
Chapter 35: Major Depressive Disorder

Jack E. Fincham, BS, PhD
Professor of Pharmacy Practice
School of Pharmacy
University of Missouri-Kansas City
Kansas City, Missouri
Chapter 1: Introduction

Jeffrey J. Fong, PharmD
Critical Care Fellow
Northeastern University School of Pharmacy
Tufts-New England Medical Center
Boston, Massachusetts
Chapter 15: Peptic Ulcer Disease

Steven Gabardi, PharmD, BCPS
Renal Transplant Clinical Specialist
Department of Pharmacy Services
Brigham and Women's Hospital
Assistant Professor
Northeastern University
Boston, Massachusetts
Chapter 52: Solid Organ Transplantation

Angie L. Goeser, PharmD
Assistant Professor
Department of Pharmacy Practice
Creighton University School of Pharmacy and Health Professions
Omaha, Nebraska
Chapter 62: Common Skin Disorders

S. Diane Goodwin, PharmD, FCCP
Clinical Pharmacist
Rex Healthcare
Raleigh, North Carolina
Chapter 67: Central Nervous System Infections

A. Christie Graham, PharmD
Clinical Assistant Professor
University of Wyoming School of Pharmacy
Laramie, Wyoming
Chapter 70: Skin and Soft Tissue Infections

Maqual R. Graham, PharmD
Associate Professor of Pharmacy Practice
University of Missouri–Kansas City
Clinical Pharmacy Specialist
Veterans Affairs Medical Center–Kansas City
Kansas City, Missouri
Chapter 99: Overweight and Obesity

Kendra J. Grande, RPh
Consultant Pharmacist
Abelian Consulting
Stevensville, Maryland
Chapter 60: Minor Ophthalmic Disorders

Brian A. Greenlee, MD
Assistant Professor of Psychiatry
Neuropsychiatry Clinic Director
University of Kentucky
Lexington, Kentucky
Chapter 37: Generalized Anxiety Disorder, Panic Disorder, and Social Anxiety Disorder

David R. P. Guay, PharmD, FCCP
Professor
Department of Experimental and Clinical Pharmacology
College of Pharmacy
University of Minnesota
Consultant
Division of Geriatrics
HealthPartners Inc.
Minneapolis, Minnesota
Chapter 50: Urinary Incontinence and Pediatric Enuresis

John G. Gums, PharmD
Professor of Pharmacy and Medicine
Departments of Pharmacy Practice and Community Health and Family Medicine
University of Florida
Gainesville, Florida
Chapter 55: Osteoarthritis

Sally K. Guthrie, PharmD
Associate Professor of Pharmacy
College of Pharmacy and Department of Psychiatry
The University of Michigan
The University of Michigan Hospitals
Ann Arbor, Michigan
Chapter 33: Substance-Related Disorders

Tracy M. Hagemann, PharmD
Associate Professor of Pharmacy Practice
University of Oklahoma College of Pharmacy
Clinical Pediatric Specialist
Oklahoma City, Oklahoma
Chapter 65: Sickle Cell Disease

Kristine Hahn, PharmD
Postdoctoral Fellow
University of Wisconsin Comprehensive Cancer Center
Madison, Wisconsin
Chapter 86: Breast Cancer

Stuart T. Haines, PharmD, FCCP, FASHP
Professor and Vice Chair
Pharmacotherapy Specialist
University of Maryland Department of Pharmacy Practice and Science
University of Maryland Medical Center-Antithrombosis Services
Baltimore, Maryland
Chapter 7: Venous Thromboembolism

Karen L. Hall, MD
Associate Professor and Residency Program Director
Department of Community Health and Family Medicine
University of Florida
Gainesville, Florida
Chapter 55: Osteoarthritis

Alma Hamidovic, PharmD
Postdoctoral Oncology Fellow
University of Wisconsin Comprehensive Cancer Center
Madison, Wisconsin
Chapter 64: Coagulation Disorders

Charles Hartis, PharmD
Antibiotic Management/Clinical Improvement Pharmacist
Forsyth Medical Center
Winston-Salem, North Carolina
Chapter 67: Central Nervous System Infections

Kathleen B. Haynes, PharmD, BCPS
Disease Management Pharmacist
VEI/Community Health Network
Carmel, Indiana
Chapter 45: Contraception

Nancy Heideman, PharmD, BCPS
Assistant Professor of Pharmacy Practice
University of New Mexico College of Pharmacy
Albuquerque, New Mexico
Chapter 92: Acute Leukemias

Brian A. Hemstreet, PharmD, BCPS
Assistant Professor
University of Colorado School of Pharmacy
Denver, Colorado
Chapter 16: Inflammatory Bowel Disease

Elizabeth D. Hermsen, PharmD, MBA
Antimicrobial Specialist
The Nebraska Medical Center
Adjunct Assistant Professor
University of Nebraska Medical Center College of Pharmacy
Omaha, Nebraska
Chapter 73: Gastrointestinal Infections

Catherine A. Heyneman, MS, PharmD
Associate Professor of Pharmacy Practice
Idaho State University College of Pharmacy
Director of Idaho Drug Information Service
Pocatello, Idaho
Chapter 48: Erectile Dysfunction

Kristi N. Hofer, PharmD
Scientific Project Manager
ASHP Advantage
Charlottesville, Virginia
Chapter 59: Allergic Rhinitis

James M. Hoffman, PharmD, MS
Medication Outcomes Coordinator
Pharmaceutical Department
St. Jude Children's Research Hospital
Memphis, Tennessee
Chapter 63: Anemias

Marlon Honeywell, PharmD
Associate Professor of Pharmacy Practice
Florida A&M University
Clinical Pharmacist
Bond Community Health Center
Tallahassee, Florida
Chapter 77: Sexually Transmitted Infections

Thomas R. Howdieshell, MD, FACS, FCCP
Associate Professor of Surgery
Department of Surgery
University of New Mexico Health Science Center
Division of Trauma/Surgical Critical Care
Albuquerque, New Mexico
Chapter 74: Intraabdominal Infections

Matthew K. Ito, PharmD, FCCP, BCPS
Chair, Department of Pharmacy Practice
Professor of Pharmacy Practice
College of Pharmacy
Oregon State University
Portland, Oregon
Chapter 9: Hyperlipidemia

Ziba Jalali, MD
Assistant Professor
University of Nebraska Medical Center
College of Medicine
Omaha, Nebraska
Chapter 73: Gastrointestinal Infections

John T. Johnson, PharmD, CDE
Clinical Associate Professor
University of Georgia College of Pharmacy
Athens Primary Care
Mercy Health Center
Athens, Georgia
Chapter 40 : Diabetes Mellitus

Mikael D. Jones, PharmD, BCPS
Assistant Professor
College of Pharmacy and Nursing
University of Kentucky
Lexington, Kentucky
Chapter 58: Glaucoma

Maher Karam-Hage, MD
Assistant Professor, Addiction Psychiatrist
Medical Director Tobacco Treatment Program (TTP)
University of Texas
MD Anderson Cancer Center
Houston, Texas
Chapter 33: Substance-Related Disorders

Angela D. M. Kashuba, BScPharm, PharmD, DABCP
Associate Professor
School of Pharmacy
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina
Chapter 84: Human Immunodeficiency Virus Infection

Michael D. Katz, PharmD
Associate Professor and Coordinator, International Education
University of Arizona College of Pharmacy
Department of Pharmacy Practice and Science
Tucson, Arizona
Chapter 41: Thyroid Disorders

Deanna L. Kelly, PharmD, BCPP
Associate Professor
University of Maryland
Maryland Psychiatric Research Center
Baltimore, Maryland
Chapter 34: Schizophrenia

Joseph J. Kishel, Jr., PharmD, BCPS
Adjunct Instructor of Pharmacology
Penn State College of Medicine
Clinical Pharmacy Specialist–Infectious Diseases
M.S. Hershey Medical Center
Hershey, Pennsylvania
Chapter 20: Pancreatitis

Julie M. Koehler, PharmD
Associate Professor and Chair of Pharmacy Practice
Butler University College of Pharmacy and Health Sciences
Clinical Pharmacist
Family Medicine
Clarian Health Partner and the Indiana University-Methodist
Family Residency Program
Indiana University School of Medicine
Indianapolis, Indiana
Chapter 45: Contraception

Jill M. Kolesar, PharmD, BCPS, FCCP
Associate Professor
School of Pharmacy
University of Wisconsin
Madison, Wisconsin
Chapter 89: Prostate Cancer

Michael D. Kraft, PharmD
Clinial Assistant Professor
University of Michigan College of Pharmacy
Clincial Coordinator and Clinical Pharmacist-Surgery/Nutrition Support
University of Michigan Health System
Ann Arbor, Michigan
Chapter 97: Parenteral Nutrition

Rebecca M. T. Law, BScPharm, PharmD
Associate Professor
School of Pharmacy
Memorial University of Newfoundland
Newfoundland, Canada
Chapter 61: Psoriasis

Cara Lawless-Liday, PharmD
Associate Professor
Idaho State University
Intermountain Medical Clinic
Pocatello, Idaho
Chapter 48: Erectile Dysfunction

W. Greg Leader, PharmD
Associate Dean
Academic Affairs
University of Louisiana Monroe
College of Pharmacy
Monroe, Louisiana
Chapter 11: Asthma

Mary Lee, PharmD, BCPS, FCCP
Dean and Professor
Midwestern University Chicago College of Pharmacy
Chicago, Illinois
Chapter 49: Benign Prostatic Hyperplasia

Gary M. Levin, PharmD, BCPP, FCCP
Dean and Professor
LECOM-Bradenton
School of Pharmacy
Bradenton, Florida
Chapter 32: Alzheimer's Disease

Russell E. Lewis, PharmD
Associate Professor
University of Houston College of Pharmacy
Clinical Pharmacy Specialist
Infectious Diseases
Department of Infectious Diseases
The University of Texas M.D. Anderson Cancer Center
Houston, Texas
Chapter 81: Invasive Fungal Infections

Teresa V. Lewis, PharmD
Pediatric Pharmacotherapy Fellow
University of Oklahoma College of Pharmacy
Oklahoma City, Oklahoma
Chapter 65: Sickle Cell Disease

Edward C. Li, PharmD
Assistant Professor
Wilkes University
Nesbitt College of Pharmacy and Nursing
Wilkes-Barre, Pennsylvania
Chapter 63: Anemias

Cameron C. Lindsey, PharmD, BC-ADM
Associate Professor of Pharmacy Practice
University of Missouri–Kansas City School of Pharmacy
Clinical Pharmacy Specialist
Veterans Affairs Medical Center–Kansas City
Kansas City, Missouri
Chapter 99: Overweight and Obesity

Karl Madaras-Kelly, PharmD, MPH
Associate Professor
College of Pharmacy
Idaho State University
Boise, Idaho
Chapter 66: Antimicrobial Regimen Selection

Mark A. Malesker, PharmD, FCCP
Associate Professor of Pharmacy Practice and Medicine
Clinical Pharmacy Specialist
Creighton University Medical Center
Omaha, Nebraska
Chapter 24: Fluids and Electrolytes
Chapter 25: Acid-Base Disturbances

J. Russell May, PharmD, FASHP
Clinical Professor
University of Georgia College of Pharmacy
Clinical Pharmacist
Medical College of Georgia Health System
Augusta, Georgia
Chapter 51: Allergic and Pseudoallergic Drug Reactions

Michelle W. McCarthy, PharmD
Drug Information Specialist
University of Virginia Health System
Charlottesville, Virginia
Chapter 59: Allergic Rhinitis

Jeannine S. McCune, PharmD
Associate Professor
University of Washington
Affiliate Investigator
Fred Hutchinson Cancer Research Center
Seattle, Washington
Chapter 95: Hematopoietic Cell Transplantation

Timothy R. McGuire, BS, PharmD, FCCP
Associate Professor
Pharmacy Practice
University of Nebraska Medical Center
College of Pharmacy
Omaha, Nebraska
Chapter 93: Chronic Leukemias and Multiple Myeloma

Patrick J. Medina, PharmD, BCOP
Associate Professor
University of Oklahoma College of Pharmacy
Oklahoma City, Oklahoma
Chapter 88: Colorectal Cancer

Laura Boehnke Michaud, PharmD
Clinical Pharmacy Specialist
The University of Texas M.D. Anderson Cancer Center
Houston, Texas
Chapter 86: Breast Cancer

Sarah J. Miller, PharmD, BCNSP
Professor, Pharmacy Practice
University of Montana Skaggs School of Pharmacy
Pharmacy Clinical Coordinator
Saint Patrick Hospital
Missoula, Montana
Chapter 98: Enteral Nutrition

Beverly Mims, PharmD
Associate Professor of Pharmacy Practice
Howard University School of Pharmacy
Clinical Pharmacist
Howard University Hospital
Washington, DC
Chapter 18: Constipation, Diarrhea, and Irritable Bowel Syndrome

Abby Morris, MD
Family Medicine Resident
Thomas Jefferson University Hospital
Philadelphia, Pennsylvania
Chapter 46: Menstruation-Related Disorders

Lee E. Morrow, MD, MS
Assistant Professor of Medicine
Creighton University Medical Center
Omaha, Nebraska
Chapter 24: Fluids and Electrolytes
Chapter 25: Acid-Base Disturbances

Rocsanna Namdar, PharmD
Assistant Professor
University of New Mexico
College of Pharmacy
Albuquerque, New Mexico
Chapter 72: Tuberculosis

Melinda Margaret Neuhauser, PharmD
Clinical Pharmacy Specialist
Infectious Diseases
U.S. Department of Veterans Affairs
Pharmacy Benefits Management Strategic Health Care Group
Hines, Illinois
Chapter 78: Osteomyelitis

Tien M. H. Ng, PharmD, BCPS
Assistant Professor of Clinical Pharmacy and Pharmaceutical Economics and Policy
Department of Pharmacy
University of Southern California
Los Angeles, California
Chapter 3: Heart Failure

Kimberly J. Novak, PharmD
Adjunct Clinical Assistant Professor
The Ohio State University College of Pharmacy
Clinical Pharmacy Specialist/Pediatric
Pulmonary Medicine
Children's Hospital
Columbus, Ohio
Adjunct Assistant Professor
West Virginia University School of Pharmacy
Morgantown, West Virginia
Chapter 13: Cystic Fibrosis

Edith A. Nutescu, PharmD
Clinical Associate Professor
Department of Pharmacy Practice
Director
Antithrombosis Center
University of Illinois at Chicago College of Pharmacy
Chicago, Illinois
Chapter 7: Venous Thromboembolism

Catherine M. Oliphant, PharmD
Associate Professor of Pharmacy Practice
Idaho State University College of Pharmacy
Clinical Pharmacist
St. Luke's Internal Medicine
Boise, Idaho
Chapter 66: Antimicrobial Regimen Selection

Ali J. Olyaei, PharmD, BCPS
Associate Professor
Nephrology and Hypertension
Oregon Health and Sciences University
Clinical Pharamcotherapist
University Hospital
Portland, Oregon
Chapter 52: Solid Organ Transplantation

Christine K. O'Neil, PharmD, BCPS, CGP, FCCP
Associate Professor
Duquesne University
Mylan School of Pharmacy
Director
Center for Pharmacy Care
Pittsburgh, Pennsylvania
Chapter 30: Pain Management

David Parra, PharmD, BCPS
Clinical Pharmacy Specialist in Cardiology
Department of Cardiology
Veterans Affairs Medical Center
Clinical Assistant Professor
Experimental and Clinical Pharmacology Department
University of Minnesota
Minneapolis, Minnesota
Chapter 2: Hypertension

Charles A. Peloquin, PharmD
Clinical Professor of Pharmacy and Medicine
University of Colorado
Director
Infectious Disease Pharmacokinetics Laboratory
National Jewish Medical and Research Center
Denver, Colorado
Chapter 72: Tuberculosis

Susan L. Pendland, MS, PharmD
Adjunct Associate Professor of Pharmacy Practice
University of Illinois at Chicago
Chicago, Illinois
Chapter 78: Osteomyelitis

Trinh Pham, PharmD, BCOP
Assistant Clinical Professor
University of Connecticut, School of Pharmacy
Assistant Clinical Professor
Yale New Haven Hospital
New Haven, Connecticut
Chapter 94: Skin Cancer

Beth Bryles Phillips, PharmD, BCPS
Assistant Professor (Clinical)
University of Iowa College of Pharmacy
Clinical Pharmacy Specialist
Ambulatory Care
University of Iowa Hospitals and Clinics
Iowa City, Iowa
Chapter 53: Osteoporosis

Bradley G. Phillips, PharmD
Associate Professor
University of Iowa
College of Pharmacy
Iowa City, Iowa
Chapter 38: Sleep Disorders

Amy M. Pick, PharmD
Assistant Professor of Pharmacy Practice
Creighton University
Oncology Clinical Pharmacist
Nebraska Methodist Hospital
Omaha, Nebraska
Chapter 93: Chronic Leukemias and Multiple Myeloma

Brian A. Potoski, PharmD
Assistant Professor
Department of Pharmacy and Therapeutics
University of Pittsburgh School of Pharmacy
Clinical Specialist
Antibiotic Management Program
University of Pittsburgh Medical Center
Presbyterian University Hospital
Pittsburgh, Pennsylvania
Chapter 76: Urinary Tract Infection

Frank Pucino, Jr., PharmD, BCPS, FASHP, FDPGEC
Ambulatory Care Clinical Pharmacy Team Leader
National Institutes of Health Clinical Center
Bethesda, Maryland
Chapter 42: Adrenal Gland Disorders
Chapter 43: Pituitary Gland Disorders

Phillip David Rogers, PharmD, PhD, FCCP
First Tennessee Chair of Excellence in Pediatric Clinical Pharmacy
Associate Professor and Vice Chair for Research
Department of Clinical Pharmacy
Associate Professor, Departments of Pharmaceutical Sciences, Molecular Sciences, and Pediatrics
University of Tennessee Health Science Center
Memphis, Tennessee
Chapter 81: Invasive Fungal Infections

Leigh Ann Ross, PharmD, BCPS, CDE
Assistant Professor
University of Mississippi School of Pharmacy
Director
Pharmaceutical Care Services
University of Mississippi Medical Center
Jackson, Mississippi
Chapter 31: Headache

Brendan S. Ross, MD
Assistant Professor
University of Mississippi School of Pharmacy
Staff Physician
G. V. (Sonny) Montgomery Veterans Affairs Medical Center
Jackson, Mississippi
Chapter 31: Headache

John C. Rotschafer, PharmD, FCCP
Professor
Department of Experimental and Clinical Pharmacology
College of Pharmacy
University of Minnesota
Minneapolis, Minnesota
Chapter 82: Antimicrobial Prophylaxis in Surgery

Laurajo Ryan, PharmD, BCPS, CDE
Clinical Assistant Professor
University of Texas at Austin
University of Texas Health Science Center San Antonio
San Antonio, Texas
Chapter 19: Portal Hypertension and Cirrhosis

Melody Ryan, PharmD
Associate Professor
University of Kentucky College of Pharmacy
Clinical Specialist in Neurology
Veterans Affairs Medical Center
Lexington, Kentucky
Chapter 26: Multiple Sclerosis

Jeremy A. Schafer, PharmD
Senior Clinical Pharmacist
Prime Therapeutics
Eagan, Minnesota
Chapter 82: Antimicrobial Prophylaxis in Surgery

Lauren S. Schlesselman, PharmD
Assistant Clinical Professor
University of Connecticut School of Pharmacy
Department of Pharmacy Practice
Storrs, Connecticut
Chapter 80: Superficial Fungal Infections

Kristine S. Schonder, PharmD
Assistant Professor
University of Pittsburgh School of Pharmacy
Clinical Specialist
Thomas E. Starzl Transplantation Institute
Pittsburgh, Pennsylvania
Chapter 23: Chronic and End-Stage Renal Disease

Roohollah Sharifi, MD, FACS
Professor of Urology
University of Illinois at Chicago
College of Medicine
Section Chief of Urology
Westside Veterans Administration Hospital
Chicago, Illinois
Chapter 49: Benign Prostatic Hyperplasia

Judith A. Smith, PharmD, BCOP
Assistant Professor
University of Texas M.D. Anderson Cancer Center
Houston, Texas
Chapter 91: Ovarian Cancer

Philip H. Smith, MD, FAAAAI, FACAAI
Assistant Professor of Medicine
Allergy and Immunology
Medical College of Georgia
Assistant Professor
Medical College of Georgia
Childrens' Medical Center
Augusta, Georgia
Chapter 51: Allergic and Pseudoallergic Drug Reactions

Melissa A. Somma, PharmD, CDE
Assistant Professor of Pharmacy and Family Medicine
University of Pittsburgh Schools of Pharmacy and Medicine
Director
University of Pittsburgh/Rite Aid Patient Care Initiative
Rite Aid Corporation
Pittsburgh, Pennsylvania
Chapter 47: Hormone Replacement Therapy in Menopause

Sarah A. Spinler, PharmD, FCCP
Professor of Clinical Pharmacy
Residency and Fellowship Program Coordinator
Philadelphia College of Pharmacy
University of the Sciences in Philadelphia
Philadelphia, Pennsylvania
Chapter 5: Acute Coronary Syndromes

Mary K. Stamatakis, BS, PharmD
Associate Dean and Associate Professor
West Virginia University School of Pharmacy
Morgantown, West Virginia
Chapter 22: Acute Renal Failure

Brad L. Stanford, PharmD, BCOP
Assistant Professor of Pharmacy Practice
Texas Tech University Health Sciences Center
School of Pharmacy
Lubbock, Texas
Chapter 96: Oncologic Emergencies

Robert J. Straka, PharmD, FCCP
Associate Professor
Department of Experimental and Clinical Pharmacology
College of Pharmacy
University of Minnesota
Minneapolis, Minnesota
Chapter 2: Hypertension

Deborah Sturpe, PharmD, BCPS
Assistant Professor
University of Maryland School of Pharmacy
Baltimore, Maryland
Chapter 44: Pregnancy and Lactation: Therapeutic Considerations

S. Scott Sutton, PharmD, BCPS
Associate Clinical Professor
South Carolina College of Pharmacy
University of South Carolina
Clinical Pharmacist
WJB Dorn Veterans Affairs Medical Center
Columbia, South Carolina
Chapter 79: Sepsis and Septic Shock

Eljim P. Tesoro, PharmD
Clinical Assistant Professor
University of Illinois at Chicago
Pharmacotherapist
Department of Neurosurgery
University of Illinois at Chicago Medical Center
Chicago, Illinois
Chapter 28: Status Epilepticus

Michael D. Thompson, PharmD, BCNSP
Assistant Dean for Clinical Affairs and Professor
Florida A&M University
Residency Coordinator and Clinical Pharmacy Director
American Home Patient
Tallahassee, Florida
Chapter 77: Sexually Transmitted Infections

James E. Tisdale, PharmD
Professor
School of Pharmacy and Pharmaceutical Sciences
Purdue University
Adjunct Professor
School of Medicine
Indiana University
Indianapolis, Indiana
Chapter 6: Arrhythmias

Elena M. Umland, BS, PharmD
Associate Dean for Academic Affairs
Associate Professor of Clinical Pharmacy
Jefferson School of Pharmacy
Jefferson College of Health Professions
Thomas Jefferson University
Philadelphia, Pennsylvania
Chapter 46: Menstruation-Related Disorders

Heather L. VandenBussche, PharmD
Associate Professor of Pharmacy Practice
Ferris State University College of Pharmacy
Kalamazoo, Michigan
Chapter 69: Upper Respiratory Tract Infections

Orly Vardeny, PharmD
Assistant Professor
Pharmacy Practice Division
University of Wisconsin–Madison
School of Pharmacy
Madison, Wisconsin
Chapter 3: Heart Failure

Nicole D. Verkleeren, PharmD
Adjunct Clinical Professor
West Virginia University School of Pharmacy
Pharmacy Practice Resident
West Virginia University Hospitals
Morgantown, West Virginia
Clinical Pharmacist
The Western Pennsylvania Hospital
Forbes Regional Campus
Monroeville, Pennsylvania
Chapter 12: Chronic Obstructive Pulmonary Disease

William E. Wade, PharmD
Professor and Associate Head
College of Pharmacy
University of Georgia
Clinical Pharmacist
Saint Mary's Health Care Systems
Athens, Georgia
Chapter 40: Diabetes Mellitus

Mary Louise Wagner, MS, PharmD
Associate Professor
Ernest Mario School of Pharmacy
Rutgers–State University of New Jersey
Piscataway, New Jersey
Chapter 29: Parkinson's Disease

Geoffrey C. Wall, PharmD, BCPS
Associate Professor of Pharmacy Practice
Drake University
College of Pharmacy and Health Sciences
Internal Medicine Clinical Pharmacist
Iowa Methodist Medical Center
Des Moines, Iowa
Chapter 56: Gout and Hyperuricemia

Elaine Weiner, MD
Assistant Professor
University of Maryland Medical School
Medical Director
Maryland Psychiatric Research Center
Outpatient Research Program
Catonsville, Maryland
Chapter 34: Schizophrenia

Lara Carson Weinstein, MD
Instructor
Department of Family and Community Medicine
Jefferson Medical College
Thomas Jefferson University
Jefferson Family Medicine
Philadelphia, Pennsylvania
Chapter 46: Menstruation-Related Disorders

Timothy E. Welty, PSPharm, MA, PharmD
Professor
McWhorter School of Pharmacy
Samford University
Adjunct Associate Research Professor
Department of Neurology
University of Alabama Birmingham
Birmingham, Alabama
Chapter 27: Epilepsy

Randy Wesnitzer, BS Pharm, PharmD
Clinical Coordinator
Wyoming Medical Center
Department of Pharmacy
Casper, Wyoming
Chapter 70: Skin and Soft Tissue Infections

Tara Whetsel, PharmD
Clinical Assistant Professor
West Virginia University School of Pharmacy
Morgantown, West Virginia
Chapter 12: Chronic Obstructive Pulmonary Disease

Sheila Wilhelm, PharmD
Assistant Professor
Wayne State University
Clinical Pharmacy Specialist
Internal Medicine
Harper University Hospital
Detroit, Michigan
Chapter 17: Nausea and Vomiting

Dianne B. Williams, PharmD, BCPS
Clinical Assistant Professor
University of Georgia College of Pharmacy
Drug Information and Formulary Coordinator
MCG Health, Inc.
Augusta, Georgia
Chapter 14: Gastroesophageal Reflux Disease

Susan R. Winkler, PharmD, BCPS
Clinical Associate Professor
Pharmacy Practice
Assistant Director
Ambulatory Clinical Services
Department of Pharmacy Practice
University of Illinois at Chicago College of Pharmacy
Chicago, Illinois
Chapter 8: Stroke

G. Christopher Wood, PharmD
Associate Professor of Pharmacy
University of Tennessee Health Science Center
Clinical Pharmacist
Regional Medical Center at Memphis
Memphis, Tennessee
Chapter 10: Hypovolemic Shock

Rosa F. Yeh, PharmD
Assistant Professor
University of Houston College of Pharmacy
Houston, Texas
Chapter 84: Human Immunodeficiency Virus Infection

Reviewers

Beth Alexander, PharmD, BCPS
Associate Professor of Physician Assistant Studies
Augsburg College
Minneapolis, Minnesota

Rita Alloway, PharmD, BCPS
Research Professor
University of Cincinnati College of Medicine
Cincinnati, Ohio

Buge Apampa, PhD, BPharm, MRPharmS
Clinical Lecturer
Pharmacy Practice
Universities of Kent and Greenwich at Medway
Chatham Maritime
Kent, United Kingdom

Laurel Ashworth, PharmD
Professor of Clinical and Administrative Sciences & Director
Drug Information Center
Mercer University School of Pharmacy and Allied Health Sciences
Atlanta, Georgia

Sara Augustin, PharmD, BCPP
Clinical Pharmacist
Dekalb Regional Crisis Center
Decatur, Georgia

Ebrahim A. Balbisi, PharmD
Assistant Clinical Professor
St. John's University College of Pharmacy & Allied Health Professions
Jamaica, New York

Phyllis Barks, PA, MPH
Assistant Professor & Technology Development Coordinator
Oregon Health & Science University School of Medicine
Division of Physician Assistant Education
Portland, Oregon

Bonnie Bata-Jones, MS, RN, FNP
Instructor
University of Minnesota
Excelsior, Minnesota

Kathryn R. Bauer, MA, MS, APRN
Instructor
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Kathleen L. Becker, MS, CRNP
Assistant Professor and Coordinator
Adult Nurse Practitioner Program
The Johns Hopkins University School of Nursing
Adult Nurse Practitioner
Health Care for the Homeless
Baltimore, Maryland

Judith L. Beizer, PharmD, CGP, FASCP
Clinical Professor
St. John's University College of Pharmacy & Allied Health Professions
Jamaica, New York

Renee Bellanger, PharmD, BSPharm
Assistant Professor
Pharmacy Practice
The University of the Incarnate Word
San Antonio, Texas

Mary Mescher Benbenek, MS, RN, CFNP, CPNP
Teaching Specialist
University of Minnesota
Minneapolis, Minnesota

Marialice Bennett, RPh, FAPhA
Professor of Clinical Pharmacy
The Ohio State University
Columbus, Ohio

Heather K.T. Bidinger, MMS, PA-C
Clinical Coordinator and Assistant Professor
Department of Physician Assistant Education
Augsburg College
Minneapolis, Minnesota

Sarah Bland, RPh
Clinical Instructor
University of Wisconsin-Madison
Madison, Wisconsin

Patricia J. Blumi, MSN, ARNP
Advanced Registered Nurse Practitioner—Radiation Therapy
Via-Christi Cancer Center
Wichita, Kansas

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John A. Bosso, PharmD, FCCP, BCPS
Professor and Chair
South Carolina College of Pharmacy
Clinical Specialist in Infectious Diseases
Medical University of South Carolina Hospital
Charleston, South Carolina

Margaret Bowers, MSN, APRN, BC
Assistant Clinical Professor
Duke University School of Nursing
Durham, North Carolina

Cleopatra Branch, BSc, PharmD, MRPharmS
Teacher & Practitioner
Medway School of Pharmacy
Universities of Kent and Greenwich at Medway
Chatham Maritime
Kent, United Kingdom

Joyce Brewer, PhD, CNM, CFNP
Associate Professor
University of Mississippi Medical Center
Jackson, Mississippi

David M. Brissette, MMSc, PA-C
Assistant Professor
Yale University School of Medicine
Physician Associate Program
Physician Assistant
Internal Medicine
Yale New Haven Hospital
New Haven, Connecticut

Cori M. Brock, PharmD
Clinical Assistant Professor of Pharmacy Practice
Xavier University College of Pharmacy
New Orleans, Louisiana

Denise Buonocore, MSN, APRN, CCRN
Acute Care Nurse Practitioner
Bridgeport Hospital, Bridgeport
Connecticut, and Yale University School of Nursing
New Haven, Connecticut

Reamer L. Bushardt, PharmD, PA-C
Program Director and Assistant Professor
Department of Clinical Services
College of Health Professions
Medical University of South Carolina
Charleston, South Carolina

Wesley G. Byerly, PharmD
Executive Director for Research Regulatory Affairs
and Adjunct Assistant Professor
Wake Forest University School of Medicine
Winston-Salem, North Carolina

Cynthia Carnes, PharmD, PhD
Associate Professor of Pharmacy and Biophysics
The Ohio State University
Columbus, Ohio

Barry L. Carter, PharmD
Professor
Colleges of Pharmacy and Medicine
The University of Iowa
Iowa City, Iowa

Nina Cheigh, PharmD
Contributing Editor, The Medical Letter, Inc.
New Rochelle, New York
Clinical Associate Professor
University of Illinois College of Pharmacy
Chicago, Illinois

Deborah Chyun, PhD, RN, FAHA
Associate Professor and Director
Adult Advanced Practice Nursing
Yale University School of Nursing
New Haven, Connecticut

Lorraine Cicero, MS, PharmD
Associate Professor
Pharmacy Practice
Long Island University College of Pharmacy and Health Sciences
Brooklyn, New York

Donald Coerver, PhD, PA-C
Acting Instructor
MEDEX Northwest Division of Physician Assistant Studies
Spokane, Washington

Carmita A. Coleman, PharmD
Assistant Dean for Student Affairs and Associate Professor
of Pharmacy Practice
Feik School of Pharmacy
University of the Incarnate Word
San Antonio, Texas

Lynn Convery, RN, MS, CNP
Gerontological Nurse Practitioner
HealthPartners Partnering Care Senior Services
Minneapolis, Minnesota

Keely L. Cook, MPAS, PA-C
Assistant Professor
Doisy College of Health Sciences
Saint Louis University
St. Louis, Missouri

Sarah Corlett, PhD, MRPharmS
University of Greenwich
Medway School of Pharmacy
Chatham Maritime
Kent, United Kingdom

Joseph E. Crea, DO, MHA
Assistant Professor
The University of Findlay School of Pharmacy
Findlay, Ohio

Patricia Cunningham, DNSc, APRN, BC
Assistant Professor
University of Tennessee Health Science Center
College of Nursing
Memphis, Tennessee

Petra Czarniak, BPharm, MPS
Lecturer in Pharmaceutics
Division of Health Sciences
Murcoch University School of Pharmacy
Murdoch
Western Australia, Australia

Bonnie A. Dadig, EdD, PA-C
Chair, Physician Assistant Department
Medical College of Georgia
Director
Physician Assistant Program
Medical College of Georgia Hospitals and Clinics
Augusta, Georgia

Larry Danziger, PharmD
Professor of Pharmacy Practice
University of Illinois at Chicago College of Pharmacy
Chicago, Illinois

Lawrence Davidow, PhD, RPh
Clinical Assistant Professor
University of Kansas School of Pharmacy
Lawrence, Kansas

Jillian H. Davis, PhD
Assistant Professor
Hampton University School of Pharmacy
Hampton, Virginia

Michelle Devereaux, MA, RN, CNP
Partnering Care Senior Services
Bloomington, Minnesota

Thomas C. Dowling, PharmD, PhD
Associate Professor
University of Maryland
Baltimore, Maryland

Allan Ellsworth, PharmD, PA-C
Professor of Pharmacy and Family Medicine
University of Washington Schools of Pharmacy and Medicine
Seattle, Washington

Katherine Erdman, MPAS, PA-C
Assistant Director
Physician Assistant Program
Baylor College of Medicine
Houston, Texas

Jennifer Fair, PharmD
Clinical Pharmacy Program
University of Georgia
College of Pharmacy
Medical College of Georgia
Augusta, Georgia

Jingyang Fan, PharmD, BCPS
Assistant Professor of Pharmacy Practice
University of Southern Nevada College of Pharmacy
Henderson, Nevada

Carl E. Fasser, PA
Associate Professor of Family & Community Medicine
and Physician Assistant
Baylor College of Medicine
Houston, Texas

Maisha Kelly Freeman, PharmD, BCPS
Assistant Professor and Drug Information Specialist
Samford University McWhorter School of Pharmacy
Birmingham, Alabama

Mark Garrison, PharmD
Associate Professor of Pharmacotherapy & Assistant Dean
of Student Services
Washington State University-Spokane
Spokane, Washington

Margit B. Gerardi, MS, MSA, MSN, RN-WHNP
Clinical Instructor
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Stuart Gill-Banham, MRPharmS, MCMHP
Teacher Practitioner
Universities of Kent and Greenwich at Medway
Medway School of Pharmacy
Chatham Maritime
Kent, United Kingdom

Sveinbjörn Gizurarson, PhD
Professor of Pharmaceutics
Biopharmaceutics and Clinical Therapeutics
University of Iceland
Reykjavík, Iceland

Nancy Goldstein, MSN, CRNP, RNC
Instructor
The Johns Hopkins University School of Nursing
Baltimore, Maryland

Justine Schuller Gortney, PharmD, BCPS
Clinical Assistant Professor
Mercer University
Atlanta, Georgia

Erich J. Grant, MMS, PA-C
Instructor
Physician Assistant Program
Wake Forest University School of Medicine
Winston-Salem, North Carolina

Hillary Wall Grillo, PharmD
Adjunct Assistant Professor
Shenandoah University School of Pharmacy
Winchester, Virginia

Sara Haddow, MSA, PA-C
Instructor
Physician Assistant Department
Medical College of Georgia
Augusta, Georgia

Robert Hadley, PhD, PA-C
Associate Professor
University of Kentucky Physician Assistant Program
Lexington, Kentucky

David Hawkins, PharmD
Senior Associate Dean
Professor of Pharmacy Practice
South University School of Pharmacy
Savannah, Georgia

Mary S. Hayney, PharmD, BCPS, FCCP
Associate Professor of Pharmacy
University of Wisconsin School of Pharmacy
Madison, Wisconsin

Mark A. Heisler, PharmD, BCPS
Adjunct Faculty
Grand Canyon University College of Nursing
Phoenix, Arizona
Adjunct Faculty
Arizona State University College of Nursing
Tempe, Arizona
Clinical Pharmacist
Banner Desert Medical Center
Mesa, Arizona

Pamela Helms, RN, MN, FNP-C
Assistant Professor & Clinical Director
UNACARE Health Center
University of Mississippi School of Nursing
Ridgeland, Mississippi

Elizabeth Hermsen, PharmD, MBA
Antimicrobial Specialist
The Nebraska Medical Center
Adjunct Assistant Professor
University of Nebraska Medical Center College
of Pharmacy
Omaha, Nebraska

Michael K. Jensen, BSPharm, MS
Clinical Adjunct Associate Professor of Pharmacy
University of Utah College of Pharmacy
Clinical Specialist Ophthalmology
University of Utah Health Sciences Center
John A. Moran Eye Center
Salt Lake City, Utah

Jill T. Johnson, PharmD, BCPS
Associate Professor
University of Arkansas for Medical Sciences College
of Pharmacy
Little Rock, Arkansas

June Felice Johnson, PharmD, BCPS, FASHP, CDM-diabetes
Associate Professor of Pharmacy Practice & Director of Faculty
& Site Development
Drake University College of Pharmacy & Health Sciences
Des Moines, Iowa

Nikki L. Katalanos, PhD, PA-C
Assistant Professor and Physician Assistant
Physician Assistant Program
Department of Family & Community Medicine
The University of New Mexico School of Medicine
Albuquerque, New Mexico

Nancy Kawahara, PharmD, MSEd
Associate Professor and Chair
Department of Pharmacy Practice
Loma Linda University School of Pharmacy
Loma Linda, California

Michael Kelsch, PharmD, BCPS
Assistant Professor
North Dakota State University College of Pharmacy
Fargo, North Dakota

Lynn G. Kirkland, DNSc, WHNP, CNM
Assistant Professor
University of Tennessee Health Science Center
Women's Health Nurse Practitioner/Certified Nurse Midwife
Memphis Obstetrics and Gynecological Association P.C.
Bartlett, Tennessee

Julie Kissack, PharmD, BCCP
Associate Professor
Mercer University
Southern School of Pharmacy
Atlanta, Georgia

Michael E. Klepser, PharmD, FCCP
Professor of Pharmacy
Ferris State University College of Pharmacy
and Borgess Medical Center
Kalamazoo, Michigan

Carrie Foust Koenigsfeld, PharmD
Associate Professor of Pharmacy Practice
Drake College of Pharmacy and Health Sciences
Des Moines, Iowa

Annette C. Larson, MSPAS
Assistant Professor
University of North Dakota School of Medicine
Physician Assistant
Altru Health Care System
Grand Forks, North Dakota

Esther M. Law, BScPhm
Director, Pharmaceuticals
Shopper's Drug Mart
North York, Ontario
Canada

Rebecca M. T. Law, BScPhm, PharmD
Associate Professor
School of Pharmacy
Memorial University of Newfoundland
St. John's, Newfoundland, Canada

Helen Leather, BPharm, Grad Dip Hosp Pharm (Dist)
Clinical Pharmacy Specialist
Hematopoietic Stem Cell Transplantation/Leukemia Shands
at the University of Florida
Clinical Assistant Professor
University of Florida College of Pharmacy
Gainesville, Florida

Thomas L. Lenz, PharmD, MA
Assistant Professor of Pharmacy Practice
Creighton University
Omaha, Nebraska

Sonia Lin, PharmD, BCPS
Clinical Associate Professor
University of Rhode Island
Kingston, Rhode Island

Michael Mancano, PharmD
Associate Chair
Department of Pharmacy Practice, and
Clinical Associate Professor
Temple University School of Pharmacy
Philadelphia, Pennsylvania

Donald Maner, PharmD, MHSc, PA-C
Assistant Professor
Medical College of Georgia
Physician Assistant Department
Evans, Georgia

Harold J. Manley, PharmD, FASN, FCCP, BCPS
Associate Professor
Department of Pharmacy Practice
Albany College of Pharmacy
Albany, New York

Henry J. Mann, PharmD, FASHP, FCCM, FCCP
Professor
University of Minnesota College of Pharmacy
Department of Experimental and Clinical Pharmacology
Director
Center for Excellence in Critical Care
University of Minnesota
Academic Health Center
Minneapolis, Minnesota

Karen F. Marlowe, PharmD, BCPS
Associate Professor
Auburn University Harrison School of Pharmacy
Adjunct Assistant Professor
University of South Alabama School of Medicine
Mobile, Alabama

Phyllis Mason, MS, RN, CRNP
Instructor
The Johns Hopkins University School of Nursing
Baltimore, Maryland

Jeanie McHugo, MS, PA-C
Assistant Professor
University of North Dakota Physician Assistant Program
Grand Forks, North Dakota

Kimberly Ann Meyer, MPAS
Infectious Diseases Physician Assistant
University of Nebraska Medical Center
Omaha, Nebraska

Candis M. Morello, PharmD, CDE, FCSHP
Assistant Professor of Clinical Pharmacy
Skaggs School of Pharmacy and Pharmaceutical Sciences
University of California
San Diego
La Jolla, California

Carla Moschella, PA-C, MS, RD
Assistant Professor and Academic Coordinator
Department of Physician Assistant Studies
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Dana N. Nadolo, MHS, PA-C
Physician Assistant
Academic Faculty, Physician Assistant Program
Instructor, Allied Health Sciences
Baylor College of Medicine
Houston, Texas

Jadwiga Najib, BS, PharmD
Associate Professor of Pharmacy Practice
Arnold & Marie Schwartz College of Pharmacy
and Health Sciences
Long Island University
Brooklyn, New York

Jacquelin S. Neatherlin, RN, PhD, CNRN
Associate Professor
Baylor University
Dallas, Texas

Robert Nelson, PharmD, BCPS
Assistant Professor
North Dakota State University College of Pharmacy
Nursing, and Allied Sciences
Clinical Pharmacy Manager
MeritCare Health System
Fargo, North Dakota

Christopher Nemergut, PharmD
Clinical Pharmacist
Center for Drug Policy
University of Wisconsin Hospital and Clinics
Madison, Wisconsin

Ayman Noreddin, PhD, RPh
Associate Professor
University of Minnesota College of Pharmacy
Duluth, Minnesota

Deborah A. Opacic, EdD, PA-C
Assistant Professor
Rangos School of Health Sciences
Duquesne University
Pittsburgh, Pennsylvania

Victor A. Padron, RPh, PhD
Associate Professor
Department of Pharmacy Sciences
Creighton University
Omaha, Nebraska

Amy Pakyz, PharmD, MS
Assistant Professor
Virginia Commonwealth University School
of Pharmacy/Medical College of Virginia Campus
Richmond, Virginia

Cynthia Pentz, EdD, PA-C
Director
Physician Assistant Program
University of Findlay
Findlay, Ohio

Todd Pillen, PA-C/SA, MPAS
Manager
Solid Organ Transplant
Children's Healthcare of Atlanta-Egleston
and Emory University Hospital
Atlanta, Georgia

Therese I. Poirier, PharmD, MPH, BCPS, FASHP, FCCP
Professor and Associate Dean
Academic Affairs
Southern Illinois University-Edwardsville
Edwardsville, IIllinois

Jane Pruemer, PharmD, BCOP, FASHP
Associate Professor of Clinical Pharmacy Practice
University of Cincinnati College of Pharmacy
Cincinnati, Ohio

Edward W. Randell, PhD, DCC, FCACB
Chief
Division of Biochemical Pathology Health Sciences Centre
Associate Professor
Laboratory Medicine
Faculty of Medicine
Memorial University of Newfoundland
St. John's, Newfoundland, Canada

Mette Rasmussen, PhD
Professor
Faculty of Pharmaceutical Sciences
Department of Pharmacology and Pharmacotherapy
Section of Clinical pharmacy
University of Copenhagen
Copenhagen, Denmark

Michael D. Reed, PharmD, FCCP, FCP
Director
Pediatric Clinical Pharmacology and Toxicology
Rainbow Babies and Children's Hospital and Professor of Pediatrics
School of Medicine
Case Western Reserve University
Cleveland, Ohio

Kathleen Reeve, DrPH, AOCN, ANP
Associate Professor of Clinical Nursing
The University of Texas Health Science Center at Houston
Houston, Texas

Suzanne Reich, PA-C, MPAS
Assistant Professor
Department of Physician Assistant Studies
Wake Forest University School of Medicine
Winston-Salem, North Carolina

Warren Richards, BSPharm, MBA, PhD
Associate Professor
Lloyd L. Gregory School of Pharmacy
Palm Beach Atlantic University School of Pharmacy
West Palm Beach, Florida

Keith A. Rodvold, PharmD
Professor of Pharmacy Practice & Associate Professor
of Medicine in Pharmacy
University of Illinois at Chicago
Chicago, Illinois

Carol J. Rollins, MS, RD, PharmD, BCNSP
Program Director: Nutrition Support Pharmacy Practice
Arizona Health Sciences Center
Clinical Associate Professor
College of Pharmacy
University of Arizona
Tucson, Arizona

Wendella Rose-Facey, APRN, CCRN, FNP, MSN
Adjunct Professor
Adelphi University
Critical Care Specialist at Kingsbrook Jewish Medical Center
Brooklyn, New York

Elaine Rosenblatt, MSN, APRN, BC
Clinical Professor
University of Wisconsin
Director of Health Services and Quality Improvement
University of Wisconsin Medical Foundation
Madison, Wisconsin

Polly Royal, MS, RN-BC
Clinical Assistant Professor
Purdue University School of Nursing
West Lafayette, Indiana

Michael Rybak, PharmD, MPH
Associate Dean for Research & Professor of Pharmacy and Medicine
Director of Anti-Infective Research Laboratory
Wayne State University College of Pharmacy & Health Sciences
Detroit, Michigan

Kiranpal S. Sangha, PharmD
Clinical Pharmacy Specialist-CNS
The University Hospital
Cincinnati, Ohio
Adjunct Assistant Professor of Clinical Pharmacy
The University of Cincinnati College of Pharmacy
Cincinnati, Ohio

JoAnne M. Saxe, RN, MS, ANP
Clinical Professor & Director of the Adult Nurse
Practitioner Program
University of California
San Francisco School of Nursing
San Francisco, California

Dana Sayre-Stanhope, EdD, PA-C
Associate Professor
Saint Louis University
Doisy College of Health Sciences
St. Louis, Missouri

Sarah L. Scarpace, PharmD, BCOP
Assistant Professor
Albany College of Pharmacy
Albany, New York

Denise Schentrup, MN, ARNP, BC
Clinical Assistant Professor
University of Florida
College of Nursing
Gainesville, Florida

Karin Schurrer-Erickson, MA, RN, CNP
Teaching Specialist
University of Minnesota School of Nursing
Minneapolis, Minnesota

Catherine Shull, PA-C, MPAS
Instructor
Department of Physician Assistant Studies
Wake Forest University School of Medicine
Winston-Salem, North Carolina

Susan M. Stein, MS, RPh
Assistant Dean for Clinical Education and Student Development
Pacific University School of Pharmacy
Hillsboro, Oregon

Henry Stoll, PA-C
Senior Lecturer
University of Washington School of Medicine
Seattle, Washington

Marc A. Sweeney, RPh, MDiv, PharmD
Chair & Associate Professor
Pharmacy Practice
The University of Findlay School of Pharmacy
Findlay, Ohio

Mohammad J. Tafreshi, PharmD, BCPS
Associate Professor
Midwestern University College of Pharmacy-Glendale
Glendale, Arizona

Brenda J. J. Talarico, MPAS, PA-C
Assistant Professor
Department of Physician Assistant Studies
Augsburg College
Minneapolis, Minnesota

Candace Smith, PharmD
Associate Clnical Professor
St. John's University College of Pharmacy
& Allied Health Professions
Jamaica, New York

Christopher J. Sullivan, MD, FACP
Adjunct Professor of Pharmacy
University of Minnesota
Birchwood Village, Minnesota

Damary Castanheira Torres, PharmD, BCOP
Associate Clinical Professor
St. John's University College of Pharmacy
& Allied Health Professions
Jamaica, New York

Mary Fran Tracy, PhD, RN, CCRN, CCNS, FAAN
Critical Care Clinical Nurse Specialist
University of Minnesota Medical Center
Fairview
Minneapolis, Minnesota

Marianne Vail, MS, PA-C
Department of Physician Assistant Studies
Massachusetts College of Pharmacy & Health Sciences
Boston, Massachusetts

Lee Vermeulen, RPh, MS, FCCP
Director
Center for Drug Policy
University of Wisconsin Hospital and Clinics
Madison, Wisconsin

Angie Veverka, BS, PharmD
Assistant Professor of Pharmacy
Wingate University School of Pharmacy
Wingate, North Carolina

Heather Vezina, PharmD
Assistant Professor
University of Minnesota School of Medicine & College of Pharmacy
Minneapolis, Minnesota

Vicki Waters, MS, PA-C
Assistant Director for Experiential Learning
Physician Assistant Program
School of Allied Health Sciences
Baylor College of Medicine
Houston, Texas

Christine Werner, PA-C, PhD
Assistant Professor
Saint Louis University
Doisy College of Health Sciences
St. Louis, Missouri

Thomas White, JD, PA-C
Academic Coordinator
Physician Assistant Program
University of New Mexico School of Medicine
Albuquerque, New Mexico

Siu-Fun Wong, PharmD, FASHP, FCSHP
Associate Professor of Pharmacy Practice
Western University of Health Sciences
Faculty-in-Residence
Hematology-Oncology Medical Group of Orange County, Inc.
Pomona, California

Daniel Wood, MPAS, PA-C
Clinical Assistant Professor
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Kathleen Woodruff, MS, CRNP
Instructor
The Johns Hopkins University School of Nursing
Baltimore, Maryland

Monty Yoder, PharmD, BCPS
Pharmaceutical Care Coordinator
Wake Forest University Baptist Medical Center
Winston-Salem, North Carolina

Dawn Zwick, MSN, CRNP
Lecturer
College of Nursing
Kent State University
Kent, Ohio

Continuing Education Credits

Chap. 1 – Introduction

Chap. 2 – Hypertension
Universal Program Number:
014-999-07-014-H04
Three (3.0) contact hours (0.30 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 3 – Heart Failure
Universal Program Number:
014-999-07-015-H04
Four (4.0) contact hours (0.40 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 4 – Ischemic Heart Disease
Universal Program Number:
014-999-07-016-H06
Three (3.0) contact hours (0.30 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 5 – Acute Coronary Syndromes
Universal Program Number:
014-999-07-017-H04
Two and half (2.5) contact hours (0.25 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 6 – Arrhythmias
Universal Program Number:
014-999-07-018-H04
Three and half (3.5) contact hours (0.35 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 7 – Venous Thromboembolism
Universal Program Number:
014-999-07-019-H04
Three and half (3.5) contact hours (0.35 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 8 – Stroke
Universal Program Number:
014-999-07-020-H04
Two (2.0) contact hours (0.20 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 9 – Hyperlipidemia
Universal Program Number:
014-999-07-021-H04
Two and half (2.5) contact hours (0.25 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 10 – Hypovolemic Shock
Universal Program Number:
014-999-07-022-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 11 – Asthma
Universal Program Number:
014-999-07-025-H04
Three (3.0) contact hours (0.30 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 12 – Chronic Obstructive Pulmonary Disease
Universal Program Number:
014-999-07-026-H04
Two (2.0) contact hours (0.20 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 13 – Cystic Fibrosis
Universal Program Number:
014-999-07-027-H04
Two (2.0) contact hours (0.20 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 14 – Gastroesophageal Reflux Disease
Universal Program Number:
014-999-07-028-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 15 – Peptic Ulcer Disease
Universal Program Number:
014-999-07-029-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 16 – Inflammatory Bowel Disease
Universal Program Number:
014-999-07-030-H04
Two (2.0) contact hours (0.20 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 17 – Nausea and Vomiting
Universal Program Number:
014-999-07-031-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 18 – Constipation, Diarrhea, and Irritable Bowel Syndrome
Universal Program Number:
014-999-07-032-H04
Two and half (2.5) contact hours (0.25 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 19 – Portal Hypertension and Cirrhosis
Universal Program Number:
014-999-07-033-H04
Two (2.0) contact hours (0.20 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 20 – Pancreatitis
Universal Program Number:
014-999-07-034-H04
One (1.0) contact hours (0.10 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 21 – Viral Hepatitis
Universal Program Number:
014-999-07-035-H04
Two (2.0) contact hours (0.20 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 22 – Acute Renal Failure
Universal Program Number:
014-999-07-036-H04
Two (2.0) contact hours (0.20 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 23 – Chronic and End-Stage Renal Disease
Universal Program Number:
014-999-07-037-H04
Four (4.0) contact hours (0.40 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 24 – Fluids and Electrolytes
Universal Program Number:
014-999-07-038-H01
Two (2.0) contact hours (0.20 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 25 – Acid-Base Disturbances
Universal Program Number:
014-999-07-039-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 26 – Multiple Sclerosis
Universal Program Number:
014-999-07-040-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 27 – Epilepsy
Universal Program Number:
014-999-07-041-H04
Two (2.0) contact hours (0.20 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 28 – Status Epilepticus
Universal Program Number:
014-999-07-042-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 29 – Parkinson's Disease
Universal Program Number:
014-999-07-043-H04
Two (2.0) contact hours (0.20 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 30 – Pain Management
Universal Program Number:
014-999-07-044-H04
Two (2.0) contact hours (0.20 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 31 – Headache
Universal Program Number:
014-999-07-047-H04
Two (2.0) contact hours (0.20 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 32 – Alzheimer's Disease
Universal Program Number:
014-999-07-048-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 33 – Substance-Related Disorders
Universal Program Number:
014-999-07-049-H04
Three (3.0) contact hours (0.30 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 34 – Schizophrenia
Universal Program Number:
014-999-07-050-H04
Two and half (2.5) contact hours (0.25 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 35 – Major Depressive Disorder
Universal Program Number:
014-999-07-051-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 36 – Bipolar Disorder
Universal Program Number:
014-999-07-052-H04
Two and half (2.5) contact hours (0.25 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 37 – Generalized Anxiety Disorder, Panic Disorder, and Social Anxiety Disorder
Universal Program Number:
014-999-07-053-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 38 – Sleep Disorders
Universal Program Number:
014-999-07-054-H04
One (1.0) contact hours (0.10 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 39 – Attention-Deficit Hyperactivity Disorder
Universal Program Number:
014-999-07-055-H04
Half (0.5) contact hours (0.05 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 40 – Diabetes Mellitus
Universal Program Number:
014-999-07-056-H04
Two (2.0) contact hours (0.20 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 41 – Thyroid Disorders
Universal Program Number:
014-999-07-057-H04
Two (2.0) contact hours (0.20 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 42 – Adrenal Gland Disorders
Universal Program Number:
014-999-07-058-H04
One (1.0) contact hours (0.10 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 43 – Pituitary Gland Disorder
Universal Program Number:
014-999-07-123-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 44 – Pregnancy and Lactation: Therapeutic Considerations
Universal Program Number:
014-999-07-059-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 45 – Contraception
Universal Program Number:
014-999-07-060-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 46 – Menstruation-Related Disorders
Universal Program Number:
014-999-07-061-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 47 – Hormone-Replacement Therapy in Menopause
Universal Program Number:
014-999-07-062-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 48 – Erectile Dysfunction
Universal Program Number:
014-999-07-063-H04
One (1.0) contact hours (0.10 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 49 – Benign Prostatic Hyperplasia
Universal Program Number:
014-999-07-064-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 50 – Urinary Incontinence and Pediatric Enuresis
Universal Program Number:
014-999-07-065-H04
Two (2.0) contact hours (0.20 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 51 – Allergic and Pseudoallergic Drug Reactions
Universal Program Number:
014-999-07-066-H04
One (1.0) contact hours (0.10 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 52 – Solid-Organ Transplantation
Universal Program Number:
014-999-07-067-H04
Two and half (2.5) contact hours (0.25 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 53 – Osteoporosis
Universal Program Number:
014-999-07-068-H04
One (1.0) contact hours (0.10 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 54 – Rheumatoid Arthritis
Universal Program Number:
014-999-07-069-H04
One (1.0) contact hours (0.10 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 55 – Osteoarthritis
Universal Program Number:
014-999-07-070-H04
One (1.0) contact hours (0.10 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 56 – Gout and Hyperuricemia
Universal Program Number:
014-999-07-071-H04
Half (0.5) contact hours (0.05 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 57 – Musculoskeletal Disorders
Universal Program Number:
014-999-07-072-H04
One (1.0) contact hours (0.10 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 58 – Glaucoma
Universal Program Number:
014-999-07-073-H04
Two (2.0) contact hours (0.20 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 59 – Allergic Rhinitis
Universal Program Number:
014-999-07-074-H04
One (1.0) contact hours (0.10 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 60 – Minor Ophthalmic Disorders
Universal Program Number:
014-999-07-075-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 61 – Psoriasis
Universal Program Number:
014-999-07-076-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 62 – Common Skin Disorders
Universal Program Number:
014-999-07-077-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 63 – Anemia
Universal Program Number:
014-999-07-078-H04
One (1.0) contact hours (0.10 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 64 – Coagulation Disorders
Universal Program Number:
014-999-07-079-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 65 – Sickle Cell Disease
Universal Program Number:
014-999-07-080-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 66 – Antimicrobial Regimen Selection
Universal Program Number:
014-999-07-081-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 67 – Central Nervous System Infections
Universal Program Number:
014-999-07-082-H04
One (1.0) contact hours (0.10 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 68 – Lower Respiratory Tract Infections
Universal Program Number:
014-999-07-083-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 69 – Upper Respiratory Tract Infections
Universal Program Number:
014-999-07-084-H04
One (1.0) contact hours (0.10 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 70 – Skin and Soft Tissue Infections
Universal Program Number:
014-999-07-085-H04
One (1.0) contact hours (0.10 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 71 – Infective Endocarditis
Universal Program Number:
014-999-07-086-H04
One (1.0) contact hours (0.10 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 72 – Tuberculosis
Universal Program Number:
014-999-07-087-H04
One (1.0) contact hours (0.10 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 73 – Gastrointestinal Infections
Universal Program Number:
014-999-07-088-H04
One (1.0) contact hours (0.10 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 74 – Intraabdominal Infections
Universal Program Number:
014-999-07-089-H04
One (1.0) contact hours (0.10 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 75 – Parasitic Diseases
Universal Program Number:
014-999-07-090-H04
Two (2.0) contact hours (0.20 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 76 – Urinary Tract Infection
Universal Program Number:
014-999-07-091-H04
One (1.0) contact hours (0.10 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 77 – Sexually Transmitted Infections
Universal Program Number:
014-999-07-092-H04
Two and half (2.5) contact hours (0.25 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 78 – Osteomyelitis
Universal Program Number:
014-999-07-093-H04
One (1.0) contact hours (0.10 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 79 – Sepsis and Septic Shock
Universal Program Number:
014-999-07-094-H04
Two (2.0) contact hours (0.20 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 80 – Superficial Fungal Infections
Universal Program Number:
014-999-07-095-H04
One and half (1.5) contact hours (0.15 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 81 – Invasive Fungal Infections
Universal Program Number:
014-999-07-096-H04
Two and half (2.5) contact hours (0.25 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 82 – Antimicrobial Prophylaxis in Surgery
Universal Program Number:
014-999-07-097-H01
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Chap. 84 – Human Immunodeficiency Virus Infection
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Chap. 86 – Breast Cancer
Universal Program Number:
014-999-07-101-H04
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Chap. 87 – Lung Cancer
Universal Program Number:
014-999-07-102-H04
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Chap. 88 – Colorectal Cancer
Universal Program Number:
014-999-07-103-H04
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Chap. 89 – Prostate Cancer
Universal Program Number:
014-999-07-104-H04
One (1.0) contact hours (0.10 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 90 – Malignant Lymphomas
Universal Program Number:
014-999-07-105-H04
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Chap. 91 – Ovarian Cancer
Universal Program Number:
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Chap. 92 – Acute Leukemias
Universal Program Number:
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Chap. 93 – Chronic Leukemias and Multiple Myeloma
Universal Program Number:
014-999-07-108-H04
One (1.0) contact hours (0.10 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 94 – Skin Cancer
Universal Program Number:
014-999-07-109-H04
Two (2.0) contact hours (0.20 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 95 – Hematopoietic Cell Transplantation
Universal Program Number:
014-999-07-110-H04
Two (2.0) contact hours (0.20 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 96 – Oncologic Emergencies
Universal Program Number:
014-999-07-111-H04
Two and half (2.5) contact hours (0.25 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 97 – Parenteral Nutrition
Universal Program Number:
014-999-07-112-H04
Two (2.0) contact hours (0.20 CEUs) will be awarded and statements issued for successful program completion and request for continuing education.

Chap. 98 – Enteral Nutrition
Universal Program Number:
014-999-07-113-H04
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Chap. 99 – Overweight and Obesity
Universal Program Number:
014-999-07-114-H04
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PREFACE

Practitioners who design, implement, monitor, and evaluate medication therapy bear an important responsibility to their patients and society. Development of these abilities requires an integration of knowledge, skills, attitudes, and values that can be acquired only through a structured learning process that includes classroom work, independent study, hands-on practice, and, ultimately, involvement with actual patients.

Pharmacotherapy Principles & Practice is designed to meet the classroom and independent study needs of today's learners in the health professions. Chapters are written or reviewed by pharmacists, nurse practitioners, physician assistants, and physicians who are authorities in their fields and were subjected to rigorous review by experts. The book is written in a concise style that facilitates an in-depth level of understanding of the essential concepts. The disease states covered and the drugs discussed in the text focus on those disorders most often seen in actual practice.

Each chapter reviews etiology, epidemiology, pathophysiology, and disease presentation, followed by clear therapeutic recommendations for drug selection, dosing, and patient monitoring. The learning features used in *Pharmacotherapy Principles & Practice* were designed in collaboration with educational design specialists to enhance learning and retention. These features include:

- *Structured learning objectives.* These are listed at the beginning of each chapter, and information in the text that corresponds to each learning objective is identified by a vertical rule in the margin, which allows the reader to find content related to each objective quickly.
- *Key concepts related to patient assessment and treatment.* Designed to help focus learning, these key concepts are listed at the beginning of each chapter. Textual material that develops these concepts is easily identified by numbered icons throughout the chapter.
- *Patient encounter vignettes.* Distributed throughout each chapter, these case scenarios facilitate critical thinking skills and lend clinical relevance to the scientific foundation provided.
- *Patient care and monitoring guidelines.* This section, placed near the end of each chapter, is designed to assist students in their general approach to assessing, treating, and monitoring patients for therapeutic response and adverse events.
- *Up-to-date literature citations.* A comprehensive reference list for each chapter is provided on the Online Learning Center to substantiate treatment recommendations.
- *Key references and readings.* Placed at the end of each chapter, this list provides a mechanism to acquire a deeper understanding of the subject matter.
- *Generous use of tables, figures, text boxes, and algorithms.* These visual features enhance understanding of pathophysiology, clinical presentation, drug selection, pharmacokinetics, and patient monitoring.
- *Medical abbreviations and their meanings.* Placed at the end of each chapter, these lists facilitate learning the accepted shorthand used in real-world medical practice.
- *Glossary of medical terms.* The glossary is one of the appendices at the end of the book; the first use of each glossary term in a chapter appears in bold font.
- *Self-assessment questions and answers for each chapter.* Located in the Online Learning Center, these questions are designed to evaluate student learning and may be used to obtain approximately 170 hours of continuing education credit for licensed pharmacists, nurse practitioners, physicians, and physician assistants.
- *Laboratory values expressed as both conventional units and Systemè International (SI) units.* Including both units of measurement facilitates use of this book throughout the world.
- *Appendices useful to students and practitioners.* These appendices include: 1) conversion factors and anthropometrics; 2) common laboratory tests and their reference ranges; and 3) common medical abbreviations.

An electronic version of *Pharmacotherapy Principles & Practice* can be downloaded to a desktop or laptop computer using the access number that appears on the card inserted in the middle of this book. The Online Learning Center at www.ChisholmPharmacotherapy.com provides complete reference lists, self-assessment questions, a testing center that has the ability to grade and provide immediate feedback on the self-assessment questions as well as reporting capabilities, and other features designed to support learning.

Pharmacotherapy Principles & Practice is a valuable and unique learning tool that combines state-of-the-art, comprehensive, yet concise chapters, unique learning features, and the Online Learning Center.

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We would like to acknowledge the commitment and dedication of the 161 contributing authors and 145 reviewers of the chapters contained in this text (a list of contributors and a list of reviewers are included in the frontmatter of this book). We also extend our thanks to the McGraw-Hill Medical Publishing Division, especially Michael Brown, Maya Barahona, and Robert Pancotti, for their dedication to this project. Finally, we thank our families for their patience and support of this work and of our goal to improve patient care by enhancing learning of pharmacotherapeutics across the health professions.

The Editors
July 2007

Part One

Basic Concepts of Pharmacotherapy Principles and Practice

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1 Introduction

Jack E. Fincham

The prescribing of a drug is the most common outcome of a patient visit to a physician; 60% of physician visits result in a prescription or injection for patients. It is incumbent on health professionals to ensure that this process of receiving and taking medications benefits and does not harm patients. Clinicians are often called upon to identify, resolve, and prevent problems that occur due to undertreatment, overtreatment, or inappropriate treatment. Problems occurring with the use of drugs can include:

- Suboptimal drug, dose, regimen, dosage form, and duration of use;
- Unnecessary drug therapy;
- Therapeutic duplication;
- Drug-drug, drug-disease, drug-food, or drug-nutrient interactions;
- Drug allergies; or
- Adverse drug effects, some of which are preventable.

The readers of this book can help to reverse these problems, improve outcomes of care both clinically and economically, and enable drug use to meet stated goals and objectives. This text provides a thorough analysis and summary of treatment options for commonly occurring diseases and the medications or alternative therapies used to successfully treat these conditions.

The use of drugs as a form of medical treatment in the United States is an enormously complex process. Individuals can purchase medications through numerous outlets. Over-the-counter (OTC) medications can be purchased in pharmacies, grocery stores, supermarkets, convenience stores, via the Internet, and through any number of additional outlets. OTCs are widely used by all age groups. Prescriptions can be purchased through traditional channels (community chain and independent pharmacies), from mail order pharmacies, through the Internet, from physicians, from health care institutions, and elsewhere. Herbal remedies are marketed and sold in numerous outlets. The monitoring of the positive and negative outcomes of the use of these drugs, both prescription and OTC, can be disjointed and incomplete. Clinicians and health professions students need to take ownership of these problems and improve patient outcomes resulting from drug use.

It is important to realize that although clinicians are the gatekeepers for patients to obtain prescription drugs, patients can obtain prescription medications from numerous sources. Patients may also borrow from friends, relatives, or even casual acquaintances. In addition, patients obtain OTC medications from physicians through prescriptions, on advice from pharmacists and other health professionals, through self-selection, or through the recommendations of friends or acquaintances. Through all of this, it must be recognized that there are both formal (structural) and informal (word of mouth) components at play. Health professionals may or may not be consulted regarding the use of medications, and in some cases are unaware of the drugs patients are taking. In addition, herbal remedies or health supplements may be taken without the knowledge or input of a health professional.

External variables may greatly influence patients and their drug-taking behaviors. Coverage for prescribed drugs allows those with coverage to obtain medications with varying cost sharing requirements. However, many do not have insurance coverage for drugs or other health-related needs. With the advent of Medicare coverage for prescription medications, more of the elderly will have access to needed therapy—more than ever before.[1]

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SELF-MEDICATION

Self-medication can be broadly defined as a decision made by a patient to consume a drug with or without the approval or direction of a health professional. The self-medication activities of patients have increased dramatically in the late twentieth and early twenty-first centuries. Many factors affecting patients have continued to fuel this increase in self-medication. There are ever increasing ways to purchase OTC medications. There have been many prescription items switched to OTC classification in the last 50 years. In addition, patients are increasingly becoming comfortable with self-diagnosing and self-selection of OTC remedies. The number of switched products is dramatically and significantly fueling the rapid expansion of OTC drug usage. Dean[2] noted in the past that in many studies, self-medication with nonprescribed therapies exceeds the use of prescription medications.

Patients' use of self-selected products has the potential to bring enormous benefits to patients, as well as others.[3] Through the rational use of drugs, patients may avoid more costly therapies or expenditures for other professional services. Self-limiting conditions and even some chronic health conditions (e.g., allergies and dermatologic conditions), if appropriately treated through patient self-medication, allow the patient to have a degree of autonomy in health care decisions. This book provides a thorough analysis of common disease states, discussion of therapies to treat these conditions, and specific advice to provide to patients to help them self-medicate when appropriate and safe to do so.

COMPLIANCE WITH MEDICATION REGIMENS

Both self-medication and patient compliance behaviors are exceedingly complex. McDonald and colleagues[4] point out that patient interventions to impact compliance are complex, labor intensive, and not particularly effective. McDonald and colleagues[4] further suggest that more convenient care, reminders, self-monitoring by patients, reinforcement, family therapy, and additional attention may need to be in play for compliance to improve. Meredith[5] notes that a focus on the individual, rather than a general approach, is more likely to be successful. Haynes and colleagues[6] call for better approaches to enhance compliance that are more efficient and more effective.

For the most part, with regard to compliance-enhancing strategies, the more things that can be done the better the chances of success. Enhancing compliance is more art than science, and more trial and error than precisely delineated. Success may be frustratingly difficult to achieve, but enhanced and suitable patient compliance should be the ultimate goal of the prescribing, dispensing, and therapeutic monitoring process. Clinicians can have no more rewarding, yet vexing, opportunity than trying and succeeding in helping patients comply with medication regimens and achieve treatment goals.

Compliance Issues

Patient noncompliance with prescription regimens is one of the most understated problems in the health care system. The effects of noncompliance have enormous ramifications for patients, caregivers, and health professionals. Compliance with medications is a worldwide problem, and measures that are effective in one country may not have work elsewhere.

In the recently released book on worldwide compliance issues (*Adherence to Long-term Therapies, Evidence for Action*),[7] published by the World Health Organization, researchers indicate that the problem of noncompliance is worse in countries in the developing world than in countries in the industrialized world. Many parts of the United States have similar morbidity and mortality rates as countries in the Third World.[8] Specific disease states may have significant additional noncompliance ramifications due to the development of drug-resistant strains of bacteria.[9] Many times what is necessary is referral to specific clinicians for individualized treatment and monitoring to enhance compliance. The case histories provided in this text will allow you to follow what others have done in similar situations to optimally help patients succeed in improving compliance rates and subsequent positive health outcomes.

DRUG COSTS

Spending for prescription drugs in the United States has skyrocketed in the recent past. Between 1990 and 2003, the amount spent on prescription drugs in the United States quadrupled, far outstripping the increase in cost of other commodities in the United States health care system.[10] This large increase in spending has stressed financing of the health care system. Americans pay the highest prices for prescription drugs in the world.[11] United States prices are 72% higher than those in Canada, and 102% higher than those in Mexico.[11] An increase of 25% in the percentage of expenditures for prescription drugs as a percentage of all health care costs has occurred over the past 5 years.

Numerous types of marketing have impacted the usage of prescription drugs, and marketing has come under increasing scrutiny as one reason for the use of costly alternatives rather than less expensive therapies that might be equally efficacious. More and more of these types of comparisons are appearing in the lay press (magazines and newspapers). A good share of the success of the pharmaceutical industry is due to lobbying efforts, which have been substantive and effective. Knowledgeable clinicians can counter the misleading marketing that sometimes occurs, and in doing so provide a significant service that improves the prescribing and drug use process.

DRUG USE BY THE ELDERLY

Various components of drug use in the elderly are worth noting. Problems with health literacy (i.e., the understanding of medical

terminology and directions from providers) are more common among the elderly.[12] The burgeoning population of the elderly coupled with their lack of health literacy means that this issue will become even more problematic in the future.[12]

Over the next decade, seniors will spend $1.8 trillion on prescription medications. Medicare proposals to provide a drug benefit for seniors have been suggested to cost $400 billion over a 10-year period. Thus, the most elaborate of the current drug programs will pay only 22% of seniors' drug costs. Enhanced use of pharmacoeconomic tenets to select appropriate therapy while considering cost and therapeutic benefits for seniors and others will become even more crucial for clinicians in the future.

IMPACTING THE PROBLEMS OF DRUG USE

Medication Errors

Brass,[13] commenting on the change from prescription to over-the-counter status of many medications, notes increasing problems with polypharmacy. This is no surprise to anyone considering the several classes of drugs that can cause problems. These problem drugs include analgesics, sleep preparations, pseudoephedrine, caffeine, cough and cold preparations, and laxatives. The problems with these drugs have been also noted in studies elsewhere.[14] Inaccurate self-diagnosis leads to suboptimal therapy, high patient cost, and more adverse effects and/or drug interactions.[13]

Elsewhere, it was found that errors by physicians and others is often not reported to patients, and surprisingly, 23% of physicians and 11% of patients in one study did not feel that physicians should report such errors to patients.[15] Clinicians in the future will be expected to interact more, and more effectively, with patients. These expectations for improved interaction with patients will help both clinicians and patients to reach their therapeutic goals. The authors of the chapters in this text have worked through patient care problems that are commonly seen in practice, and the reader will benefit by using similar tactics to help their patients.

Health Literacy and Indigent Care

The negative influence of health illiteracy on all affected patients has tangible outcomes, namely higher rates of hospitalization with lower rates of health literacy.[16] Much of the elaborate technology used by the United States health care system is not accessible to the uninsured. It is estimated that $1.1 billion per year in additional expenditures are needed to deal with undertreatment of myocardial infarction, cataracts, and depression.[17] As governmental programs expand to provide drug coverage for more seniors in Medicare Part D, and for patients shifted from drug coverage under Medicaid to Medicare coverage, the impacts of health illiteracy and the need for clinicians to provide interventions that will enhance drug use will dramatically increase.

Health professionals are at a crucial juncture as we face an uncertain, yet promising future. Technological advances, including electronic prescribing, may stem the tide of medication errors and inappropriate prescribing. Pilot studies have implemented these technological enhancements for physician order entry (via personal data assistants or through web access to pharmacies) in order to reduce drug errors. The skills and knowledge that enable effective pharmacotherapy practice have never been more daunting among the numerous health professions. Sophisticated computer technology can further empower health professionals to play an ever increasing and effective role in helping patients and fellow health professionals to practice safe and effective medicine.

This book, which incorporates materials written by some of the finest minds in pharmacy practice and education, can enable the reader to play a crucial role in improving the drug use process for patients, providers, payers, and society. The purpose of this book is to help hone your skills so you can make a real improvement in the therapies you provide to your patients. Current and future clinicians can rely on the information laid out here to enhance your knowledge and allow you to assist your patients with the sound advice that they expect you to provide. Use the text, case histories, and numerous examples detailed here to expand your therapeutic skills, and to help positively impact your patients in the years to come.

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Part Two

Disorders of Organ Systems

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2 Hypertension

Robert J. Straka, R. Todd Burkhardt, and David Parra



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Classify blood pressure levels and treatment goals.
2. Recognize the underlying causes and contributing factors in the development of hypertension.
3. Describe the appropriate measurement of blood pressure.
4. Recommend appropriate lifestyle modifications and pharmacotherapy for patients with hypertension.
5. Identify populations requiring special consideration when designing a treatment plan.
6. Construct an appropriate monitoring plan to assess hypertension treatment.

Key Concepts

❶ Hypertension is widely prevalent and accounts for significant morbidity and mortality, as well as billions of dollars in direct and indirect costs.

❷ The cause of hypertension is unknown in the majority of cases (primary hypertension), but for those with secondary hypertension, specific causes are indicated.

❸ Patients failing to achieve goal blood pressure despite maximum doses of three antihypertensives including a diuretic should be carefully screened for resistant hypertension.

❹ The pathophysiology of primary hypertension is heterogeneous, but ultimately exerts its effects through the two primary determinants of blood pressure: cardiac output and peripheral resistance.

❺ Appropriate technique in measuring blood pressure is a vital component to the diagnosis and continued management of hypertension in the outpatient setting.

❻ Drug selection for the management of patients with hypertension should be considered as adjunctive to nonpharmacologic approaches for blood pressure lowering, and ultimately the attainment of target blood pressure in many cases may be more important than the antihypertensive agent used.

❼ Implementation of lifestyle modifications successfully lowers blood pressure, often with results similar to those of therapy with a single antihypertensive agent.

❽ An approach to selection of drugs for the treatment of patients with hypertension should be evidence-based with considerations regarding the individual's co-existing disease states, co-prescribed medications, and practical patient-specific issues including costs.

❾ While the main goal of antihypertensive therapy is to achieve target blood pressures, the selection of agents for an individual should also account for certain special considerations and a patient's comorbidities. Specific antihypertensive therapy is warranted for certain patients with comorbid conditions that may elevate their level of risk for cardiovascular disease.

❿ The frequency of follow-up visits for patients with hypertension will vary based on individual cases, but will be influenced by severity of hypertension, comorbidities, and choice of agent selected.

National and international trends over the past 15 years depict modest improvements in the treatment and/or control of blood pressure (BP) for hypertensive patients. This observation is made despite efforts to promote awareness, treatment, and the means available to aggressively manage high blood pressure. Over 65 million Americans have hypertension, which was listed as the primary cause of death for over 261,000 individuals in the United States in 2002.[1] Hypertension is also a significant cause of end-stage renal disease and heart failure. National and international organizations continually refine their recommendations of how

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clinicians should approach the management of patients with high blood pressure, including methods of measurement, patient education, medication adherence, and overall benefits of reduced blood pressure. Although approaches vary to some degree, there are clear themes that emerge regardless of which national or international organization's algorithm is followed. The purpose of this chapter is to provide a summary of key issues associated with the management of patients with hypertension. We will discuss the basic approach to treating patients with hypertension and provide a functional summary of the currently prevailing themes of national guidelines, including their grounding in relevant landmark trials. Finally, we will summarize salient pharmacotherapeutic issues essential for clinicians to consider when managing patients with hypertension.

Various algorithms recommending nonpharmacologic and pharmacologic management for typical and atypical patients are proposed, with the underlying theme that achievement of blood pressure targets mitigate end-organ damage, leading to substantial reductions in stroke, myocardial infarction, and heart failure. Although references to other algorithms will be mentioned, this chapter will focus primarily on the *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure,* more commonly referred to as the JNC 7 report.[2]

The JNC 7 report describes four stages of blood pressure classification and provides guidance on nonpharmacologic and pharmacologic approaches to managing patients with hypertension. The four stages of blood pressure classification include normal, prehypertension, stage 1 hypertension, and stage 2 hypertension (Table 2–1). These stages are defined as such to connote a level of risk and thus the need for varying intensities of intervention with drug therapy (Fig. 2–1). With the exception of individuals with "compelling indications," recommendations for drug therapy typically begin with one or two (in the case of stage 2) antihypertensive drugs as an initial step. Specific drug selection is guided by the presence of compelling indications—specific comorbid conditions. These compelling indications, such as heart failure, diabetes, and chronic kidney disease (CKD), represent specific conditions for which explicit evidence in the literature exists to document the utility of a particular agent or class of agents. Selection of drug therapy consequently involves an iterative process of considering multiple antihypertensive drugs as needed to achieve target blood pressures of less than 140/90 mm Hg for all patients, with more aggressive targets of less than 130/80 mm Hg for patients with diabetes or chronic kidney disease.[3] Treatment with drug therapy should be done in combination with recommended lifestyle modifications to manage hypertension and minimize risk.

EPIDEMIOLOGY

❶ *Hypertension is widely prevalent and accounts for significant morbidity and mortality, as well as billions of dollars in direct and indirect costs.* Worldwide prevalence of hypertension is estimated to include 1 billion individuals. There are an estimated 7 million deaths per year that may be related to the diagnosis of hypertension.[4] The prevalence of hypertension in the United States is estimated to include 65 million individuals and accounts for an estimated 59.7 billion dollars annually in direct and indirect costs.[1]

The prevalence of hypertension differs based on age, sex, and ethnicity. As individuals become older, their risk of high blood pressure increases. Individuals 55 years of age who do not have hypertension are estimated to have a lifetime risk of 90% of eventually developing hypertension. The National Health and Nutrition Examination Survey from 1999 to 2000 indicated that hypertension is slightly more prevalent in men (30.1%) than women (27.1%). However, the prevalence increased by 5.6% in women and has remained unchanged in men from 1988 to 2000.[5] Hypertension prevalence is highest in African-Americans when compared to non-Hispanic whites and Mexican-Americans.[1]

Hypertension is strongly associated with type 2 diabetes.[6] The added comorbidity of hypertension in diabetes leads to a higher risk of cardiovascular disease (CVD), stroke, renal disease, and diabetic retinopathy leading to greater health care costs.[7]

TABLE 2–1. Classification of Blood Pressure (BP) in Children, Adolescents, and Adults Defined as 18 Years Old or Greater[2,70]

BP Classification	Adult SBP (mm Hg)	Adult DBP (mm Hg)	Children/Adolescents SBP or DBP Percentile[a]
Normal	Less than 120	and less than 80	Less than 90th
Prehypertension	120–139	or 80–89	90–95th or 120/80 mm Hg
Stage 1 hypertension	140–159	or 90–99	95–99th + 5 mm Hg[b]
Stage 2 hypertension	Greater than or equal to 160	Greater than or equal to 100	Greater than 99th + 5 mm Hg[c]

[a]Tables contain the 50th, 90th, and 99th percentiles of systolic blood pressure (SBP) and diastolic blood pressure (DBP) standards based on percentile height by age and sex, which is used to compare the child's measured blood pressure on three separate occasions. The difference in blood pressure of the 95th and 99th percentiles are 7–10 mm Hg which requires an adjustment of 5 mm Hg to accurately categorize stage 1 or 2 hypertension. If the systolic and diastolic percentile categories are different, then classify hypertension by the higher blood pressure value.
[b]Children and adolescents' stage 1 hypertension is classified by blood pressure levels that range from the 95th percentile to 5 mm Hg above the 99th percentile.
[c]Children and adolescents' stage 2 hypertension is classified by blood pressure levels that are greater than 5 mm Hg above the 99th percentile.

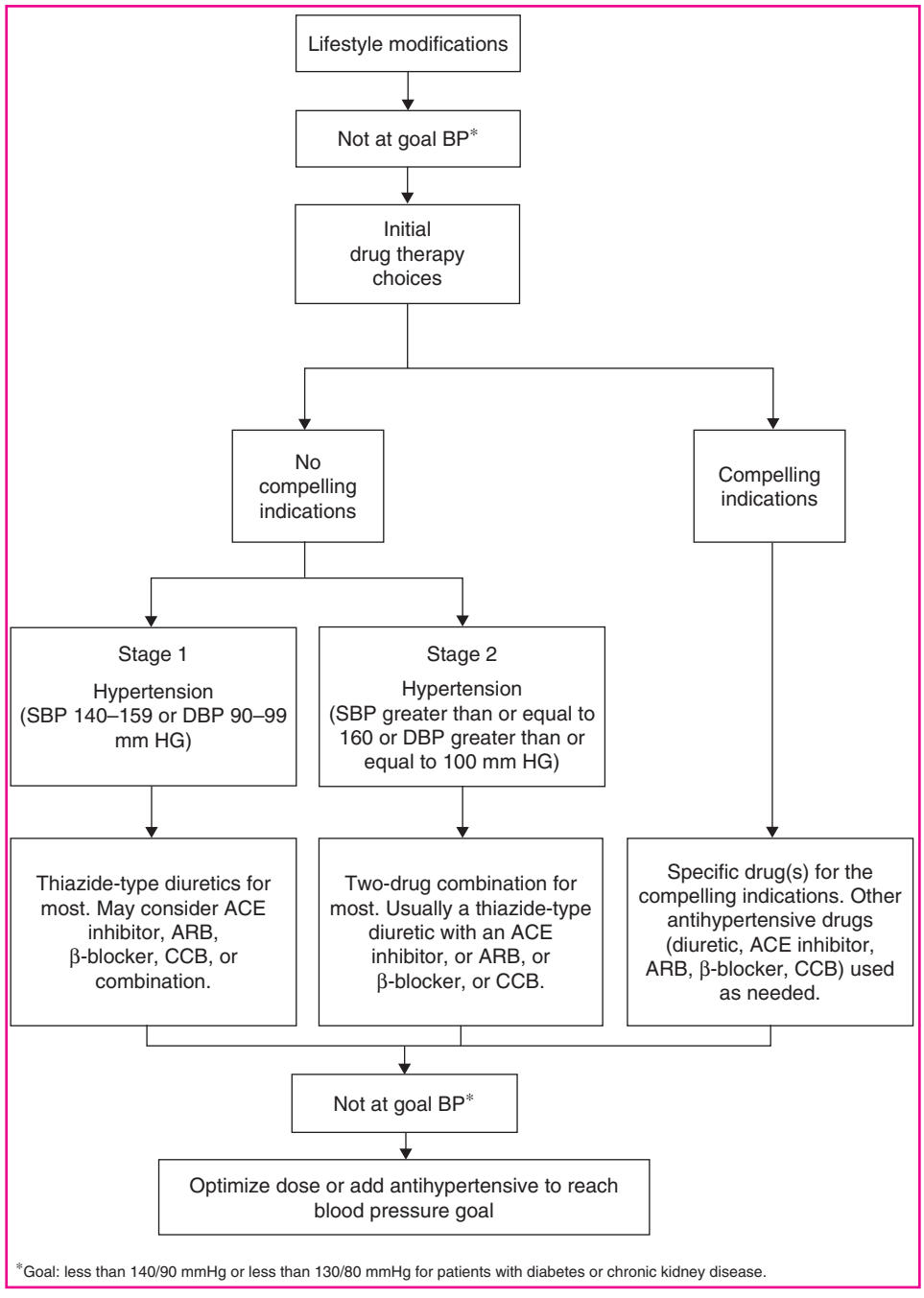


FIGURE 2–1. Algorithm for treatment of hypertension when patients are not at their goal blood pressure. Compelling indications refer to specific indications where the selection of a particular antihypertensive drug class for a defined high-risk population is highly recommended. These recommendations are usually based on results from landmark randomized placebo-controlled outcome trials or consensus statements from clinical guidelines and are usually based on findings documenting superior outcomes in terms of morbidity and mortality. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker agent; DBP, diastolic blood pressure; SBP, systolic blood pressure. (Adapted from JNC 7; Modified from Saseen JJ, Carter BL. Hypertension. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 194, with permission.)

ETIOLOGY

❷ *In the majority of patients, up to 95%, the cause of hypertension is unknown and it is referred to as essential, or more appropriately, as primary hypertension.*[8] *However, in some patients there is an identifiable cause of which the most common are:*[2]

- *Chronic kidney disease*
- *Coarctation of the aorta*
- *Cushing's syndrome and other glucocorticoid excess states*
- *Drug induced/related (Table 2–2)*
- *Pheochromocytoma*
- *Primary aldosteronism and other mineralocorticoid excess states*
- *Renovascular hypertension*
- *Sleep apnea*
- *Thyroid or parathyroid disease*

Hypertension caused by any of these conditions is referred to as secondary hypertension. Identification of a secondary cause of hypertension is often not initially pursued unless suggested by routine clinical and laboratory evaluation of the patient, or failure to achieve blood pressure control.

TABLE 2–2. Causes of Resistant Hypertension[2]

Improper blood pressure measurement
Volume overload
• Excess sodium intake
• Volume retention from kidney disease
• Inadequate diuretic therapy
Ineffective cardiac pump function
• Diastolic dysfunction
Drug-induced
• Non-steroidal anti-inflammatory drugs; cyclooxygenase 2 inhibitors
• Cocaine, amphetamines, and other illicit drugs
• Sympathomimetics (decongestants, anorectics, and stimulants)
• Oral contraceptive hormones
• Adrenal steroid hormones
• Cyclosporine and tacrolimus
• Erythropoietin
• Licorice (including some chewing tobacco)
• Select over-the-counter dietary supplements and non-traditional medicines (e.g., ephedra, ma huang, and bitter orange)
Therapeutic circumstances
• Failure to receive or take antihypertensive medications
• Inadequate doses (sub-therapeutic)
• Improper antihypertensive selection or combination
• Drug-drug or drug-food interactions
Associated conditions
• Obesity
• Excess alcohol intake

In addition to primary and secondary hypertension, the clinician may encounter what is referred to as resistant hypertension. ❸ *Patients failing to achieve goal blood pressure despite maximum doses of three antihypertensives including a diuretic should be carefully screened for resistant hypertension.* Several causes of resistant hypertension are listed in Table 2–2 and should be carefully considered in such patients.

PATHOPHYSIOLOGY

❹ *The pathophysiology of primary hypertension is heterogeneous, but ultimately exerts its effects through the two primary determinants of blood pressure:* ***cardiac output*** *and* ***peripheral resistance.*** The processes influencing these two determinants are numerous and complex (Fig. 2–2).[9] The underlying cause of primary hypertension is unknown and most likely multifactorial. Although several hypotheses exist, we will limit our discussion to a few while recognizing that only a minority of patients with hypertension may have an identifiable cause. For a detailed discussion of the pathophysiology behind these secondary causes, the reader is referred to additional texts.[10,11] Discussion of the management of patients with select secondary causes are found elsewhere in this chapter.

Genetics

Multiple genetic polymorphisms have been associated with hypertension. It is estimated that up to 30% to 50% of variability in blood pressure may have a genetic basis.[12] The majority of these polymorphisms appear to be involved directly or indirectly in renal sodium reabsorption, which may represent future therapeutic drug targets.[13] In addition, the identification of genetic factors contributing to variability in response to drug therapy should allow for specific tailoring of individual patient therapy, thereby optimizing the effectiveness of antihypertensive therapy while minimizing costs and adverse events.

Cardiac Output

Cardiac output is an important determinant of blood pressure. Factors which elevate cardiac output may, in theory, contribute to the development of primary hypertension. Increases in cardiac output and subsequent blood pressure may arise from factors that increase preload (fluid volume) or contractility

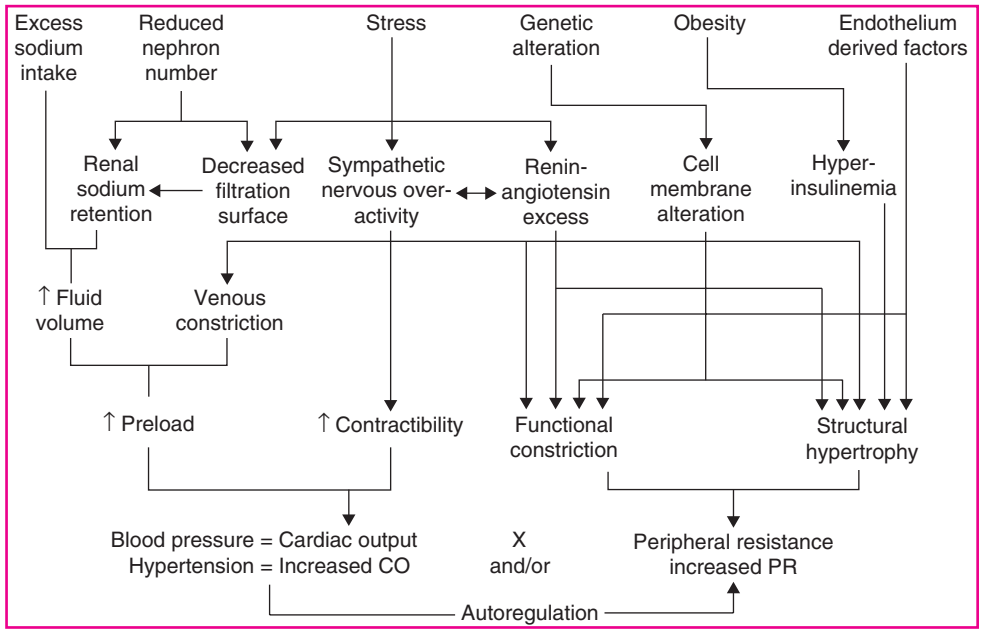


FIGURE 2–2. Factors which are involved in the pathogenesis of hypertension are summarized. Some of the factors involved in the control of blood pressure affect the basic equation: blood pressure = cardiac output × peripheral resistance. The figure depicts the complex nature of various factors which may play a role in the development of hypertension. Each of these factors may individually or collectively modulate blood pressure through their actions upon various physiologic systems at the cellular, organ, and organ system level. CO, cardiac output; PR, peripheral resistance. (From Kaplan NM. Primary hypertension: Pathogenesis. In: Kaplan's Clinical Hypertension. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2002: 63, with permission.)

of the heart. Nonetheless, even if increased cardiac output may be involved in the development of primary hypertension, these increases do not appear to persist over time. As a consequence, elevated cardiac output is not considered a hemodynamic hallmark of established primary hypertension.

Sodium Regulation

The contribution of sodium to the development of primary hypertension is related to excess sodium intake and/or abnormal sodium excretion by the kidneys. It is generally accepted that dietary salt is associated with increases in blood pressure that can be lowered with reduction of sodium intake.[2,14] There appears to be a threshold effect of sodium intake in the range of 50 to 100 mmol/day [1.2 to 2.4 grams of sodium per day is equivalent to 3 to 6 grams of sodium chloride per day (50 to 100 mmol/day)] and its impact on blood pressure. The mean sodium intake per day is 175 mmol (4.1 grams) for men and 120 mmol (2.7 grams) for women in the United States, with the majority derived from processed foods.[2] However, not all individuals appear to be susceptible to a high sodium intake, with about 50% of hypertensive patients being classified as sodium-sensitive. The proposed mechanisms behind high sodium intake and blood pressure include increases in intracellular calcium, insulin resistance, paradoxical rise in **atrial natriuretic peptide,** and other pressor effects.[9] Proposed mechanisms behind salt sensitivity include a defect in renal sodium excretion and an increased rate of proximal sodium reabsorption, among others.[9]

In addition to excess sodium intake, abnormal renal sodium retention may be the primary event in the development of hypertension, and it includes abnormalities in the pressure-natriuresis mechanism. In hypertensive individuals, this theory proposes a shift in the control mechanism preventing the normalization of blood pressure. The mechanisms behind the resetting of the pressure-natriuresis curve may include afferent arteriolar vasoconstriction, decreased glomerular ultrafiltration, or an increase in tubular sodium reabsorption.[4] Other theories supporting abnormal renal sodium retention suggest a congenital reduction in the number of nephrons, enhanced renin secretion from nephrons that are ischemic, or an acquired compensatory mechanism for renal sodium retention.[9]

Given that the majority of patients with hypertension have no recognizable etiology for their elevated blood pressure, it is important to understand systems involved in blood pressure regulation as a means to employ drug therapy to affect these systems. One such system which is central to the understanding of hypertension and drug therapies is the renin-angiotensin-aldosterone system (RAAS).

Renin-Angiotensin-Aldosterone System

Since the discovery of renin over 100 years ago, the RAAS has been extensively studied as a prime target or site of action for many effective antihypertensives.[15] Renin is produced and stored in the juxtaglomerular cells of the kidney, and its release is stimulated by impaired renal perfusion, salt depletion, and β_1-adrenergic stimulation. The release of renin is the rate-limiting step in the eventual formation of angiotensin II, which is primarily responsible for the pressor effects mediated by the RAAS (Fig. 2–3). Evidence indicates that renin's pressor effects occur at the cellular level (autocrine), the local environment (paracrine), and throughout the systemic circulation (endocrine).[16] The role of the RAAS in primary hypertension is supported by the presence of high levels of renin, suggesting that the system is inappropriately activated. Proposed mechanisms behind this inappropriate activation include increased sympathetic drive, defective regulation of the RAAS (non-modulation), and the existence of a sub-population of ischemic nephrons which release excess renin.[9] However, there are also patients with primary hypertension and low levels of renin. This observation suggests that alternate mechanisms for hypertension unrelated to renin levels or activity may be in play.[17]

Sympathetic Overactivity

Overactivation of the sympathetic nervous system (SNS) may also play a role in the development and maintenance of primary hypertension for some individuals. Among other effects, direct activation of the SNS may lead to enhanced sodium retention, insulin resistance, and baroreceptor dysfunction.[9] Regardless of which mechanism(s) underlie the role the SNS may play in the development of primary hypertension, the SNS remains a target of many antihypertensive agents.

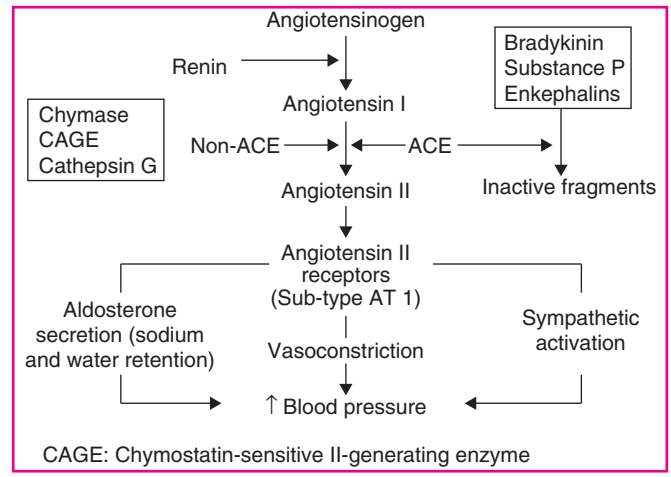


FIGURE 2–3. Diagram of the renin-angiotensin-aldosterone system. The renin-angiotensin-aldosterone system is a key system involved in the modulation of blood pressure. The diagram depicts the pathways involved in the action of various antihypertensives including ACE inhibitors, ARBs, diuretics, and aldosterone antagonists. By inhibiting the action of angiotensin-converting enzyme, ACE inhibitors reduce both the formation of the vasoconstrictor angiotensin II, and the degradation of vasodilating substances including bradykinin. ARBs primarily act through inhibition of the action of angiotensin II on the angiotensin-1 receptors which modulate vasoconstriction. Aldosterone antagonists directly inhibit the actions of aldosterone while diuretics affect sodium and water retention at a renal level. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; AT1, angiotensin-1.

Peripheral Resistance

Elevated peripheral arterial resistance is a hallmark of primary hypertension. The increase in peripheral resistance typically observed may be due to a reduction in the arterial lumen size as a result of vascular remodeling. This remodeling, or change in vascular tone, may be modulated by various endothelium-derived vasoactive substances, growth factors, and cytokines. This increase in arterial stiffness or reduced compliance results in the observed increase in systolic blood pressure.[9]

Other Contributing Processes and Factors

Obesity appears to promote the development of primary hypertension via activation of the SNS and the RAAS and is well-recognized as a global risk factor for CVD. Given the rapid increase in the prevalence of obesity worldwide and its association with insulin resistance, diabetes, and dyslipidemia, weight loss should be a prime target of interventions aimed at reducing overall cardiovascular risk.

Many other processes are proposed to contribute to the development of hypertension, including physical inactivity, insulin resistance, potassium and magnesium depletion, chronic moderate alcohol consumption, and transient effects of cigarette smoking and caffeine intake.[9] Ultimately, the management of global cardiovascular risk suggests addressing each one of these factors where relevant in all patients while pursuing target blood pressures through nonpharmacologic and pharmacologic means.

CLINICAL PRESENTATION AND CO-EXISTING RISK FACTORS



Presentation of Primary (Essential) Hypertension

General

Age: prevalence of hypertension is likely to be highest with middle-age or older patients.
Sex: men have a higher prevalence of hypertension than women until age 55.

Symptoms The primary hypertension patient may be asymptomatic or may have major cardiovascular disease risk factors.

Signs Adult patients with an average of two or more previous blood pressure readings (systolic, SBP; diastolic, DBP) indicating either:

	SPB (mm Hg)	DBP (mm Hg)
Normal	Less than 120	or less than 80
Pre-hypertension	120–139	or 80–89
Stage 1 hypertension	140–159	or 90–99
Stage 2 hypertension	Greater than or equal to 160	or greater than or equal to 100

Laboratory Tests (Not necessarily indicative of hypertension, but may be seen in hypertensive patients)
Fasting lipid panel
- Low-density lipoprotein greater than 160 mg/dL (4.14 mmol/L)
- Total cholesterol greater than 240 mg/dL (6.22 mmol/L)
- High-density lipoprotein less than 40 mg/dL (1.04 mmol/L)
- Triglycerides greater than 200 mg/dL (2.26 mmol/L)

Fasting blood serum or plasma glucose
- Impaired fasting glucose of 100–125 mg/dL (5.55–6.94 mmol/L)
- Diagnose diabetes with glucose greater than or equal to 126 mg/dL (7 mmol/L)

Abnormal test may indicate hypertension-related damage.
- Serum creatinine elevated (greater than 1.2 mg/dL [106 µmol/L])
- **Microalbuminuria** (protein in urine which is excreted at a rate of 30–300 mg per 24 hours or 20–200 mcg/minute)

Presentation of Hypertension and Co-existing Risk Factors in a Diabetic Patient

General (Not necessarily indicative of hypertension, but may be seen in hypertensive patients)
Hypertension is a common comorbidity in diabetics.
Insulin resistance (metabolic syndrome)
Dyslipidemia
Microalbuminuria
Family history
Central obesity
Physical inactivity
Tobacco use

Symptoms Many patients who are hypertensive also have diabetes. The diabetic patient may be asymptomatic or may have ischemic heart disease.

Signs Patient has previous blood pressure measurements indicating SBP greater than 130 or DBP greater than 80 mm Hg in clinic, or is currently taking antihypertensive medication(s).

Laboratory Tests The following tests may indicate additional cardiovascular risk factors or poor control of diabetes.
- Elevated fasting lipid panel
- Elevated fasting blood glucose
- Hemoglobin A_{1c} greater than 7.0%

Abnormal test may indicate hypertension related to kidney damage
- Elevated blood urea nitrogen
- Elevated serum creatinine
- Microalbuminuria/proteinuria

Target Organ Damage
Eyes (retinopathy)
Heart (angina, coronary artery disease, myocardial infarction, or heart failure)
Kidney (chronic kidney disease)
Brain (transient ischemic attack, stroke)

Regardless of the initiating process or processes leading to the development of hypertension, the ultimate goal is to reduce the risk of cardiovascular events and minimize target organ damage. This clearly requires the early identification of risk factors and treatment of patients with hypertension.

❺ *Appropriate technique in measuring blood pressure is a vital component to the diagnosis and continued management of hypertension in the outpatient setting.* Accurate measurement of a patient's blood pressure identifies and controls for factors that may influence the variability in the measure. Failure to consider how each of these factors may influence blood pressure measurement results in significant variation in measurements, leading to misclassification or inaccurate assessments of risk. Factors including body position, cuff size, device selection, auscultatory technique, and dietary intake prior to the clinic visit may contribute to such inaccuracies. Clinicians should instruct patients to avoid exercise, alcohol, caffeine, or nicotine consumption 30 minutes before blood pressure measurement. Patients should be sitting comfortably with their back supported and arm free of constrictive clothing with legs uncrossed for a minimum of 5 minutes before the first reading. In addition to these important positions, patients should have their feet uncrossed and flat on the floor.

The selection of blood pressure cuff size based on a patient's arm circumference is crucial for the accurate measurement of blood pressure. Systolic and diastolic blood pressure tend to increase when the cuff size is too small relative to the patient's arm circumference. This circumstance is important due to the increasing prevalence of obesity in developed nations. Currently, the guidelines of the American College of Cardiology/American Heart Association (ACC/AHA) Blood Pressure Measurement in Humans recommends cuff sizes for small, standard, and large adults with an optimal 2:1 ratio of cuff length/width based on arm circumference.[18]

Mercury sphygmomanometers are recommended for routine office measurements, but concerns of patient exposure and environmental contamination of mercury has fostered the development of other devices to measure blood pressure. However, there is no general concensus among health care providers as to an acceptable replacement for mercury sphygmomanometers.

To reduce deviations in blood pressure measurement in the clinic, the patient and clinician should not talk during blood pressure readings. The measurement arm is supported and positioned at heart level with the blood pressure cuff encircling at least 80% of arm circumference. If a mercury or aneroid device is used, then the palpatory method must be used first to estimate the systolic blood pressure.[18] If an automated device is used, this is not necessary. After the patient's cuff is inflated above the systolic pressure, the mercury column should drop at a rate of 2 to 3 mm per second. A stethoscope placed over the brachial artery in the antecubital fossa identifies the first and last audible **Korotkoff sounds,** which should be taken as systolic and diastolic pressure, respectively. A minimum of two readings at least 1 minute apart are then averaged. If measurements vary by more than 5 mm Hg between the two readings, then one or two additional blood pressure measurements are collected and the multiple readings averaged. Details and further recommendations for accurate measurement of blood pressure in special populations can be reviewed in the ACC/AHA Blood Pressure Measurement in Humans statement for health care professionals.[18]

Finally, the measurement of clinic or office blood pressures is poorly correlated with assessments of blood pressure in other settings. Because of this, the use of a 24-hour ambulatory blood pressure monitoring device has become more common. The device can be useful in identifying patients with **white coat hypertension** or with elevations of blood pressure during the nighttime (non-dippers). Its use has also aided in the management of refractory hypertensives with minor target organ damage, those with suspected autonomic neuropathy, and patients with large differences between home and clinic blood pressure measurements. The prognostic significance of an average level with ambulatory blood pressure monitoring may be that this measure is better at predicting cardiovascular risk than clinic blood pressure.

TREATMENT

Desired Outcomes

Hypertension management by nonpharmacologic and pharmacologic therapies has proven useful in reducing the risk of heart attack, heart failure, stroke, and kidney disease morbidity and mortality. For every 20 mm Hg systolic or 10 mm Hg diastolic increase in blood pressure, there is a doubling of mortality for both ischemic heart disease and stroke.[19] The goal of blood pressure management is to reduce the risk of cardiovascular disease and target organ damage.

General Approach to Treatment

❻ *As is the case with dyslipidemia and other cardiovascular conditions, drug selection for the management of patients with hypertension should be considered as adjunctive to nonpharmacologic approaches for blood pressure lowering. Previous clinical research has established the relative value of using individual antihypertensive drugs versus placebo to achieve reduction in morbidity and mortality by lowering blood pressure. However, as newer antihypertensive agents are developed by pharmaceutical companies, it is difficult to ethically justify the comparison of newer agents to placebo. Consequently, there have been attempts to conduct large outcome-based, multi-center trials comparing one specific agent versus another antihypertensive pharmacologic agent. These "head-to-head" comparisons and meta-analyses of multidrug regimen trials have provided convincing evidence supporting the position that the overall importance of which drug to initiate therapy with is less important than the achievement of targeted blood pressure goals.* Inherent in this position is the

realization that nonpharmacologic approaches alone are rarely successful in attaining target blood pressures, and multidrug therapy (sometimes as many as three or more agents) is necessary for most patients with hypertension.[20] Furthermore, JNC 7 continues to focus on targeting blood pressure goals in contrast to the European Society of Cardiology, which utilizes a broader approach such as the Systematic Coronary Risk Evaluation (SCORE) system.[21] In spite of global variance in approaches, this chapter will focus on the importance of advocating nonpharmacologic approaches and provide specific guidance on these steps, keeping in mind the JNC 7 theme that achievement of blood pressure goals should remain the focus.

Nonpharmacologic Treatment: Lifestyle Modifications

Therapeutic lifestyle modifications consisting of nonpharmacologic approaches to blood pressure reduction should be an active part of all treatment plans for patients with hypertension. The most widely studied interventions demonstrating effectiveness include:

- Weight reduction in overweight or obese individuals
- Adoption of a diet rich in potassium and calcium
- Dietary sodium restriction
- Physical activity
- Moderation of alcohol consumption

❼ *Implementation of these lifestyle modifications successfully lowers blood pressure (Table 2–3), often with results similar to those of therapy with a single antihypertensive agent.*[22] Combinations of two or more lifestyle modifications can have even greater effects with blood pressure lowering. Weight reduction in overweight individuals would ideally lead to attainment and maintenance of a normal body weight and should be encouraged. Blood pressure lowering in overweight patients may be seen by a weight loss of as few as 10 pounds (4.5 kilograms). The Dietary Approaches to Stop Hypertension (DASH) trial demonstrated that a diet high in fruits, vegetables, and low-fat dairy products, along with a reduced intake of total and saturated fat, significantly reduced blood pressure in as little as 8 weeks.[22] Sodium restriction in moderate amounts lowers blood pressure, is generally well-accepted, and is free of adverse effects. Restriction of sodium intake to 2.4 grams (100 mmol) of elemental sodium [6 grams of sodium chloride (100 mmol) or 1 teaspoon of table salt] should be easily achievable in most patients simply by avoidance of highly salted processed foods.[23] Simple dietary advice and instructions on reading packaging labels should be introduced to the patient initially and assessed and reinforced at subsequent office visits. As is

TABLE 2–3. Lifestyle Modifications to Manage Hypertension[2,a,b]

Modification	Recommendation	Approximate Systolic BP Reduction, Range
Weight reduction	Maintain normal body weight (body mass index 18.5–24.9 kg/m^2)	5–20 mm Hg/10 kg
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8–14 mm Hg
Dietary sodium restriction	Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride)	2–8 mm Hg
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 minutes per day, most days of the week)	4–9 mm Hg
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks [e.g., 24 oz (710 mL) beer, 10 oz (296 mL) wine, or 3 oz (89 mL) 80-proof whiskey] per day in most men and to no more than 1 drink per day in women and lighter weight persons	2–4 mm Hg

BP, blood pressure; DASH, Dietary Approaches to Stop Hypertension.
[a] For overall cardiovascular risk reduction, stop smoking.
[b] The effects of implementing these modifications are dose- and time-dependent and could be greater for some individuals.

the case with weight loss, changes in physical activity do not need to be profound in order to have a significant effect on blood pressure. It is generally accepted that 30 minutes of moderately intense aerobic activity (e.g., brisk walking) most days of the week will lower blood pressure.[24] While most patients can safely engage in moderately intense aerobic activity, individuals with known cardiovascular disease, multiple risk factors with symptoms, or selected diabetic patients should undergo medical examination, possibly including exercise testing, prior to participation.[25,26] The effects of alcohol on blood pressure are variable. Initially, acute ingestion leads to a fall in blood pressure followed by a rise several hours later,[27] and binge drinking is associated with a higher risk of stroke. Furthermore, abstinence from alcohol in heavy drinkers leads to a reduction in blood pressure.[28] Alcohol also attenuates the effects of antihypertensive therapy, which is mostly reversible within 1 to 2 weeks with moderation of intake.

In addition to their beneficial effects on lowering blood pressure, lifestyle modifications also have a favorable effect on other risk factors such as dyslipidemia and insulin resistance, which are commonly encountered in the hypertensive population, and lifestyle modifications should be encouraged for this reason as well. Smoking cessation should also be encouraged for overall cardiovascular health despite its lack of chronic effects on blood pressure.[29,30] Although lifestyle modifications have never been documented to reduce cardiovascular morbidity and mortality in patients with hypertension, they do effectively lower blood pressure to some extent in most hypertensive patients. This may obviate the need for drug therapy in those with mild elevations in blood pressure or minimize the doses or number of antihypertensive agents required in those with greater elevations in blood pressure.



Patient Encounter 1

RS, a 67-year-old Hispanic man, comes to your clinic with results from a health fair he attended last week. He is concerned because his blood pressure at that time was 150/70 mm Hg, and when repeated was 154/68 mm Hg. Upon examination, seated blood pressure is 134/82 mm Hg in the left arm and 136/80 mm Hg in the right arm. Repeat measurements 5 minutes later are 142/84 and 138/76 mm Hg in the left and right arms, respectively.

- Based on the above information, should RS be classified as having hypertension?
- What factors may have contributed to the discrepancy between the health fair and office-based blood pressure readings?
- What additional information do you need to know before creating a treatment plan for RS?

Pharmacologic Treatment

8 *An approach to selection of drugs for the treatment of patients with hypertension should be evidence-based decision making with considerations regarding the individual's co-existing disease states, co-prescribed medications, and practical patient-specific issues including cost. The current JNC 7 report recommends drug therapy that is largely grounded in the best available evidence for superiority in outcomes—specifically morbidity and mortality.[2] The approach is often tempered with practical considerations relating to competing options for specific comorbidities and practical issues regarding a patient's experience or tolerance for side effects, and in some cases, the cost of medications.*

Although landmark trials, such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), have provided some objective basis for comparisons between initiating antihypertensive drug therapy with one class of antihypertensives versus another, there is room for criticism of these studies.[20,31,32] Consequently, practical interpretations of their conclusions must always leave room for individualization based on clinical judgment. Overall, JNC 7 provides a reasonable basis for guiding the selection of drug classes for individuals based on their stage of hypertension, comorbidities, and special circumstances. The following section will summarize key features of specific drug classes and summarize the JNC 7–based recommendations for patients with hypertension. Finally, an overview of the specific oral antihypertensive drug classes in common use is summarized in Table 2–4.

Diuretics

Many authorities recognize the value of diuretics as first-line agents for the majority of patients with hypertension. Extensive experience with using diuretics, as well as their practical attributes (acquisition cost and availability as combination agents), make thiazide-type diuretics a seemingly attractive selection as first-line agents. The endorsement by JNC 7 as an initial drug therapy selection for stage 1 and stage 2 hypertensive patients without compelling indications is based on a litany of placebo-controlled studies, and in no small way, on the results of active controlled outcome studies such as ALLHAT.[20] This landmark double-blind study attempted to test the hypothesis that newer antihypertensive agents would outperform thiazide-type diuretics when selected as initial drug therapy. After 4.9 years of follow-up in over 42,000 patients, the primary endpoint of fatal coronary heart disease and non-fatal myocardial infarction was indistinguishable between chlorthalidone versus either amlodipine or lisinopril. A fourth arm examining doxazosin was terminated early based on a higher risk of heart failure for doxazosin compared with chlorthalidone.[33] In spite of these findings for the primary endpoint, differences in outcomes for select secondary endpoints demonstrated superiority of chlorthalidone over either of the two remaining comparison groups. These observations, along with perceived cost-effectiveness

TABLE 2–4. Oral Antihypertensive Drugs by Pharmacologic Class[2]

Class	Drug Name and Oral Dose (mg/day)	Compelling Indications[2]	Clinical Trials	Select Adverse Events	Comments
Diuretics					
	Chlorthalidone (Hygroton) 6.25–25	Heart failure stage A (chlorthalidone)	ALLHAT[20]	Hypokalemia; Negative effect on glucose and lipids	Monitor electrolytes (e.g., decreased potassium)
		High coronary disease risk (chlorthalidone)	ALLHAT[20]		Chlorthalidone is about twice as potent as hydrochlorothiazide
		Diabetes (chlorthalidone)	ALLHAT[20]		
	Indapamide (Lozol) 2.5–5	Stroke (perindopril + indapamide)	PROGRESS[53]		
	Hydrochlorothiazide (Microzide) 12.5–50				
Aldosterone Antagonists					
	Spironolactone (Aldactone) 25–50	Heart failure (spironolactone)	RALES[73]	Hyperkalemia; Gynecomastia (spironolactone)	Monitor electrolytes (e.g., increased potassium)
	Eplerenone (Inspra) 50–100	Heart failure post-MI (eplerenone)	EPHESUS[42]		Eplerenone contraindicated in patients with estimated creatinine clearance less than 50 mL/minute or serum creatinine greater than 1.8 mg/dL (159.12 mmol/L) in women or greater than 2 mg/dL (176.8 mmol/L) in men
β-Blockers					
	Metoprolol extended-release (Toprol XL) 50–200	Heart failure (metoprolol XL, carvedilol)	MERIT-HF[74]	Bradycardia; Heart block; Fatigue	Caution with heart rate less than 60 bpm
	Carvedilol (Coreg) 12.5–50	Heart failure post-MI (carvedilol)	COPERNICUS[75] CAPRICORN[76]		Selectivity of β_1 agents is diminished at higher doses
	Propranolol (Inderal) 160–480	Post-MI (propranolol, β_1-antagonists)	BHAT[77]		Abrupt discontinuation may cause rebound hypertension
	Propranolol long-acting (Inderal LA, InnoPran XL) 80–320	High coronary disease risk			
	Metoprolol (Lopressor) 50–200				
	Atenolol (Tenormin) 25–100	Diabetes (atenolol)	UKPDS 33[78]		

Calcium Channel Blockers					
	Verapamil sustained-release (Calan SR, Isoptin SR, Verelan) 180–480 Amlodipine (Norvasc) 5–10 Nifedipine long-acting (Adalat CC, Procardia XL) 30–90 Diltiazem sustained-release (Cardizem SR) 180–360	High coronary disease risk (verapamil) Diabetes	INVEST[79]	Peripheral edema (amlodipine)	Caution with heart rate less than 60 bpm (verapamil, diltiazem) Extended-release formulations are preferred for once- or twice-daily medication administration
Angiotensin-Converting Enzyme Inhibitors					
	Benazepril (Lotensin) 10–40 Captopril (Capotan) 12.5–150 Enalapril (Vasotec) 5–40 Fosinipril (Monopril) 10–40 Lisinopril (Priniril, Zestril, Various) 10–40 Moexipril (Univasc) 7.5–30 Perindopril (Aceon) 4–16 Quinapril (Accupril) 10–80 Ramipril (Altace) 2.5–10 Trandolapril (Mavik) 1–4	Heart failure (enalapril) High coronary disease risk (ramipril, trandolapril) Heart failure post-MI (ramipril, trandolapril) Post-MI (captopril) Diabetes (captopril) Chronic kidney disease (captopril, ramipril) High coronary disease risk (perindopril) Stroke (perindopril + indapamide)	SOLVD[80] HOPE[65] AIRE[81] TRACE[82] SAVE[83] UKPDS 33[78] Captopril Trial[50] EUROPA[64] PROGRESS[53]	Hyperkalemia; Cough	Monitor electrolytes (e.g., increased potassium) Monitor rental function with serum creatinine Contraindicated in pregnancy, do not use
Angiotensin Receptor Blockers					
	Valsartan (Diovan) 80–320 Candesartan (Atacand) 4–32 Losartan (Cozarr) 25–100 Irbesartan (Avapro) 150–300	Heart failure (valsartan, candesartan) High coronary disease risk (losartan) Diabetes Chronic kidney disease (irbesartan, losartan)	ValHEFT[84] CHARM[54] LIFE[58] RENAAL[58] IDNT[57] IRMA-II[60]	Hyperkalemia	Monitor electrolytes (e.g., increased potassium) Monitor renal function with serum creatinine Contraindicated in pregnancy, do not use May use when patient develops cough with ACE inhibitor
α_1-Blockers					
	Doxazosin (Cardura) Terazosin (Hytrin) Prazosin (Minipress)	No recommendations at this time		Syncope Dizziness Palpitations	May be used in elderly males with prostatism

TABLE 2–4. Oral Antihypertensive Drugs by Pharmacologic Class[2] (*Continued*)

Class	Drug Name and Oral Dose (mg/day)	Compelling Indications[2]	Clinical Trials	Select Adverse Events	Comments
Central α_2-Agonists					
	Methyldopa Clonidine (Catapres) Guanabenz Guanfacine (Tenex) Guanadrel	No recommendations at this time		Transient sedation initially	First-line in pregnancy (methyldopa)
Direct Vasodilators					
	Isosorbide dinitrate 20 mg and hydralazine 37.5 (BiDil) 1–2 tablets three times a day Minoxidil (Loniten) Hydralazine	Heart failure (isosorbide dinitrate + hydralazine in African-Americans)	A-HeFT[66]	Edema (minoxidil) Tachycardia Lupus-like syndrome (hydralazine)	
Other Agents					
	Reserpine	No recommendations at this time		Mental depression	May be used in resistant hypertension when combined with a thiazide

Antihypertensive drug name and dose is associated with compelling indications which are based on benefits from outcome studies or clinical guidelines. For example, the drug class aldosterone antagonists have eplerenone dosed at 25–50 mg per day which is indicated for heart failure patients after an MI and supported by the EPHESUS trial.

A-HeFT, African-American Heart Failure trial; AIRE, Acute Infarction Ramipril Efficacy Study; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; BHAT, Beta-Blocker Heart Attack Trial; bpm, beats per minute; CAPRICORN, Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction Trial; Captopril Trial, Collaborative Study Captopril Trial ("The Effect of Angiotensin-Converting Enzyme Inhibition on Diabetic Nephropathy"); CHARM, Candesartan in Heart Failure Assessment of Reduction in Morbidity and Mortality Trial; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Trial; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; EUROPA, European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease Trial; HOPE, Heart Outcomes Prevention Evaluation Study; IDNT, Irbesartan Diabetic Nephropathy Trial; INVEST, International Verapamil-Trandolapril Study; IRMA-II, Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria study; ISA, intrinsic sympathomimetic activity; LIFE, Losartan Intervention For Endpoint reduction in hypertension study; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; MI, myocardial infarction; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; RALES, Randomized Aldactone Evaluation Study; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study; SAVE, Survival and Ventricular Enlargement trial; SOLVD, Studies of Left Ventricular Dysfunction; TRACE, Trandolapril Cardiac Evaluation; UKPDS, UK Prospective Diabetes Study; VALUE, Valsartan Antihypertensive Long-term Use Evaluation; ValHEFT, Veterans Affairs Cooperative I study.

(which was not specifically evaluated in this study), led the authors and JNC 7 to endorse diuretics as keys to initial drug therapy for most patients with hypertension. Nonetheless, substantial criticism of this trial has undermined some of the enthusiasm for diuretics in some clinicians' minds as well as international guideline committees.[34] Criticism of the differential blood pressures achieved in the various treatment groups, the artificial construct guiding the use of add-on drugs to base therapy, and the overrepresentation of African-Americans exhibiting select endpoints have weakened the interpretability of the authors' conclusions. Furthermore, other contemporary studies[31,35] have also challenged the status of diuretics as ideal baseline choices for initial antihypertensive drug therapy for all patients. Specifically, the Australian-New Zealand Blood Pressure-2 (ANBP2) Study[35] seemingly demonstrated (in particular for the male cohort) a superior outcome for angiotensin-converting enzyme (ACE) inhibitor–based therapy versus diuretic-based therapy in over 6,000 relatively older patients treated for over 4 years. Similarly, the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA)[31] study demonstrated in over 19,000 patients treated for approximately 5 years more favorable outcomes for the dual therapy of a calcium channel blocker agent (CCBA)/ACE inhibitor–based approach versus a β-blocker/ diuretic–based approach. Needless to say, all three of these major trials are subject to significant criticism related to study design issues, including inequities of achievement in blood pressure targets between groups for the ALLHAT and ASCOT-BPLA studies.[36] Nonetheless, diuretics continue to receive support for use as baseline initial therapy for most hypertensive patients who do not have compelling indications.[37]

Key features of diuretics that must be kept in mind, along with evidence from outcome-based studies, include the diversity between the sub-types of diuretics and their corresponding diversity of pharmacologic actions. The four sub-types include thiazides, loop diuretics, potassium-sparing agents, and aldosterone antagonists. The latter will be discussed as a separate entity. Each sub-type has clinically based properties which distinguish their roles in select patient populations. Thiazide diuretics are by far the most commonly prescribed sub-type with the greatest number of outcome-based studies supporting their use. In the United States, hydrochlorothiazide and chlorthalidone represent the most commonly prescribed thiazide-type diuretics and have been the subject of the majority of large outcome-based studies. Although subtle differences in pharmacokinetics between these agents exist, practical differences are limited to their relative diuretic potency. Chlorthalidone is considered approximately 1.5 to 2 times more potent than hydrochlorothiazide for blood pressure reduction.[38] Since the relationship between antihypertensive efficacy and metabolic/electrolyte-related side effects of thiazide diuretics is considered to be dose-related, attention to this differential in potency may be important. Specifically, select metabolic effects (hyperlipidemic and hyperglycemic) and electrolyte-related effects (hypokalemic, hypomagnesemic, hyperuricemic, and hypercalcemic) seem to increase with higher doses. This has led to national guidelines[2] recommending doses not exceeding 6.25 to 25 mg/day for chlorthalidone versus 12.5 to 50 mg/day for hydrochlorothiazide. These metabolic effects may clearly complicate the management of higher-risk patients with common comorbidities such as dyslipidemia or diabetes, or even those likely to be sensitive to the potassium- or magnesium-wasting effects of diuretics (patients with dysrhythmias or those taking digoxin). While rates of diabetes are higher following administration of thiazides, there is plenty of evidence that this can be greatly minimized by keeping potassium in the high normal range (i.e., above 4.0 mEq/L [4 mmol/L]).[39] Nonetheless, clinicians should rarely approach the upper limits of these dosage ranges without careful assessment of their metabolic effects or potential to induce electrolyte disturbances. In this way, optimization of blood pressure lowering potential may be achieved while minimizing potential adverse outcomes.

Another key feature of the thiazide-type diuretics is their limited efficacy in patients whose estimated renal function is reduced, such as the elderly. For example, patients with estimates of reduced renal function, such as those with a glomerular filtration rate (GFR) below 30 mL/minute, should be considered for more potent loop type diuretics such as furosemide. Clinicians often fail to either reconsider the role of thiazide diuretics prescribed to individuals whose renal function has been declining or fail to recognize the likely prevalence of renal compromise in the elderly to begin with.

Renal function is often estimated by formulas that attempt to predict GFR. As stated above, when predicted GFR is less than 30 mL/minute, the natural course of action would be to consider more potent diuretics. The loop diuretics, such as furosemide, bumetanide, torsemide, and ethacrynic acid, have a common site of action in the thick ascending limb of the loop of Henle.[40] Responsible for reabsorption of over 65% of the filtered sodium, their diuretic activity is clearly greater than that of the thiazides, potassium-sparing diuretics, and mineralocorticoid-acting agents. Practically speaking, furosemide is the most common agent used as a functional alternative for patients whose renal compromise precludes effective diuresis from thiazide-type agents. In situations in which a patient has poor renal function, a loop diuretic should be given at least twice a day, with the exception of furosemide to augment blood pressure control with combination antihypertensive therapy. Diuretic resistance may result from extended use of loop diuretics. In these circumstances, the addition of a thiazide to a loop diuretic may dramatically enhance overall diuresis. The most significant adverse effects related to loop diuretic use concern their potential for excessive diuresis leading to hyponatremia or hypotension. Additionally, hypokalemia, hypomagnesemia, and hypocalcemia may develop over time and contribute to the potential for cardiac arrhythmias. Overall relevance of drug-drug interactions and potential for aggravating select conditions (hyperglycemia, dyslipidemias, and hyperuricemia)

should be routinely considered in the monitoring plan for those taking loop diuretics for extended periods of time.

Potassium-sparing diuretics that do not act through mineralocorticoid receptors include triamterene and amiloride. These agents are often prescribed with potassium-wasting diuretics in an attempt to mitigate the loss of potassium. When administered as a single entity or as one component of a combination product, these agents result in moderate diuresis. Potassium-sparing diuretics act on the late distal tubule and collecting duct and thereby have limited ability to affect sodium reabsorption, which translates into modest diuresis. The most important adverse effects associated with these agents are their potential to contribute to hyperkalemia. This is especially relevant in the context of those patients receiving other agents with potassium-sparing properties, such as ACE inhibitors, angiotensin receptor blockers (ARBs), and potassium supplements, as well nonsteroidal anti-inflammatory drugs (NSAIDs), in those with mild to moderate renal impairment.

Aldosterone Antagonists

Aldosterone antagonism has recently been recognized as more than an alternate means of achieving diuresis. Indeed, spironolactone, and more recently eplerenone in the RAAS system (Fig. 2–3), have been recognized as important modulators of vascular tone through a variety of mechanisms. These inhibitors of aldosterone are commonly used in patients as components of select combination drug therapies to balance the potassium-wasting effects of more potent diuretics, such as thiazide or loop diuretics, as well as for their direct antihypertensive effects through aldosterone modulation. Patients with resistant hypertension with and without primary aldosteronism had significant additive blood pressure reductions when adding low-dose spironolactone (12.5 to 50 mg/day) to diuretics, ACE inhibitors, and ARBs.[41] Although functional for these purposes, it is important to recognize their potential to cause hyperkalemia when used in conjunction with other select agents or in patients with comorbidities resulting in reduced renal function. Classic examples include co-administration with ACE inhibitors and ARBs, known for their potassium-sparing effects, as well as agents that may directly or indirectly alter renal potassium load (e.g., potassium supplements) or potassium excretory function (e.g., NSAIDs). The most commonly used potassium-sparing diuretic is spironolactone; however, eplerenone has been increasingly used in patients with heart failure following acute myocardial infarction.[42] Although spironolactone is commonly associated with gynecomastia, eplerenone rarely causes this complication.[43] The risk of hyperkalemia is also more commonly reported with patients on spironolactone.[44]

Beta-Blockers

The JNC 7 identifies β-blockers as agents appropriate for first-line therapy for many individuals with hypertension. Based on JNC 7, the role of β-blockers in patients with select comorbidities is extensive (Table 2–5). Patients with comorbidities such as heart failure, recent myocardial infarction, and diabetes represent opportunities for β-blocker use on the basis of proven outcome-based studies. The role of β-blockers for patients with ischemic conditions including acute myocardial infarction is based on their hemodynamic effects on heart rate, blood pressure, and cardiac output, as well as their possibly antiarrhythmic properties.[40] Given their reputation for negative inotropic and chronotropic effects, any role of β-blockers in heart failure would at first appear counterintuitive. This is based on the fact that heart failure patients with systolic dysfunction would seem to be poor candidates for therapeutic agents that reduce inotropicity or contractility. Nonetheless, in the long run β-blockers, when judiciously used in patients with heart failure, have consistently been shown to reduce morbidity and mortality relative to standard heart failure therapies. Similarly, given their effects on pancreatic β-cell release of insulin and metabolic effects, such as reducing gluconeogenesis and glycogenolysis, their role in managing diabetic patients would also seem illogical. However, randomized trials strongly support β-blockers in both of these populations. In contrast, a meta-analysis by Lindholm and associates[45] has shown a higher risk of stroke with β-blocker treatment compared to other antihypertensive therapy in the treatment of patients with primary hypertension. The drug with the most prominent difference in the increased risk of stroke between the three β-blocker subgroups was atenolol. Moreover, Messerli and colleagues[46] showed that

TABLE 2–5. Compelling Indications for Individual Drug Classes

	Recommended Drug Class						
Compelling Indication	**Diuretic**	**Ald Ant**	**BB**	**CCBA**	**ACE-I**	**ARB**	**Dir Vaso**
Heart failure	•	•	•		•	•	•
Post-myocardial infarction		•	•		•		
High coronary disease risk	•		•		•		
Diabetes	•		•	•	•	•	
Chronic kidney disease				•	•	•	
Recurrent stroke prevention	•				•		

ACE-I, angiotensin-converting enzyme inhibitor; Ald Ant, aldosterone antagonist; ARB, angiotensin receptor blocker; BB, beta-blocker; CCBA, calcium channel blocking agent; Dir Vaso, direct vasodilator.

β-blocker therapy was ineffective in preventing coronary heart disease, cardiovascular mortality, and all-cause mortality when compared to diuretics for elderly patients (60 years of age or greater) treated for primary hypertension. Clearly, the effects of β-blockers on blood pressure are complex and difficult to ascribe to one or two mechanisms. Rather, the varied effects of negative chronotropic and inotropic properties along with reduced renin levels (Fig. 2–3) appear to result in an overall reduction in cardiac output and/or reduction in peripheral resistance.

The specific pharmacologic properties of various β-blockers are varied and diverse. An understanding of these properties may be useful in order to prioritize selection of one agent over others given a patient's specific condition(s). One of these properties is cardioselectivity—the property of some β-blockers that preferentially block β_1- versus β_2-receptors. Another property exhibited by some β-blockers is membrane stabilization activity, which relates to the propensity of the β-blocker to possess some capacity for antiarrhythmic properties, in addition to β-receptor blocking properties. Some β-blockers (Fig. 2–4) possess properties referred to as intrinsic sympathomimetic activity (ISA). β-Blockers possessing this property effectively block the β-receptor at higher circulating catecholamine levels, such as during exercise, while having modest β-blocking activity at times of lower catecholamine levels, such as at rest.[47]

Each of these properties may be exploited to some extent when prescribing a β-blocker, while others (membrane stabilization activity and ISA) are more of theoretical interest, with less relative value in clinical practice. For example, consider a patient with mild asthma, chronic obstructive pulmonary disease, or peripheral vascular disease (intermittent claudication). A β-blocker with relative cardioselectivity to block β_1-receptors may be more desirable in such a patient, while a nonselective β-blocker (Fig. 2–4) may be potentially disadvantageous. In such a patient, low doses of cardioselective β-blockers may achieve adequate blockade of β_1-receptors in the heart and kidneys while minimizing the undesirable effects of β_2-receptor blockade on the smooth muscle lining the bronchioles. In doing so, hypertension may be managed while avoiding complications of the co-existing reactive airway disease, which is mediated by β_2-receptor stimulation. Similarly, either because of a reduction in the β_2-mediated vascular blood flow or by enhanced unopposed β-agonist–mediated vasoconstriction, a patient with peripheral vascular disease (intermittent claudication) may experience a worsening of symptoms with use of a nonselective β-blocker (Fig. 2–4). It is important to remember that cardioselectivity is dependent upon dose, with diminished selectivity exhibited with higher doses.

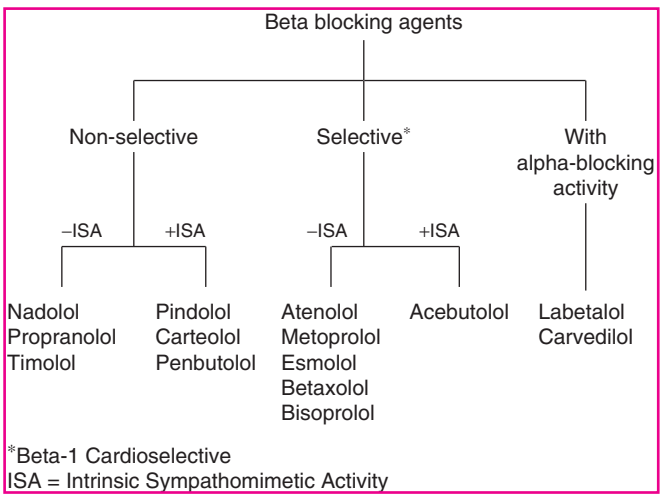


FIGURE 2–4. Flowchart listing various β-blocking agents separated by β-receptor activity and intrinsic sympathomimetic activity.

Membrane stabilization activity and ISA are two pharmacologic properties of some β-blockers whose value in the clinical setting is less well established. Generally, membrane stabilization activity may correlate with antiarrhythmic properties, while β-blockers with ISA properties have the theoretical advantage of mitigating reductions in resting heart rate while acting as classic β-blockers, at higher sympathetic tone.[40] Since neither has directly proven value in the clinical setting, they will not be discussed further other than to point out that β-blockers with ISA are not recommended for use in the post–myocardial infarction patient.[48]

A limited number of β-blockers possess properties that block β-receptors and antagonize α-receptors (Fig. 2–4). β-Blockers with α-receptor–blocking activity also have a clinical role that is theoretically beneficial, yet somewhat difficult to prove as a clinical advantage. Such is the case for carvedilol and labetalol. Both these β-blockers possess α-receptor–blocking activity in addition to their β-receptor–blocking properties. In the case of carvedilol, reductions in peripheral resistance through α-receptor–mediated blockade, in addition to β-blockade, may be thought of as a benefit for patients with hypertension. Such a combination should theoretically contribute to enhanced reductions in vascular tone. Nonetheless, there has been no proven evidence of superior outcome from the use of β-blockers with α-blocking activity compared to those with only β-blocking activity. Blocked α-receptors may represent a theoretical disadvantage for carvedilol when used to manage patients with chronic heart failure. In such patients, when recommended therapy is prescribed,[49] there is often a risk of lowering peripheral vascular resistance too much (through α- and β-receptor blockade) in such patients, who may have precious little reserve blood pressure. Nonetheless, carvedilol has enjoyed considerable clinical and proven success as a mainstay of managing patients with chronic heart failure.[49]

The adverse effects of β-blockers logically follow their pharmacology. Initiating β-blockers for hypertension in all patients may have the potential to precipitate bradycardia, various degrees of heart block, or signs and symptoms of heart failure. The latter is usually limited to those with a subclinical diagnosis and should be considered in the elderly or those with documented reductions in left ventricular function. Conversely, abrupt discontinuation of β-blockers has been cited as a precipitating factor in the development of ischemic syndromes—especially for those patients in whom β-blockers were used for extended periods of time or at higher doses, In such cases, the dose of these agents should be reduced (tapered) over a period of several days to perhaps 1 or even 2 weeks depending on patient-related factors.

Calcium Channel Blocking Agents

Exhibiting considerable interclass diversity, calcium channel blocking agents (CCBAs) have been recognized as effective antihypertensives, for the elderly in particular. Earlier trials demonstrated effective event reduction for patients with isolated systolic hypertension and clearly established the effectiveness of the blood pressure–lowering effects of dihydropyridine CCBAs. Comparative data between specific CCBAs as part of combination drug therapy versus other combination regimens have been forthcoming as of late. Specifically, the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial compared valsartan-based therapy to amlodipine-based therapy in over 15,000 patients who were at high risk for cardiac events. In spite of an attempt to achieve identical blood pressure reductions, differences were noted early and sustained throughout the 4.2-year length of the study. Overall the primary endpoint (composite cardiac mortality and morbidity) was not statistically significantly different between the groups, but cause-specific outcomes did favor the regimen affording the achievement of lower blood pressures—namely the amlodipine-based therapy. This theme of unequal reductions in BP accounting for differences in cause-specific outcomes was shared by the findings of the ASCOT-BPLA study, which compared amlodipine-based therapy versus atenolol-based therapy in over 19,000 hypertensives for 5.5 years. Again although no statistically significant reduction in the primary endpoint was observed, the study was stopped prematurely because of fewer individuals achieving the primary endpoint while receiving the amlodipine-based regimen compared to those taking the atenolol-based regimen. These observations appear to confirm a critical theme that regardless of the agents used, the overwhelming evidence appears to indicate that the amount of blood pressure lowering achieved has more to do with event reduction than with the agents or combinations of agents used to achieve them. Primary endpoints aside, certain secondary endpoints demonstrated differences between regimens. Protection from the development of new-onset diabetes over the duration of the study was noted for the amlodipine-based therapy in the ASCOT-BPLA study and favored the ARB-based regimen over the CCBA-based regimen in the VALUE study.

Often used to augment blood pressure lowering, CCBAs are most commonly used as add-on therapy for patients who are in need of further blood pressure lowering above and beyond that afforded by diuretics or other antihypertensives. Nonetheless, they have demonstrated their efficacy in select patient populations as very effective blood pressure lowering agents.

The diversity of pharmacologic properties within the CCBA class is significant. Knowledge of their subclass helps the clinician to recognize their predominant effects on the cardiovascular system and probable side-effect profile. Dihydropyridine CCBAs such as amlodipine are commonly associated with edema, especially when used at higher doses. Phenylalkylamine-verapamil and benzothiazepine-diltiazem are more commonly recognized for their effects on the cardiac conduction system and their propensity to be negative inotropes and negative chronotropes. Many of these pharmacologic properties are exploited for their specific clinical utility. Given that verapamil and diltiazem (both are nondihydropyridine CCBAs) effectively block cardiac conduction through the atrioventricular node, their value in the management of patients with atrial fibrillation in addition to hypertension is obvious. In contrast, the dihydropyridine subclass of agents has no utility in managing atrial dysrhythmias. Similarly, all three subclasses of CCBAs possess some coronary vasodilating properties and hence may be used in select patients for the management of patients with angina, in addition to their antihypertensive benefits.

ACE Inhibitors

ACE inhibitors are a key class of antihypertensive agents used in a vast array of patients with or without comorbidities and/or cardiovascular risk factors. As the target agents of choice for numerous outcome trials, they have been extensively studied across a wide variety of patient types and thus have considerable applicability to a wide array of potential patients. This broad utility extends to the list of compelling indications (Table 2–5) for patients as described in JNC 7. These compelling indications include their qualified role in managing patients with hypertension who have type 1 diabetes,[50] heart failure,[49] post–myocardial infarction,[48] type 2 diabetes,[3] chronic kidney disease,[51,52] or recurrent stroke prevention.[53] Comparative trials between ACE inhibitors and various other agents as initial drug therapy have also demonstrated some differences in outcomes for this class. In the case of ALLHAT,[20] ACE inhibitors appeared to perform less well than diuretics in terms of incidence of combined cardiovascular disease and heart failure. On the other hand, the ANBP2 trial[35] seemed to suggest that ACE inhibitors may be equivalent to diuretics in terms of overall outcomes. Since there are legitimate criticisms of both these trials, it may only be safe to conclude that both diuretics and ACE inhibitors represent formidable agents as either first- or second-line hypertensive

therapies that effectively achieve a target blood pressure goal for most patients with or without comorbidities.

Although generally well-tolerated by most, classic side effects associated with ACE inhibitors include their potential to cause hyperkalemia and a persistent dry cough. Modest elevations in serum potassium should be anticipated. This is particularly true in patients with compromised renal function, those receiving concurrent NSAIDs, or those taking potassium supplementation. The elevations in potassium should be anticipated if not prospectively considered when starting or increasing the dose of an ACE inhibitor. Hyperkalemia is rarely a reason for discontinuation of this otherwise reasonably well-tolerated class of agents. Nonetheless, periodic monitoring of serum potassium is prudent for patients receiving ACE inhibitors.

Another effect of ACE inhibitors includes their propensity to cause a dry cough. This cough is thought to be caused by accumulation of bradykinin resulting from a direct effect of inhibiting ACE. It can be a troubling source of nonadherence to this class of agents. Although mild forms are tolerable, should cough become the source of poor compliance with the agent, ARBs should be considered as possible alternative agents. This is particularly true for patients in whom there is a need for RAAS inhibition.

In general, the effects of ACE inhibitors on diminished renal function and potassium can be predicted given an understanding of their pharmacologic actions (Fig. 2–3). Inhibition of the generation of angiotensin II through ACE inhibition (or direct blockage of the angiotensin II receptor by angiotensin II receptor blockers) naturally would reduce the efferent renal artery tone thereby changing the intraglomerular pressure. Although changes in the afferent renal artery tone also occur, the overall effects usually translate into a reduction in GFR[52] with resulting elevations of up to 30% in serum creatinine values. It is important to recognize that such elevations in serum creatinine are not usually indications to discontinue use of the ACE inhibitor. Rather, possible dose reduction and continued monitoring for further increases in serum creatinine remains prudent. Alternatively, should elevations in serum creatinine exceed 30%, discontinuation is prudent until further evaluation can be made.

More rare forms of adverse effects of ACE inhibitors include blood dyscrasias, angioedema, and more serious effects of ACE inhibitors on renal function such as acute renal failure in those with preexisting kidney dysfunction or renal artery stenosis. With incidences usually less than 1%, these adverse effects are rarely seen by many clinicians. Nonetheless, given their potential for serious consequences, they remain important to consider given the widespread use of ACE inhibitors for a variety of cardiovascular conditions. Specifically, the insidious nature of the development of neutropenia and agranulocytosis and the acute effects of lip and tongue swelling accompanying angioedema or acute renal failure in a patient with bilateral renal artery stenosis can have potentially life-threatening complications.

Angiotensin Receptor Blockers

ARBs are another key class of agents whose role in managing patients with hypertension has been further defined by recently completed studies. ARBs are inhibitors of the angiotensin-1 (AT1) receptors (Fig. 2–3). AT1 receptor stimulation evokes a pressor response via a host of accompanying effects on catecholamines, aldosterone, and thirst.[40] Consequently, inhibition of AT1 receptors directly prevents this pressor response and results in up-regulation of the RAAS. Up-regulation of the RAAS results in elevated levels of angiotensin II, which have the added effect of stimulating the angiotensin-2 (AT2) receptors. AT2-receptor stimulation is generally associated with antihypertensive activity; however, long-term effects of AT2-receptor stimulation that involve cellular growth and repair are relatively unknown. What is clear is that ARBs differ from ACE inhibitors in that the former cause up-regulation of the RAAS while the latter blocks the breakdown of bradykinin. The therapeutic relevance resulting from these pharmacologic differences has yet to be fully evaluated through long-term clinical comparative trials.

At this point, ARBs have emerged as an effective class of antihypertensives whose low incidence of side effects and demonstrated clinical role in patients with specific comorbidities have afforded them an attractive position in the antihypertensive armamentarium. Like ACE inhibitors, the antihypertensive effectiveness of ARBs is greatly enhanced by combining them with diuretics. Furthermore, they have proven their value as well-tolerated alternatives to ACE inhibitors for patients with chronic kidney disease, diabetes mellitus, and post–acute myocardial infarction (AMI) (Table 2–5). As of late, the addition of ARBs to standard therapy for patients with congestive heart failure (CHF), including ACE inhibitors, have demonstrated additional incremental benefits for patients with systolic dysfunction[54] or diastolic dysfunction[55] or as alternatives to ACE inhibitors when ACE inhibitors are not tolerated.[56] Comparative studies with alternate (non-ACE inhibitors) antihypertensive regimens in patients with type 2 diabetes[57,58] and left ventricular hypertrophy[59] have demonstrated their usefulness as effective antihypertensives in these special populations. Studies (the Irbesartan Diabetic Nephropathy Trial [IDNT] and Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan [RENAAL]) have demonstrated superiority of delaying progression toward renal dysfunction for ARBs relative to alternative antihypertensives in type 2 diabetics.[57,58] Their use in treatment of diabetic nephropathy and proteinuria in patients with type 2 diabetes mellitus and hypertension has been supported by their Food and Drug Administration (FDA) approval for use in this population and inclusion in national guidelines.[3] The Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA II)[60] study demonstrated the dose dependency of these outcomes in type 2 diabetics, while the IDNT study suggested a relative superiority over alternative antihypertensives, namely CCBAs. Although



Patient Encounter 2

JT, a 55-year-old African-American woman, comes to your clinic with a recent diagnosis of hypertension. She is 5′5″ (165 cm) tall and weighs 160 pounds (72.7 kg) with a body mass index (BMI) of 26.6 kg/m^2. JT does not use tobacco or drink alcohol, and exercises about once a week. Physical exam was unremarkable, but an electrocardiogram revealed left ventricular hypertrophy. Baseline laboratory tests were significant for fasting blood glucose of 124 mg/dL (6.88 mmol/L), serum creatinine of 1.5 mg/dL (133 mmol/L), total cholesterol of 200 mg/dL (5.18 mmol/L), high-density lipoprotein cholesterol of 40 mg/dL (1.04 mmol/L), triglycerides of 200 mg/dL (2.26 mmol/L), and low-density lipoprotein cholesterol of 120 mg/dL (3.11 mmol/L). Urinalysis was positive for microalbuminuria. Blood pressure today was 165/86 mm Hg.

- What signs of target organ damage does JT exhibit?
- Is more extensive testing for identifiable causes of hypertension indicated at this time?
- Based on the information presented, create a care plan for JT's hypertension. This should include (1) goals of therapy, (2) a patient-specific therapeutic plan, and (3) a plan for appropriate monitoring to achieve goals and avoid adverse effects.

better tolerated than ACE inhibitors, ARBs have not been shown to demonstrate superiority of outcomes relative to ACE inhibitors. This key observation, in addition to their relatively higher acquisition cost, has mitigated the growth of ARB use relative to ACE inhibitors.

Alpha-Blockers

Generally, α_1-blockers are considered as second-line agents to be added on to most other agents when hypertension is not adequately controlled. They may have a specific role in the antihypertensive regimen for elderly males with prostatism; however, their use is often curtailed by complaints of syncope, dizziness, or palpitations following the first dose and orthostatic hypotension with chronic use. The roles of doxazosin, terazosin, and prazosin in the management of patients with hypertension are limited due to the paucity of outcome data and the absence of a unique role for special populations or compelling indications from JNC 7.

Central Alpha2-Agonists

Also limited by their tendency to cause orthostasis, sedation, dry mouth, and vision disturbances, clonidine, methyldopa, and guanabenz represent rare choices in contemporary treatment of patients with hypertension. Their central α_2-adrenergic stimulation is thought to reduce sympathetic outflow and enhance parasympathetic activity thereby reducing heart rate, cardiac output, and total peripheral resistance. Occasionally used for cases of resistant hypertension, these agents may have a role when other more conventional therapies appear ineffective. The availability of a transdermal clonidine patch that is applied once weekly may offer an alternative to hypertensive patients with adherence problems.

Other Agents

Direct vasodilators such as hydralazine and minoxidil represent additional alternative agents used rarely for patients with resistant hypertension. Primarily acting to relax smooth muscles in arterioles and activate baroreceptors, use of these agents in the absence of concurrently administered β-blockers and diuretics is uncommon. This is due to the need to offset their tendency to cause reflex tachycardia and fluid retention. Other more rare adverse effects include hydralazine-induced lupus-like syndrome and hypertrichosis from minoxidil. Finally, reserpine, although slow to act, represents another rarely used alternative agent for those who are recalcitrant to more standard therapy. This agent is a long-acting depleter of the catecholamine norepinephrine, which causes reduced sympathetic tone leading to reductions in peripheral resistance. Reserpine's association with numerous side effects including gastric ulceration, depression, and sexual side effects has limited its usefulness in all but the more rare cases of patients with resistant hypertension. However, the Systolic Hypertension in the Elderly (SHEP) trial[61] demonstrated the blood pressure lowering effectiveness of reserpine (0.05 mg per day) when combined with a diuretic, and similar cardiopulmonary and psychosocial side effects between the treatment and placebo groups.

SPECIAL PATIENT POPULATIONS

Compelling Indications and Special Considerations

❾ *While the main goal of antihypertensive therapy is to achieve target blood pressures, the selection of agents for an individual should also account for certain special considerations and a patient's comorbidities. Specific antihypertensive therapy is warranted for certain patients with comorbid conditions that may elevate their level of risk for cardiovascular disease.* Clinical conditions for which there is compelling evidence supporting one or more classes of drug therapy include:[2]

- Ischemic heart disease
- Heart failure

- Diabetes
- Chronic kidney disease
- Cerebrovascular disease

Compelling indications for specific drug therapies are summarized in Table 2–5.[62] In patients with hypertension and chronic stable angina, β-blockers and long-acting calcium channel blockers are indicated due to their antihypertensive and antianginal effects.[2,63] In patients at high risk of ischemic heart disease, such as diabetic patients with additional cardiovascular risk factors or chronic coronary artery or vascular disease, ACE inhibitors are particularly useful in reducing the risk of cardiovascular events regardless of whether the patient carries a concurrent diagnosis of hypertension.[2,64,65]

β-Blockers and ACE inhibitors are also indicated for post–myocardial infarction for the reduction of cardiovascular morbidity and mortality, as are aldosterone antagonists, in post–myocardial infarction patients with reduced left ventricular systolic function and diabetes or signs and symptoms of heart failure.[2,48]

Patients with asymptomatic left ventricular systolic dysfunction and hypertension should be treated with β-blockers and ACE inhibitors. Those with heart failure secondary to left ventricular dysfunction and hypertension should be treated with drugs proven to also reduce the morbidity and mortality of heart failure, including β-blockers, ACE inhibitors, ARBs, aldosterone antagonists, and diuretics for symptom control as well as antihypertensive effect. In African-Americans with heart failure and left ventricular systolic dysfunction, combination therapy with nitrates and hydralazine not only affords a morbidity and mortality benefit, but may also be useful as antihypertensive therapy if needed.[66] The dihydropyridine calcium channel blockers amlodipine or felodipine may also be used in patients with heart failure and left ventricular systolic dysfunction for uncontrolled blood pressure, although they have no effect on heart failure morbidity and mortality in these patients.[49] For patients with heart failure and preserved ejection fraction, antihypertensive therapies that should be considered include β-blockers, ACE inhibitors, ARBs, calcium channel blockers (including nondihydropyridine agents), diuretics, and others as needed to control blood pressure.[2,49]

Patients with diabetes and hypertension should initially be treated with either β-blockers, ACE inhibitors, ARBs, diuretics, or calcium channel blockers. There is a general consensus that therapy focused on RAAS inhibition by ACE inhibitors or ARBs may be optimal if the patient has additional cardiovascular risk factors such as left ventricular hypertrophy or chronic kidney disease.[2,3,59,67]

In patients with chronic kidney disease and hypertension, ACE inhibitors and ARBs are preferred, usually in combination with a diuretic.[67] ACE inhibitors in combination with a thiazide diuretic are also preferred in patients with a history of prior stroke or transient ischemic attack. This therapy reduces the risk of recurrent stroke, making it particularly attractive in these patients for blood pressure control.[53]

There are several situations in the management of hypertension requiring special considerations including, but not limited to:

- Hypertensive crisis
- Elderly populations
- Isolated systolic hypertension
- Minority populations
- Pregnancy
- Pediatrics

Hypertensive crisis can be divided into hypertensive emergencies and hypertensive urgencies. A hypertensive emergency occurs when severe elevations in blood pressure are accompanied by acute or life-threatening target organ damage such as acute myocardial infarction, unstable angina, encephalopathy, intracerebral hemorrhage, acute left ventricular failure with pulmonary edema, dissecting aortic aneurysm, rapidly progressive renal failure, accelerated malignant hypertension with papilledema, and eclampsia among others. Blood pressure is generally greater than 220/140 mm Hg, although a hypertensive emergency can occur at lower levels, particularly in individuals without previous hypertension. The goal in a hypertensive emergency is to reduce mean arterial pressure by up to 25% to the range of 160/100 to 110 mm Hg in minutes to hours.[2,68] Intravenous therapy is generally required and may consist of the agents listed in Table 2–6.[62] A hypertensive urgency is manifested as a severe elevation in blood pressure without evidence of acute or life-threatening target organ damage. In these individuals, blood pressure can usually be managed with orally administered short-acting medications (i.e., captopril, clonidine, or labetalol) and observation in the emergency department over several hours, with subsequent discharge on oral medications and follow-up in the outpatient setting within 24 hours.[2,62]

The treatment of elderly patients with hypertension, as well as those with isolated systolic hypertension, should follow the same approach as with other populations with the exception that lower starting doses may be warranted to avoid symptoms and with special attention paid to postural hypotension. This should include a careful assessment of orthostatic symptoms, measurement of blood pressure in the upright position, and caution to avoid volume depletion and rapid titration of antihypertensive therapy.[2] In individuals with isolated systolic hypertension, the optimal level of diastolic pressure is not known, and although treated patients who achieve diastolic pressures less than 60 to 70 mm Hg had poorer outcomes in a landmark trial, their cardiovascular event rate was still lower than those receiving placebo.[69]

TABLE 2–6. Parenteral Antihypertensive Agents for Hypertensive Emergency[a]

Drug	Dose	Onset of Action	Duration of Action	Adverse Effects[b]	Special Indications
Vasodilators					
Sodium nitroprusside	0.25–10 mcg/kg/minute as IV infusion[c]	Immediate	1–2 minutes	Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication	Most hypertensive emergencies; use with caution with high intracranial pressure or azotemia
Nicardipine hydrochloride	5–15 mg/hour IV	5–10 minutes	15–30 minutes, may exceed 4 hours	Tachycardia, headache, flushing, local phlebitis	Most hypertensive emergencies except acute heart failure; use with caution with coronary ischemia
Fenoldopam mesylate	0.1–0.3 mcg/kg/minute as IV infusion[c]	Less than 5 minutes	30 minutes	Tachycardia, headache, nausea, flushing	Most hypertensive emergencies; use with caution with glaucoma
Nitroglycerin	5–100 mcg/kg/minute as IV infusion	2–5 minutes	5–10 minutes	Headache, vomiting, methemoglobinemia, tolerance with prolonged use	Coronary ischemia
Enalaprilat	1.25–5 mg every 6 hours	15–30 minutes	6–12 hours	Precipitous fall in pressure in high-renin states; variable response	Acute left ventricular failure; avoid in acute myocardial infarction
Hydralazine hydrochloride	10–20 mg IV 10–40 mg IM	10–20 minutes 20–30 minutes	1–4 hours IV 4–6 hours IM	Tachycardia, flushing, headache, vomiting, aggravation of angina	Eclampsia
Adrenergic Inhibitors					
Labetalol hydrochloride	20–80 mg IV bolus every 10 minutes	5–10 minutes	3–6 hours	Vomiting, scalp tingling, dizziness, bronchoconstriction, nausea, heart block, orthostatic hypotension	Most hypertensive emergencies except acute heart failure
Esmolol hydrochloride	250–500 mcg/kg/minute IV bolus, then 50–100 mcg/kg/minute by infusion; may repeat bolus after 5 minutes or increase infusion to 300 mcg/minute	1–2 minutes	10–30 minutes	Hypotension, nausea, asthma, first-degree heart block, heart failure	Aortic dissection, perioperative
Phentolamine	5–15 mg IV bolus	1–2 minutes	10–30 minutes	Tachycardia flushing, headache	Catecholamine excess

IM, intramuscular; IV, intravenous.
[a]These doses may vary from those in the Physicians' Desk Reference (51st ed.).
[b]Hypotension may occur with all agents.
[c]Requires special delivery system.
Reproduced from Saseen JJ, Carter BL. Hypertension. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 212, with permission.



Patient Encounter 3

DW, a 78-year-old Caucasian man, presents to the emergency room with complaints of a headache persisting over the last 3 days. Repeated blood pressure measurements average 200/110 mm Hg. He reports no other symptoms and physical examination and laboratory tests are unremarkable as is his past medical history with the exception of hypertension diagnosed in his early 60s. DW reports that he is struggling on a fixed retirement income with no prescription coverage and takes "what I can afford." Blood pressure medications are carvedilol 25 mg twice daily, amlodipine 10 mg once daily, torsemide (Demadex®) 10 mg once daily, and valsartan 320 mg once daily.

- What type of hypertensive crisis is DW experiencing?
- What are likely causes of DW's loss of blood pressure control?
- Create a care plan for DW's hypertensive crisis. This should include (1) acute goals of therapy, (2) a patient-specific therapeutic plan to achieve goals, and (3) a plan for appropriate outpatient follow-up including recommendations for changes, if any, to current medications.

TABLE 2–7. Treatment of Chronic Hypertension in Pregnancy[2]

Agent	Comments
Methyldopa	Preferred first-line therapy on the basis of long-term follow-up studies supporting safety after exposure in utero. Surveillance data do not support an association between drug and congenital defects when the mother took the drug early in the first trimester.
Labetalol	Increasingly preferred to methyldopa because of reduced side effects. The agent does not seem to pose a risk to the fetus, except possibly in the first trimester.
β-Blockers	Generally acceptable on the basis of limited data. Reports of intrauterine growth restriction with atenolol in the first and second trimesters.
Clonidine	Limited data; no association between drug and congenital defects when the mother took the drug early in the first trimester, but number of exposures is small.
Calcium antagonists	Limited data; nifedipine in the first trimester was not associated with increased rates of major birth defects, but animal data were associated with fetal hypoxemia and acidosis. This agent should probably be limited to mothers with severe hypertension.
Diuretics	Not first-line agents; probably safe; available data suggest that throughout gestation a diuretic is not associated with an increased risk of major fetal anomalies or adverse fetal-neonatal events.
Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists	Contraindicated; reported fetal toxicity and death.

While the treatment approach of hypertension in minority populations is similar, special consideration should be paid to socioeconomic and lifestyle factors that may be important barriers to blood pressure control. In addition, in patients of African origin, diminished blood pressure responses have been seen with ACE inhibitors and ARBs compared to diuretics or calcium channel blockers.[2] Hypertension in pregnancy is a major cause of maternal, fetal, and neonatal morbidity and mortality. There are many categories of hypertension in pregnancy; however, preexisting hypertension and preeclampsia are treated differently. The therapeutic selection of an oral antihypertensive agent (Table 2–7) in a pregnant patient with chronic hypertension is determined with regard to fetal safety. Therapeutic options for acute severe hypertension in pre-eclampsia may be reviewed in JNC 7.[2]

Similar to the JNC 7 criteria (which has four stages for blood pressure classification in adults), the measurement of three or more blood pressures in children and adolescents are compared to tables listing the 90th, 95th, and 99th percentile blood pressures based on age, height, and gender that classify blood pressure as normal, prehypertension, and stage 1 and stage 2 hypertension (Table 2–1).[70] The prevalence of hypertension in adolescent populations is increasing and is associated with obesity, sedentary lifestyle, or a positive family history, which increases the risk of cardiovascular disease. The clinician should be aware that secondary causes are common in adolescent hypertension and the identification and aggressive modification of risk factors with nonpharmacologic and pharmacologic interventions is paramount for risk reduction of target organ damage. The 2004 National High Blood Pressure Education Program (NHBPEP) Working Group Report on Hypertension in Children and Adolescents has recommendations to modify and treat risk factors.[70] The Nelson Textbook of Pediatrics is also recommended for a comprehensive review of treatment of congenital and pediatric hypertension.[71]

PATIENT CARE AND MONITORING

⓾ *The frequency of follow-up visits for patients with hypertension will vary based on individual cases, but will be influenced by severity of hypertension, comorbidities, and choice of agent selected. However, generally speaking, assessment of response to medications may be prudent at 1-month intervals.*[2] *For patients with stage 2 hypertension or those with comorbidities (e.g., diabetes, vascular disease, CHF, or CKD) shorter time frames of 2 weeks or less may be more appropriate.*[51] Annual or semiannual monitoring for changes in serum biochemistries such as serum creatinine or potassium are recommended.[2] However, for patients with CHF, CKD, or diabetes, more frequent monitoring will be necessary to adequately control comorbid conditions. Another aspect to monitoring relates to the importance of medication adherence. Confirmation of continued use of antihypertensive medications should be considered in the routine monitoring of patients on numerous medications for hypertension. Evaluation of side effects, lab abnormalities, and/or progression to target organ damage should also be considered at appropriate intervals. Given the asymptomatic nature of hypertension, patient motivation to adhere to prescribed medications becomes a key tool in controlling hypertension.[2]

Given the chronic nature of hypertension, parsimony of medication regimens is a virtue of a good therapeutic plan. Minimizing the number of medications a patient is required to take has the potential to enhance adherence and mitigate cost. Often, control of blood pressure is achieved by use of two or even three or more antihypertensives.[20,72] Many combination products contain a diuretic as one of their active components. However, combination therapy may limit the ability of the clinician to titrate the dose of a specific agent. As such, the number of medications ("pill count") may often be reduced through use of combination products. This inherently simplifies the number of medications and co-pays a patient may have to endure to achieve effective blood pressure control. These practicalities, although obvious, go a long way to optimize compliance, another challenge to maximizing therapy effectiveness.



Patient Care and Monitoring

1. Measure patient blood pressure twice, at least 1 minute apart in a sitting position, and then average the readings to determine if blood pressure is adequately controlled.
2. Conduct a medical history. Does the patient have any compelling indications? Is the patient pregnant?
3. Conduct a medication history (prescription, over-the-counter, and dietary supplements) to determine conditions or causes of hypertension. Does the patient take any medications, supplements, herbal products, or foods that may elevate SBP or DBP? Does the patient have drug allergies?
4. Review available laboratory tests to examine electrolyte balance and renal function.
5. Discuss lifestyle modifications that may reduce blood pressure with the patient. Determine what non-pharmacologic approaches might be or have been helpful to the patient.
6. Evaluate the patient if pharmacologic treatment has reached the target blood pressure goal. If the patient is at the goal, skip to step 8.
7. If patient is not at goal BP, assess efficacy, safety, and compliance of the antihypertensive regimen to determine if a dose increase or additional antihypertensive agent (step 8) is needed to achieve goal blood pressure.
8. Select an agent to minimize adverse drug reactions and interactions when additional drug therapy is needed. Does the patient have prescription coverage or is the recommended agent in the formulary?
9. Open a dialogue to address patient concerns about hypertension and management of the condition.
10. Provide a plan to assess the effectiveness and safety of therapy. Follow-up in 2 to 4 weeks if the medication regimen has changed, otherwise semi-annual or annual clinic visits to assess blood pressure, electrolyte balance, and renal function should occur.

OUTCOME EVALUATION

- Short-term goals are to safely achieve reduction in blood pressure through the iterative process of employing drug therapy, along with non-drug therapy or lifestyle changes.
- Lifestyle changes should address other risk factors for cardiovascular disease including obesity, physical inactivity, insulin resistance, dyslipidemia, smoking cessation, and others.
- Monitoring for efficacy, adverse events, and adherence to therapy is key to achieving the long-term goals of reducing the risk of morbidity and mortality associated with cardiovascular disease.

ABBREVIATIONS

ACC/AHA:	American College of Cardiology/American Heart Association
ACE:	angiotensin-converting enzyme
A-HeFT:	African-American Heart Failure trial
AIRE:	Acute Infarction Ramipril Efficacy Study
ALLHAT:	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
AMI:	acute myocardial infarction
ANBP2:	Australian-New Zealand Blood Pressure-2 study
ARB:	angiotensin receptor blocker
ASCOT-BPLA:	Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm study

AT1:	Angiotensin-1
AT2:	Angiotensin-2
BB:	beta-blocker
BHAT:	Beta-Blocker Heart Attack Trial
BP:	blood pressure
bpm:	beats per minute
CAGE:	Chymostatin-sensitive II-generating enzyme
CAPRICORN:	Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction Trial
Captopril Trial:	Collaborative Study Captopril Trial ("The Effect of Angiotensin-Converting Enzyme Inhibition on Diabetic Nephropathy")
CCBA:	calcium channel blocking agents
CHARM:	Candesartan in Heart Failure Assessment of Reduction in Morbidity and Mortality Trial
CHF:	congestive heart failure, but the latest recommendations use HF for heart failure
CKD:	chronic kidney disease
CO:	cardiac output
COPERNICUS:	Carvedilol Prospective Randomized Cumulative Survival Trial
CVD:	cardiovascular disease
DASH:	Dietary Approaches to Stop Hypertension
DBP:	diastolic blood pressure
EPHESUS:	Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
EUROPA:	European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease Trial
FDA:	Food and Drug Administration
GFR:	glomerular filtration rate
HOPE:	Heart Outcomes Prevention Evaluation Study
IDNT:	Irbesartan Diabetic Nephropathy Trial
IM:	intramuscular
INVEST:	International Verapamil-Trandolapril Study
IRMA-II:	Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria study
ISA:	intrinsic sympathomimetic activity
IV:	intravenous
JNC 7:	Joint National Committee Seventh Report
LIFE:	Losartan Intervention For Endpoint reduction in hypertension study
MERIT-HF:	Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure
MI:	myocardial infarction
NHBPEP:	National High Blood Pressure Education Program
NIDDM:	noninsulin-dependent diabetes mellitus
NSAID:	non-steroidal anti-inflammatory drug
PR:	peripheral resistance
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
RAAS:	renin-angiotensin-aldosterone system
RALES:	Randomized Aldactone Evaluation Study
RENAAL:	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study
SAVE:	Survival and Ventricular Enlargement Trial
SBP:	systolic blood pressure
SCORE:	Systematic Coronary Risk Evaluation
SHEP:	Systolic Hypertension in the Elderly
SNS:	sympathetic nervous system
SOLVD:	Studies of Left Ventricular Dysfunction
TRACE:	Trandolapril Cardiac Evaluation
UKPDS:	UK Prospective Diabetes Study
VALUE:	Valsartan Antihypertensive Long-term Use Evaluation
ValHEFT:	Veterans Affairs Cooperative I study

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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3 Heart Failure

Orly Vardeny and Tien M. H. Ng



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Differentiate between the common underlying etiologies of heart failure, including ischemic, non-ischemic, and idiopathic causes.
2. Describe the pathophysiology of heart failure as it relates to neurohormonal activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system.
3. Identify signs and symptoms of heart failure and classify a given patient by the New York Heart Association Functional Classification and American College of Cardiology/American Heart Association Heart Failure Staging.
4. Describe the goals of therapy for a patient with acute or chronic heart failure.
5. Develop a nonpharmacologic treatment plan which includes patient education for managing heart failure.
6. Develop a specific evidence-based pharmacologic treatment plan for a patient with acute or chronic heart failure based on disease severity and symptoms.
7. Formulate a monitoring plan for the nonpharmacologic and pharmacologic treatment of a patient with heart failure.

Key Concepts

❶ The most common causes of heart failure are coronary artery disease (CAD), hypertension, and dilated cardiomyopathy.

❷ Development and progression of heart failure involves activation of neurohormonal pathways, including the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS).

❸ The clinician must identify potential reversible causes of heart failure exacerbations including prescription and nonprescription drug therapies, dietary indiscretions, and medication non-adherence.

❹ Symptoms of left-sided heart failure include dyspnea, orthopnea, and paroxysmal nocturnal dyspnea (PND), whereas symptoms of right-sided heart failure include fluid retention, gastrointestinal bloating, and fatigue.

❺ Therapeutic goals focus on alleviating symptoms, slowing or preventing disease progression, maintaining quality of life, and improving patient survival.

❻ Nonpharmacologic treatment involves dietary modifications such as sodium and fluid restriction, risk factor reduction including smoking cessation, timely immunizations, and supervised regular physical activity.

❼ Diuretics are used for relief of acute symptoms of congestion and maintenance of euvolemia.

❽ Agents with proven benefits in improving symptoms, slowing disease progression, and improving survival in chronic heart failure target neurohormonal blockade; these include angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), β-adrenergic blockers, and aldosterone antagonists.

❾ Combination therapy with hydralazine and isosorbide dinitrate is an appropriate substitute for angiotensin II antagonism in those unable to tolerate an ACE inhibitor or ARB, or as add-on therapy in African-Americans.

❿ Treatment of acute heart failure targets relief of congestion and optimization of cardiac output utilizing oral or intravenous diuretics, intravenous vasodilators, and when appropriate, inotropes.

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Heart failure (HF) is defined as the inadequate ability of the heart to pump enough blood to meet the blood flow and metabolic demands of the body.[1] High-output HF is characterized by an inordinate increase in the body's metabolic demands, which outpaces an increase in **cardiac output** (CO) of a generally normally functioning heart. More commonly, HF is a result of low CO secondary to impaired cardiac function. The term "heart failure" will refer to low-output HF for purposes of this chapter.

Heart failure is a clinical syndrome characterized by a history of specific signs and symptoms related to congestion and hypoperfusion. As HF can occur in the presence or absence of fluid overload, the term "heart failure" is preferred over the former term "congestive heart failure." Heart failure results from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.[1] Many disorders such as those of the pericardium, epicardium, endocardium, or great vessels may lead to HF, but most patients develop symptoms due to impairment in left ventricular (LV) myocardial function.

The phrase "acute heart failure" (AHF) is used to signify either an acute decompensation of a patient with a history of chronic heart failure or to refer to a patient presenting with new-onset HF symptoms. Terms commonly associated with HF, such as cardiomyopathy and LV dysfunction, are not equivalent to HF but describe possible structural or functional reasons for the development of HF.

EPIDEMIOLOGY AND ETIOLOGY

Epidemiology

Heart failure is a major public health concern affecting approximately five million people in the United States. An additional 550,000 new cases are diagnosed each year. Heart failure manifests most commonly in adults over the age of 60.[2] The growing prevalence of HF corresponds to: (1) better treatment of patients with acute myocardial infarctions (MIs) who will survive to develop HF later in life, and (2) the increasing proportion of older adults due to the aging "baby boomer" population. The relative incidence of HF is lower in women compared to men, but there is a greater prevalence in women overall due to their longer life expectancy. Acute heart failure accounts for 12 to 15 million office visits per year and 6.5 million hospitalizations annually.[2] According to national registries, patients presenting with AHF are older (mean age 75 years) and have numerous comorbidities such as CAD, renal insufficiency, and diabetes.[2]

Total estimated direct and indirect costs for managing both chronic and acute HF in the United States for 2005 was approximately $27.9 billion. Medications account for approximately 10% of that cost.[3] Heart failure is the most common hospital discharge diagnosis for Medicare patients and is the most costly diagnosis in this population.

The prognosis for patients hospitalized for AHF remains poor. Average hospital length of stay is estimated to be between 4 to 6 days, a number which has remained constant over the past decade.[3] The in-hospital mortality rate has been estimated at approximately 4%, but ranges from 2% to 20% depending on the report.[4] In-hospital mortality increases to an average of 10.6% in patients requiring an intensive care unit admission. Readmissions are also high, with up to 30% to 60% of patients readmitted within 6 months of their initial discharge date.[4] The 5-year mortality rate for chronic HF remains greater than 50%. Survival strongly correlates with severity of symptoms and functional capacity. Sudden cardiac death is the most common cause of death, occurring in approximately 40% of patients with HF.[2] Although therapies targeting the up-regulated neurohormonal response contributing to the pathophysiology of HF have clearly impacted morbidity and mortality, long-term survival remains low.

Etiology

Heart failure is the eventual outcome of numerous cardiac diseases or disorders (Table 3–1).[5] Heart failure can be classified by the primary underlying etiology as ischemic or non-ischemic, with 70% of HF related to ischemia. ❶ *The most common causes of HF are CAD, hypertension, and dilated cardiomyopathy*. Coronary artery disease resulting in an acute MI and reduced ventricular function is a common presenting history. Non-ischemic etiologies include hypertension, viral illness, thyroid disease, excessive alcohol use, illicit drug use, pregnancy-related heart disease, familial congenital disease, and valvular disorders such as mitral or tricuspid valve regurgitation or stenosis.

TABLE 3–1. Causes of Heart Failure

Systolic Dysfunction (Decreased Contractility)
- Reduction in muscle mass (e.g., myocardial infarction)
- Dilated cardiomyopathies
- Ventricular hypertrophy
  - Pressure overload (e.g., systemic or pulmonary hypertension, aortic or pulmonic valve stenosis)
  - Volume overload (e.g., valvular regurgitation, shunts, high-output states)

Diastolic Dysfunction (Restriction in Ventricular Filling)
- Increased ventricular stiffness
- Ventricular hypertrophy (e.g., hypertrophic cardiomyopathy, other examples above)
- Infiltrative myocardial diseases (e.g., amyloidosis, sarcoidosis, endomyocardial fibrosis)
- Myocardial ischemia and infarction
- Mitral or tricuspid valve stenosis
- Pericardial disease (e.g., pericarditis, pericardial tamponade)

From Parker RB, Patterson JH, Johnson JA. Heart failure. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 220, with permission.

Heart failure can also be classified based on the main component of the cardiac cycle leading to impaired ventricular function. A normal cardiac cycle is dependent on two components: systole and diastole. Expulsion of blood occurs during systole or contraction of the ventricles, while diastole relates to filling of the ventricles. **Ejection fraction** (EF) is the fraction of the volume present at the end of diastole that is pushed into the aorta during systole. Abnormal ventricular filling (**diastolic dysfunction**) and/or ventricular contraction (**systolic dysfunction**) can result in a similar decrease in CO and cause HF symptoms. Most HF is associated with evidence of LV systolic dysfunction (evidenced by a reduced EF) with or without a component of diastolic dysfunction, which coexists in up to two-thirds of patients. Isolated diastolic dysfunction, occurring in approximately one-third of HF patients, is diagnosed when a patient exhibits impaired ventricular filling with or without accompanying HF symptoms but normal systolic function. Long-standing hypertension is the leading cause of diastolic dysfunction. Ventricular dysfunction can also involve either the left or right chamber of the heart or both. This has implications for symptomatology, as right-sided failure manifests as systemic congestion whereas left-sided failure results in pulmonary symptoms.

PATHOPHYSIOLOGY

A basic grasp of normal cardiac function sets the stage for understanding the pathophysiologic processes leading to HF and selecting appropriate therapy for HF. Cardiac output is defined as the volume of blood ejected per unit of time (liters per minute) and is a major determinant of tissue perfusion. Cardiac output is the product of heart rate (HR) and stroke volume (SV): $CO = HR \times SV$. The following describes how each parameter relates to CO.

Heart rate is controlled by the autonomic nervous system, where sympathetic stimulation of β-adrenergic receptors results in an increase in HR and CO. Stroke volume is the volume of blood ejected with each systole. Stroke volume is determined by factors regulating preload, afterload, and contractility. **Preload** is a measure of ventricular filling pressure, or the volume of blood in the left ventricle (also known as LV end-diastolic volume). Preload is determined by venous return as well as atrial contraction. An increase in venous return to the left ventricle results in the stretch of cardiomyocyte sarcomeres (or contractile units) and a subsequent increase in the number of cross-bridges formed between actin and myosin myofilaments. This results in an increase in the force of contraction based on the **Frank-Starling mechanism**.[6] **Afterload** is the resistance to ventricular ejection and is regulated by ejection impedence, wall tension, and regional wall geometry. Thus, elevated aortic and systemic pressures result in an increase in afterload and reduced SV. Contractility, also known as the **inotropic** state of the heart, is an intrinsic property of cardiac muscle incorporating fiber shortening and tension development. Contractility is influenced to a large degree by adrenergic nerve activity and circulating catecholamines such as epinephrine and norepinephrine.

Compensatory Mechanisms

In the setting of a sustained loss of myocardium, a number of mechanisms aid the heart when faced with an increased hemodynamic burden and reduced CO. They include the following: the Frank-Starling mechanism, tachycardia and increased afterload, and cardiac hypertrophy and remodeling (Table 3–2).[5,7]

Preload and the Frank-Starling Mechanism

In the setting of a sudden decrease in CO, the natural response of the body is to decrease blood flow to the periphery in order to maintain perfusion to the vital organs such as the heart and brain. Therefore, renal perfusion is compromised due to both the decreased CO, as well as shunting of blood away from peripheral tissues. This results in activation of the renin-angiotensin-aldosterone system (RAAS). The decrease in renal perfusion is sensed by the juxtaglomerular cells of the kidneys leading to the release of renin and initiation of the cascade for production of angiotensin II. Angiotensin II stimulates the synthesis and release of aldosterone, which stimulates sodium and water retention in an attempt to increase intravascular volume and hence preload. In a healthy heart, a large increase in CO is usually accomplished with just a small change in preload. However, in a failing heart, alterations in the contractile filaments reduce the ability of cardiomyocytes to adapt to increases in preload. Thus, an increase in preload actually impairs contractile function in the failing heart and results in a further decrease in CO.

Tachycardia and Increased Afterload

Another mechanism to maintain CO when contractility is low is to increase heart rate. This is achieved through sympathetic nervous system (SNS) activation and the agonist effect of norepinephrine on β-adrenergic receptors in the heart. Sympathetic activation also enhances contractility by increasing cytosolic calcium concentrations. SV is relatively fixed in HF, thus HR becomes the major determinant of CO. Although this mechanism increases CO acutely, the **chronotropic** and inotropic responses to sympathetic activation increase myocardial oxygen demand, worsen underlying ischemia, contribute to proarrhythmia, and further impair both systolic and diastolic function.

Activation of both the RAAS and the SNS also contribute to vasoconstriction in an attempt to redistribute blood flow from peripheral organs such as the kidneys to coronary and cerebral circulation.[7] However, arterial vasoconstriction leads to impaired forward ejection of blood from the heart due to an increase in afterload. This results in a decrease in CO and continued stimulation of compensatory responses, creating a vicious cycle of neurohormonal activation.

TABLE 3–2. Beneficial and Detrimental Effects of the Compensatory Responses in Heart Failure

Compensatory Response	Beneficial Effects of Compensation	Detrimental Effects of Compensation
Increased preload (through sodium and water retention)	Optimize stroke volume via Frank-Starling mechanism	Pulmonary and systemic congestion and edema formation Increased MVO_2
Vasoconstriction	Maintain blood pressure and perfusion in the face of reduced cardiac output	Increased MVO_2 Increased afterload decreases stroke volume and further activates the compensatory responses
Tachycardia and increased contractility (due to SNS activation)	Increase cardiac output	Increased MVO_2 Shortened diastolic filling time β_1-Receptor down-regulation, decreased receptor sensitivity Precipitation of ventricular arrhythmias Increased risk of myocardial cell death
Ventricular hypertrophy and remodeling	Maintains cardiac output Reduces myocardial wall stress Decreases MVO_2	Diastolic dysfunction Systolic dysfunction Increased risk of myocardial cell death Increased risk of myocardial ischemia Increased arrhythmia risk

MVO_2, myocardial oxygen consumption; SNS, sympathetic nervous system.

Cardiac Hypertrophy and Remodeling

Ventricular hypertrophy, an adaptive increase in ventricular muscle mass due to growth of existing myocytes, occurs in response to an increased hemodynamic burden such as volume or pressure overload.[5] Hypertrophy can be concentric or eccentric. Concentric hypertrophy occurs in response to pressure overload such as in long-standing hypertension or pulmonary hypertension, whereas eccentric hypertrophy occurs after an acute myocardial infarction. Eccentric hypertrophy involves an increase in myoctye size in a segmental fashion, as opposed to the global hypertrophy occurring in concentric hypertrophy. Although hypertrophy helps to reduce cardiac wall stress in the short term, continued hypertrophy accelerates myocyte cell death through an overall increase in myocardial oxygen demand.

Cardiac remodeling occurs as a compensatory adaptation to a change in wall stress and is largely regulated by neurohormonal activation, with angiotensin II and aldosterone being key stimuli.[7] The process entails changes in myocardial and extracellular matrix composition and function which results in both structural and functional alterations to the heart. In HF, the changes in cardiac size, shape, and composition are pathologic and detrimental to heart function. In addition to myocyte size and extracellular matrix changes, heart geometry shifts from an elliptical to a less efficient spherical shape. Even after remodeling occurs, the heart can maintain CO for many years. However, heart function will continue to deteriorate until progression to clinical HF. The timeline for remodeling varies depending on the cardiac insult. For example, in the setting of an acute MI, remodeling starts within a few days.[5] Chronic remodeling, however, is what progressively worsens HF and therefore is a major target of drug therapy.

Models of Heart Failure

Earlier models of HF focused on the hemodynamic consequences of volume overload from excess sodium and water retention, decreased CO secondary to impaired ventricular function, and vasoconstriction.[8] Congestion was a result of fluid backup due to inadequate pump function. Therefore, drug therapy was focused on relieving excess volume using diuretics, improving pump function with inotropic agents, and alleviating vasoconstriction with vasodilators. Although these agents improved HF symptoms, they did little to slow the progressive decline in cardiac function or to improve survival.

Neurohormonal Model

❷ *Development and progression of HF involves activation of neurohormonal pathways including the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS).* This model begins with an initial precipitating event or myocardial injury resulting in a decline in CO, followed by the compensatory mechanisms previously discussed. This includes activation of neurohormonal pathways with pathologic consequences including the RAAS, SNS, endothelin and vasopressin, and those with counterregulatory properties such as the natriuretic peptides and nitric oxide. This model currently guides our therapy for chronic HF in terms of preventing disease progression and mortality.

Angiotensin II

Angiotensin II is a key neurohormone in the pathophysiology of HF. The vasoconstrictive effects of angiotensin II lead to an increase in systemic vascular resistance (SVR) and blood pressure. The resulting increase in afterload contributes to an increase in myocardial oxygen demand and opposes the desired increase in SV. In the kidneys, angiotensin II enhances renal function acutely by raising intraglomerular pressure through constriction of the efferent arterioles.[6] However, the increase in glomerular filtration pressure may be offset by a reduction in renal perfusion secondary to angiotensin II's influence over the release of other vasoactive neurohormones such as vasopressin and endothelin-1 (ET-1). Angiotensin II also potentiates the release of aldosterone from the adrenal glands and norepinephrine from adrenergic nerve terminals. Additionally, angiotensin II induces vascular hypertrophy and remodeling in both cardiac and renal cells. Clinical studies show that blocking the effects of the RAAS in HF is associated with improved cardiac function and prolonged survival. Thus, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are the cornerstone of HF treatment.

Aldosterone

Aldosterone's contribution to HF pathophysiology is also multifaceted. Renally, aldosterone causes sodium and water retention in an attempt to enhance intravascular volume and CO. This adaptive mechanism has deleterious consequences since excessive sodium and water retention worsen the already elevated ventricular filling pressures. Aldosterone also contributes to electrolyte abnormalities seen in HF patients. Hypokalemia and hypomagnesemia contribute to the increased risk of arrhythmias. In addition, evidence supports the role of aldosterone as an etiologic factor for myocardial fibrosis and cardiac remodeling.[6] Elevated aldosterone concentrations have been associated with more severe cardiac disease and a poorer prognosis in HF. Thus, aldosterone antagonism has become an important therapeutic target for improvement of long-term prognosis.

Norepinephrine

Norepinephrine is a classic marker for SNS activation. It plays an adaptive role in the failing heart by stimulating HR and myocardial contractility to augment CO and by producing vasoconstriction to maintain organ perfusion. However, excess levels are directly cardiotoxic. In addition, sympathetic activation increases the risk for arrhythmias, ischemia, and myocyte cell death through increased myocardial workload and accelerated **apoptosis** (i.e., programmed cell death). Ventricular hypertrophy and remodeling are also influenced by norepinephrine.[8]

Plasma norepinephrine concentrations are elevated proportionally to HF severity, with highest levels correlating to the poorest prognosis. Several mechanisms relate to diminished responsiveness to catecholamines (e.g., norepinephrine) as cardiac function declines.[6] Adrenergic receptor desensitization and **down-regulation** (decreased receptor number and post-receptor responses and signaling) occurs under sustained sympathetic stimulation. The desensitization contributes to further release of norepinephrine.[5] β-Adrenergic blocking agents, although intrinsically negatively inotropic, have become an essential therapy for chronic HF.

Endothelin

Endothelin-1, one of the most potent physiologic vasoconstrictors, is an important contributor to HF pathophysiology.[9] Endothelin-1 binds to two G-protein coupled receptors, endothelin-A (ET-A) and endothelin-B (ET-B). Endothelin-A receptors mediate vasoconstriction and are prevalent in vascular smooth muscle and cardiac cells. Endothelin-B receptors are expressed on the endothelium and in vascular smooth muscle, and receptor stimulation mediates vasodilation. Levels of ET-1 correlate with HF functional class and mortality.

Arginine Vasopressin

Higher vasopressin concentrations are linked to dilutional hyponatremia and a poor prognosis in HF. Vasopressin exerts its effects through vasopressin type 1a (V_{1a}) and vasopressin type 2 (V_2) receptors.[5,7] Vasopressin type 1a stimulation leads to vasoconstriction, while actions on the V_2 receptor cause free water retention through aquaporin channels in the collecting duct. Vasopressin increases preload, afterload, and myocardial oxygen demand in the failing heart.

Counterregulatory Hormones (Natriuretic Peptides, Bradykinin, and Nitric Oxide)

Atrial natriuretic peptide (ANP) and B-type (formerly brain) natriuretic peptide (BNP) are endogenous neurohormones that regulate sodium and water balance. Natriuretic peptides decrease sodium reabsorption in the collecting duct of the kidney.[10] Natriuretic peptides also cause vasodilation through the cyclic guanosine monophosphate (cGMP) pathway. Atrial natriuretic peptide is synthesized and stored in the atria, while BNP is produced mainly in the ventricles. Release of ANP and BNP is stimulated by increased cardiac chamber wall stretch usually indicative of volume load. Higher concentrations of natriuretic peptides correlate with a more severe HF functional class and prognosis. BNP is sensitive to volume status; thus, the plasma concentration can be used as a diagnostic marker in HF.[10]

Bradykinin is part of the kallikrein-kinin system, which shares a link to the RAAS through angiotensin-converting enzyme. Bradykinin is a vasodilatory peptide that is released in response to a variety of stimuli, including neurohormonal and inflammatory mediators known to be activated in HF.[9] As a

consequence, bradykinin levels are elevated in HF patients and thought to partially antagonize the vasoconstrictive peptides.

Nitric oxide, a vasodilatory hormone released by the endothelium, is found in higher concentrations in HF patients and provides two main benefits in HF: vasodilation and neurohormonal antagonism of endothelin.[9] Nitric oxide's production is affected by the enzyme inducible nitric oxide synthetase (iNOS), which is up-regulated in the setting of HF, likely due to increased levels of angiotensin II, norepinephrine, and multiple cytokines. In HF, the physiologic response to nitric oxide appears to be blunted, which contributes to the imbalance between vasoconstriction and vasodilation.

Cardiorenal Model

There is growing evidence of a link between renal disease and HF.[8] Renal insufficiency is present in one-third of HF patients and is associated with a worse prognosis. In hospitalized HF patients, the presence of renal insufficiency is associated with longer lengths of stay, increased in-hospital morbidity and mortality, and detrimental neurohormonal alterations. Conversely, renal dysfunction is a common complication of HF or results from its treatment. Renal failure is also a common cause for HF decompensation.

Proinflammatory Cytokines

Inflammatory cytokines have been implicated in the pathophysiology of HF.[9] Several proinflammatory (e.g., tumor necrosis factor-α [TNF-α], interleukin-1, interleukin-6, and interferon-γ) and anti-inflammatory cytokines (e.g., interleukin-10) are overexpressed in the failing heart. The most is known about TNF-α, a pleiotrophic cytokine that acts as a negative inotrope, stimulates cardiac cell apoptosis, uncouples β-adrenergic receptors from adenylyl cyclase, and is related to **cardiac cachexia**. The exact role of cytokines and inflammation in HF pathophysiology continues to be studied.

Precipitating and Exacerbating Factors in Heart Failure

Heart failure patients exist in one of two clinical states. When a patient's volume status and symptoms are stable, their HF condition is said to be "compensated." In situations of volume overload or other worsening symptoms, the patient is considered "decompensated." Acute decompensation can be precipitated by numerous etiologies that can be grouped into cardiac, metabolic, or patient-related causes (Table 3–3).[5]

❸ *The clinician must identify potential reversible causes of HF exacerbations including prescription and non-prescription drug therapies, dietary indiscretions, and medication non-adherence. Non-adherence with dietary restrictions or chronic HF medications deserves special attention, as it is the most common cause of acute decompensation and can be prevented. As such, an accurate history regarding diet, food choices, and the patient's knowledge regarding sodium and fluid intake (including alcohol) is valuable in assessing dietary indiscretion.* Non-adherence with medical recommendations such as laboratory and other appointment follow-up can also be indicative of non-adherence with diet or medications.

TABLE 3–3. Exacerbating or Precipitating Factors in Heart Failure

Cardiac	Metabolic	Patient-Related
Acute ischemia	Anemia	Dietary/fluid non-adherence
Arrhythmia	Hyperthyroidism/ thyrotoxicosis	HF therapy non-adherence
Endocarditis	Infection	Use of cardiotoxins (cocaine, chronic alcohol, amphetamines, sympathomimetics)
Myocarditis	Pregnancy	Offending medications (NSAIDs, COX-2 inhibitors, steroids, lithium, β-blockers, calcium channel blockers, anti-arrhythmics, alcohol, thiazolidinediones)
Pulmonary embolus	Worsening renal function	
Uncontrolled hypertension		
Valvular disorders		

COX-2, cyclooxygenase-2; HF, heart failure; NSAID, non-steroidal anti-inflammatory drug.



Patient Encounter, Part 1

BE is a 62-year-old female with a history of known coronary artery disease and type 2 diabetes mellitus who presents for a belated follow-up clinic visit (her last visit was 2 years ago). She states that she used to be able to walk over one-half mile (0.8 km) and two flights of stairs before experiencing chest pain and becoming short of breath. Since her last visit, she has had increasing symptoms and has now progressed to shortness of breath (SOB) with walking only half a block and doing chores around the house. She also notes her ankles are always swollen and her shoes no longer fit, therefore she only wears slippers. Additionally, her appetite is decreased, and she often feels bloated. She also feels full after eating only a few bites of each meal.

- What information is suggestive of a diagnosis of heart failure?
- What additional information do you need to know before creating a treatment plan for BE?

CLINICAL PRESENTATION AND DIAGNOSIS OF CHRONIC HEART FAILURE

In low-output HF, symptoms are generally related to either congestion behind the failing ventricle(s), or hypoperfusion (decreased tissue blood supply), or both. Congestion is the most common symptom in HF, followed by symptoms related to decreased perfusion to peripheral tissues including decreased renal output, mental confusion, and cold extremities. Activation of the compensatory mechanisms occurs in an effort to increase CO and preserve blood flow to vital organs. However, the increase in preload and afterload in the setting of a failing ventricle leads to elevated filling pressures and further impairment of cardiac function, which manifests as systemic and/or pulmonary congestion. It is important to remember that congestion develops behind the failing ventricle, caused by the inability of that ventricle to eject the blood that it receives from the atria and venous return. As such, signs and symptoms may be classified as left-sided or right-sided. ❹ *Symptoms of left-sided HF include dyspnea,* ***orthopnea****, and paroxysmal nocturnal dyspnea (PND), whereas symptoms of right-sided HF include fluid retention, gastrointestinal bloating, and fatigue. Although most patients initially have left ventricular failure (LVF; pulmonary congestion), the ventricles share a septal wall, and because LVF increases the workload of the right ventricle, both ventricles eventually fail and contribute to the HF syndrome. Because of the complex nature of this syndrome, it has become exceedingly more difficult to attribute a specific sign or symptom as caused by either right ventricular failure (RVF; systemic congestion) or LVF. Therefore, the numerous signs and symptoms associated with this disorder are collectively attributed to HF rather than to dysfunction of a specific ventricle.*

General Signs and Symptoms

Hypoperfusion of skeletal muscles leads to fatigue, weakness, and exercise intolerance. Decreased perfusion of the central nervous system (CNS) is related to confusion, hallucinations, insomnia, and lethargy. Peripheral vasoconstriction due to SNS activity causes pallor, cool extremities, and cyanosis of the digits. Tachycardia is also common in these patients and may reflect increased SNS activity. Patients will often exhibit **polyuria** and **nocturia**. Polyuria is a result of increased release of natriuretic peptides caused by volume overload. Nocturia occurs due to increased renal perfusion as a consequence of reduced SNS renal vasoconstrictive effects at night. In chronic severe HF, unintentional weight loss can occur which leads to a syndrome of cardiac cachexia. This results from several factors, including loss of appetite, malabsorption due to gastrointestinal edema, elevated metabolic rate, and elevated levels of proinflammatory cytokines.



Clinical Presentation and Diagnosis of Heart Failure

General

Patient presentation may range from asymptomatic to cardiogenic shock.

Symptoms

- Dyspnea, particularly on exertion
- Orthopnea
- Shortness of breath (SOB)
- Paroxysmal nocturnal dyspnea
- Exercise intolerance
- Tachypnea
- Cough
- Fatigue
- Nocturia and/or polyuria
- Hemoptysis
- Abdominal pain
- Anorexia
- Nausea
- Bloating
- Ascites
- Mental status changes
- Weakness
- Lethargy

Signs

- Pulmonary rales
- Pulmonary edema
- S_3 gallop
- Pleural effusion
- **Cheyne-Stokes respiration**
- Tachycardia
- Cardiomegaly
- Peripheral edema (e.g., pedal edema, which is swelling of feet and ankles)
- Jugular venous distension (JVD)
- **Hepatojugular reflex** (HJR)
- Hepatomegaly
- Cyanosis of the digits
- Pallor or cool extremities

Laboratory Tests

- BNP greater than 100 pg/mL (greater than 100 ng/L) or N-terminal proBNP (NT-proBNP) greater than 300 pg/mL (greater than 300 ng/L or greater than 35.4 pmol/L)
- Electrocardiogram (ECG): May be normal or could show numerous abnormalities including acute ST-T–wave changes from myocardial ischemia, atrial fibrillation, bradycardia, and LV hypertrophy.
- Serum creatinine: May be increased owing to hypoperfusion; preexisting renal dysfunction can contribute to volume overload.
- Complete blood count: Useful to determine if heart failure is due to reduced oxygen-carrying capacity.
- Chest x-ray: Useful for detection of cardiac enlargement, pulmonary edema, and pleural effusions.
- Echocardiogram: Used to assess LV size, valve function, pericardial effusion, wall motion abnormalities, and ejection fraction.

Patients can experience a variety of symptoms related to buildup of fluid in the lungs. Dyspnea, or shortness of breath, can result from pulmonary congestion or systemic hypoperfusion due to LVF. Exertional dyspnea occurs when patients describe breathlessness induced by physical activity or a lower level of activity than previously known to cause breathlessness. Patients often state that activities such as stair climbing, carrying groceries, or walking a particular distance cause shortness of breath. Severity of HF is inversely proportional to the amount of activity required to produce dyspnea. In severe HF, dyspnea will be present even at rest.

Orthopnea is dyspnea that is positional. Orthopnea is present if a patient is unable to breathe while lying flat on a bed (i.e., in the recumbent position). It manifests within minutes of a patient lying down and is relieved immediately when the patient sits upright. Patients can relieve orthopnea by elevating their head and shoulders with pillows. The practitioner should inquire as to the number of pillows needed to prevent dyspnea as a marker of worsening HF. Paroxysmal nocturnal dyspnea occurs when patients awaken suddenly with a feeling of breathlessness and suffocation. Paroxysmal nocturnal dyspnea is caused by increased venous return and mobilization of interstitial fluid from the extremities, leading to alveolar edema and usually occurs within 1 to 4 hours of sleep. In contrast to orthopnea, PND is not relieved immediately by sitting upright and often takes up to 30 minutes for symptoms to subside.

Pulmonary congestion may also cause a non-productive cough that occurs at night or with exertion. Cheyne-Stokes respiration, or periodic breathing, is common in advanced HF. It is usually associated with low-output states and may be perceived by the patient as either severe dyspnea or transient cessation of breathing. In cases of pulmonary edema, the most severe form of pulmonary congestion, patients may produce a pink, frothy sputum and experience extreme breathlessness and anxiety due to feelings of suffocation and drowning. If not treated aggressively, patients can become cyanotic and acidotic. Severe pulmonary edema can progress to respiratory failure, necessitating mechanical ventilation.

Systemic venous congestion results mainly from right ventricular failure. A clinically validated assessment of the jugular venous pressure (JVP) is performed by examining the right internal jugular vein for distention or elevation of the pulsation while reclining at a 45 degree angle. A JVP more than 4 cm above the sternal angle is indicative of elevated right atrial pressure. Jugular venous pressure may be normal at rest, but if application of pressure to the abdomen can elicit a sustained elevation of JVP, this is defined as hepatojugular reflux (HJR). A positive finding of HJR indicates hepatic congestion and results from displacement of volume from the abdomen into the jugular vein because the right atrium is unable to accept this additional blood. Hepatic congestion can cause abnormalities in liver function, which can be evident in liver function tests and/or clotting times. Development of hepatomegaly occurs infrequently and is caused by long-term systemic venous congestion. Intestinal or abdominal congestion can also be present, but usually doesn't lead to characteristic signs unless overt ascites is evident. In advanced RVF, evidence of pulmonary hypertension may be present (e.g., right ventricular heave).

The most recognized finding of systemic congestion is peripheral edema. It usually occurs in dependent areas of the body, such as the ankles (pedal edema) for ambulatory patients, or the sacral region for bedridden patients. Weight gain often precedes signs of overt peripheral edema. Therefore, it is crucial for patients to weigh themselves daily even in the absence of symptoms to assess fluid status.

Patients may complain of swelling of their feet and ankles, which can extend up to their calves or thighs. Abdominal congestion may cause a bloated feeling, abdominal pain, early satiety, nausea, anorexia, and constipation. Often patients may have difficulty fitting into their shoes or pants due to edema.

Patient History

A thorough history is crucial to identify cardiac and non-cardiac disorders or behaviors that may lead to or accelerate the development of HF. Past medical history, family history, and social history are important for identifying comorbid illnesses that are risk factors for the development of HF or underlying etiologic factors. A complete medication history (including prescription and non-prescription drugs, herbal therapy, and vitamin supplements) should be obtained each time a patient is seen to evaluate adherence, to assess appropriateness of therapy, to eliminate drugs that may be harmful in HF (Table 3–4), and to determine additional monitoring requirements. For newly

TABLE 3–4. Drugs That May Precipitate or Exacerbate Heart Failure

Agents Causing Negative Inotropic Effect
Antiarrhythmics (e.g., disopyramide, flecainide, and others)
β-Blockers (e.g., propranolol, metoprolol, atenolol, and others)
Calcium channel blockers (e.g., verapamil and others)
Itraconazole
Terbinafine
Rosiglitazone
Cardiotoxic Agents
Doxorubicin
Daunomycin
Cyclophosphamide
Agents Causing Sodium and Water Retention
Non-steroidal anti-inflammatory drugs
COX-2 inhibitors
Glucocorticoids
Androgens
Estrogens
Salicylates (high-dose)
Sodium-containing drugs (e.g., carbenicillin disodium, ticarcillin disodium)
Thiazolidinediones (e.g., rosiglitazone, pioglitazone)

COX-2, cyclooxygenase-2.

diagnosed HF, previous use of chemotherapeutic agents as well as current or past use of alcohol and illicit drugs should be assessed. In addition, for patients with a known history of HF, questions related to symptomatology and exercise tolerance are essential for assessing any changes in clinical status that may warrant further evaluation or adjustment of the medication regimen.

Heart Failure Classification

There are two common systems for categorizing patients with HF. The New York Heart Association (NYHA) Functional Classification (FC) system is based on the patient's activity level and exercise tolerance. It divides patients into one of four classes, with functional class I patients exhibiting no symptoms or limitations of daily activities, and functional class IV patients who are symptomatic at rest (Table 3–5). The NYHA FC system reflects a subjective assessment by a health care provider and can change frequently over short periods of time. Functional class correlates poorly with EF; however, EF is one of the strongest predictors of prognosis. In general, anticipated survival declines in conjunction with a decline in functional ability.

The American College of Cardiology/American Heart Association (ACC/AHA) has proposed another system based on the development and progression of the disease. Instead of classifications, patients are placed into stages A through D (Table 3–5).[11] Stage A encompasses patients who carry risk factors for the development of HF, such as CAD, hypertension, and diabetes mellitus. Stage B includes high-risk patients with documented structural heart disease (LV hypertrophy or impaired LV function). Stage C denotes patients with current or past symptoms of HF and underlying structural heart disease. Stage D is reserved for those with refractory or end-stage HF in whom special interventions may be indicated, such as mechanical circulatory support. Since the staging system is related to development and progression of HF, it also proposes management strategies for each stage including risk factor modification. The staging system is meant to complement the NYHA FC system; however, patients can move between NYHA functional classes as symptoms improve with treatment, whereas HF staging does not allow for patients to move to a lower stage (e.g., patients cannot be categorized as stage C and move to stage B after treatment). Currently, patients are categorized based on both systems. Functional classification and staging are useful from a clinician's perspective, allowing for a longitudinal assessment of a patient's risk and progress, requirements for nonpharmacologic interventions, response to medications, and overall prognosis.

TABLE 3–5. New York Heart Association (NYHA) Functional Classification and American College of Cardiology/American Heart Association (ACC/AHA) Staging

NYHA Functional Class	ACC/AHA Stage	Description
N/A	A	Patients at high risk for heart failure but without structural heart disease or symptoms of heart failure.
I	B	Patients with cardiac disease but without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	C	Patients with cardiac disease that results in slight limitations of physical activity. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	C	Patients with cardiac disease that results in marked limitation of physical activity. Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.
IV	C, D	Patients with cardiac disease that results in an inability to carry on physical activity without discomfort. Symptoms of heart failure are present at rest. With any physical activity, increased discomfort is experienced. Stage D refers to end-stage heart failure patients.



Patient Encounter, Part 2

BE's Medical History, Physical Exam, and Diagnostic Tests

PMH
Type 2 diabetes mellitus × 15 years
Coronary artery disease × 10 years (MIs in 1999 and 2002)
Tobacco use
History of back surgery in 2001

Allergies
No known drug allergies

Meds
Diltiazem CD 240 mg once daily
Nitroglycerin 0.4 mg sublingual (SL) as needed (last use yesterday after showering)
Ibuprofen 600 mg twice daily for arthritis pain
Vitamin B_{12} once daily
Multivitamin daily
Aspirin 325 mg once daily

FH
Significant for early heart disease in father (MI at age 53)

SH
She is disabled from a previous accident; she is married, has 6 children, and runs her own business; she does not drink alcohol and smokes one to two packs of cigarettes per day.

PE
Blood pressure 126/70 mm Hg, pulse 60 bpm and regular, respiratory rate 16/minute, Ht 5′8″ (173 cm), Wt 251 lb (114 kg), body mass index (BMI): 38.2 kg/m^2

(*Continued*)

Patient Encounter, Part 2 (*Continued*)

Lungs are clear to auscultation with a prolonged expiratory phase; rales are present bilaterally

CV: Regular rate and rhythm with normal S_1 and S_2; there is an S_3 and a soft S_4 present; there is a 2/6 systolic ejection murmur heard best at the left lower sternal border; point of maximal impulse is within normal limits at the midclavicular line; there is no JVD

Abd: Soft, non-tender, and bowel sounds are present; 2+ pitting edema of extremities extending to below the knees is observed

Chest x-ray: Bilateral pleural effusions and cardiomegaly

Echocardiogram: EF = 35%

Laboratory Values

Hct: 41.1%	WBC: $5.3 \times 10^3/\mu L$ ($5.3 \times 10^9/L$)
Sodium: 132 mEq/L (132 mmol/L)	Potassium: 3.2 mEq/L (3.2 mmol/L)
Bicarb: 30 mEq/L (30 mmol/L)	Chloride: 90 mEq/L (90 mmol/L)
Magnesium: 1.5 mEq/L (0.8 mmol/L)	Fasting blood sugar: 120 mg/dL (6.7 mmol/L)
Uric acid: 8 mg/dL (476 µmol/L)	Blood urea nitrogen (BUN): 40 mg/dL (14 mmol/L)
SCr: 0.8 mg/dL (71 µmol/L)	Alk Phos: 120 IU/L (2 µKat/L)

Aspartate aminotransferase: 100 IU/L (1.7 µKat/L)

- What other laboratory or other diagnostic tests are required for assessment of BE's condition?
- How would you classify BE's NYHA functional class and ACC/AHA heart failure stage?
- Identify exacerbating or precipitating factors that may worsen BE's heart failure.
- What are your treatment goals for BE?

TREATMENT OF CHRONIC HEART FAILURE

Desired Therapeutic Outcomes

There is no cure for HF. ❺ *The general management goals for chronic HF include preventing the onset of clinical symptoms or reducing symptoms, preventing or reducing hospitalizations, slowing progression of the disease, improving quality of life, and prolonging survival.* The ACC/AHA staging system described earlier provides a guide for application of these goals based on the clinical progression of HF for a given patient. The goals are additive as one moves from stage A to stage D.[1,11] For stage A, risk factor management is the primary goal. Stage B includes the addition of pharmacologic therapies known to slow the progression of the disease in an attempt to prevent the onset of clinical symptoms. Stage C involves the use of additional therapies aimed at controlling symptoms and decreasing morbidity. Finally, in stage D, the goals shift toward quality-of-life related issues. Only with aggressive management throughout all the stages of the disease will the ultimate goal of improving survival be realized. The attainment of these goals is based on designing a therapeutic approach that encompasses strategies aimed at control and treatment of contributing disorders, nonpharmacologic interventions, and optimal use of pharmacologic therapies.[12,13]

Control and Treatment of Contributing Disorders

All causes of HF must be investigated to determine the etiology of cardiac dysfunction in a given patient. Since the most common etiology of HF in the United States is ischemic heart disease, coronary angiography is warranted in the majority of patients with a history suggestive of underlying CAD. Revascularization of those with significant CAD may help restore some cardiac function in patients with reversible ischemic defects. Aggressive control of hypertension, diabetes, and obesity is also essential since each of these conditions can cause further cardiac damage. Surgical repair of valvular disease or congenital malformations may be warranted if detected. Since clinical HF is partly dependent on metabolic processes, correction of imbalances such as thyroid disease and anemia is required. Other more rare causes such as autoimmune disorders or acquired illnesses may have specific treatments. Identifying and discontinuing medications that can exacerbate HF is also an important intervention.

Nonpharmacologic Interventions

It is imperative that patients recognize the role of self-management in HF. ❻ *Nonpharmacologic treatment involves dietary modifications such as sodium and fluid restriction, risk factor reduction including smoking cessation, timely immunizations, and supervised regular physical activity. Patient education regarding monitoring symptoms, dietary and medication adherence, exercise and physical fitness, risk factor reduction, and immunizations are important for prevention of AHF exacerbations.*

Patients should be encouraged to become involved in their own care through several avenues, the first of which is self-monitoring. A general explanation of symptoms associated with HF should be included at the initiation of treatment. Home monitoring should include daily assessment of weight and exercise tolerance. Daily weights should be done first thing in the morning upon arising and before any food intake to maintain consistency. Patients should record their weight daily in a journal and bring this log to each clinic or office visit. Changes in weight can indicate fluid retention and congestion prior to onset of peripheral or pulmonary symptoms. Individuals who have an increase of 2 to 3 pounds (0.91 to 1.36 kg) in a single day or 5 pounds (2.27 kg) over 5 days should be referred to their HF care provider. Some patients may be educated about self-adjusting diuretic doses based on daily weights.

In addition to weight changes, a marked decline in exercise tolerance should also be reported to the HF care provider.

Non-adherence is an important issue as it relates to acute exacerbations of HF. Ensuring an understanding of the importance of each medication used to treat HF, proper administration, and potential adverse effects may improve adherence. Stressing the rationale for each medication is important, especially for NYHA FC I or ACC/AHA stage B patients who are asymptomatic, yet started on drugs that may worsen symptoms initially. A clinician's involvement in emphasizing medication adherence, offering adherence suggestions such as optimal timing of medications or use of weekly pill containers, and providing intensive follow-up care has been shown to reduce AHF hospitalizations.

Dietary modifications in HF consist of initiation of an AHA step II diet as part of cardiac risk factor reduction, sodium restriction, and sometimes fluid restriction. As sodium and water retention is a compensatory mechanism that contributes to volume overload in HF, salt and fluid restriction is often necessary to help avoid or minimize congestion. The normal American diet includes 3 to 6 grams of sodium per day. Most patients with HF should limit salt intake to a maximum of 2 grams per day. Patients should be educated to avoid cooking with salt and to limit intake of foods with high salt content, such as fried or processed food (lunchmeats, soups, cheeses, salted snack foods, canned food, and some ethnic food). Salt restriction can be challenging for many patients. The clinician should assess a patient's salt consumption habits and counsel to restrict salt slowly over time. Drastic dietary changes may lead to nonadherence due to an unpalatable diet. Substituting spices to flavor food is a useful recommendation. Salt substitutes should be used judiciously, as many contain large amounts of potassium which can increase the risk of hyperkalemia. Fluid restriction may not be necessary in many patients. When applicable, a general recommendation is to limit fluid intake from all sources to less than 2 liters per day.

Exercise, while discouraged when the patient is acutely decompensated to ease cardiac workload, is recommended when patients are stable. The heart is a muscle that requires activity to prevent atrophy. In addition, exercise improves peripheral muscle conditioning and efficiency, which may contribute to better exercise tolerance despite the low CO state. Regular low intensity, aerobic exercise that includes walking, swimming, or riding a bike is encouraged, while heavy weight training is discouraged. The prescribed exercise regimen needs to be tailored to the individual's functional ability, and thus it is suggested that patients participate in cardiac rehabilitation programs, at least initially. It is important that patients not overexert themselves to fatigue or exertional dyspnea.

Modification of classic risk factors, such as tobacco and alcohol consumption, is important to minimize the potential for further aggravation of heart function. Data from observational studies suggest that patients with HF who smoke have a mortality rate 40% higher than those who do not consume tobacco products.[1] All HF patients who smoke should be counseled on the importance of tobacco cessation and offered a referral to a cessation program. Patients with an alcoholic cardiomyopathy should abstain from alcohol. Whether all patients with other forms of HF should abstain from any alcohol intake remains controversial. Proponents of moderation of alcohol base their rationale on the potential cardioprotective effects. However, opponents to any alcohol intake point out that alcohol is cardiotoxic and should be avoided.

In general, it is suggested that patients remain up to date on standard immunizations. Patients with HF should be counseled to receive yearly influenza vaccinations. Additionally, a pneumococcal vaccine is recommended. Usually only one pneumonia vaccination is necessary unless a patient is vaccinated before age 65. In that case, a booster vaccination is suggested 5 years after the initial vaccination.

Pharmacologic Treatment

In addition to determining therapeutic goals, the ACC/AHA staging system delineates specific therapy options based on disease progression.[1,11] For patients in stage A, every effort is made to minimize the impact of diseases that can injure the heart. Antihypertensive and lipid-lowering therapies should be utilized when appropriate to decrease the risk for stroke, MI, and HF. ACE inhibitors should be considered in high-risk vascular disease patients. For stage B patients, the goal is to prevent or slow disease progression by interfering with neurohormonal pathways that lead to cardiac damage and mediate pathologic remodeling. The goal is to prevent the onset of HF symptoms. The backbone of therapy in these patients includes ACE inhibitors or ARBs and β-blockers. In stage C patients with symptomatic LV systolic dysfunction (EF less than 40%), the goals focus on alleviating fluid retention, minimizing disability, slowing disease progression, and reducing long-term risk for hospitalizations and death. Treatment entails a strategy that combines diuretics to control intravascular fluid balance with neurohormonal antagonists to minimize the effects of the RAAS and SNS. Aldosterone antagonists and digoxin are often added as cardiac function continues to decline. Patients with advanced stage D disease are offered more modest goals, such as improvement in quality of life. Enhancing quality of life is often achieved at the expense of expected survival. Treatment options include mechanical support, transplantation, and continuous use of intravenous vasoactive therapies, in addition to maintaining an optimal regimen of chronic oral medications.

Diuretics

Diuretics have been the mainstay for HF symptom management for many years. ❼ *Diuretics are used for relief of acute symptoms of congestion and maintenance of euvolemia.* These agents interfere with sodium retention by increasing urinary sodium and free water excretion. No prospective data exist on the effects of diuretics on patient outcomes.[14] Therefore, the

primary rationale for the use of diuretic therapy is to maintain euvolemia in symptomatic or stages C and D heart failure. Diuretic therapy is recommended for all patients with clinical evidence of fluid overload retention.[15,16] In more mild HF, diuretics may be used on an as-needed basis. However, once the development of edema is persistent, regularly scheduled doses will be required.

Two types of diuretics are used for volume management in HF: thiazides and loop diuretics. Thiazide diuretics such as hydrochlorothiazide, chlorthalidone, and metolazone block sodium and chloride reabsorption in the distal convoluted tubule. Thiazides are weaker than loop diuretics in terms of effecting an increase in urine output and therefore are not utilized frequently as monotherapy in HF. They are optimally suited for patients with hypertension who have mild congestion. Additionally, the action of thiazides is limited in patients with renal insufficiency (creatinine clearance less than 30 mL/minute) due to reduced secretion into their site of action. An exception is metolazone, which retains its potent action in patients with renal dysfunction. Metolazone is often used in combination with loop diuretics when patients exhibit diuretic resistance, defined as edema unresponsive to loop diuretics alone.

Loop diuretics are the most widely used diuretics in HF. These agents, including furosemide, bumetanide, and torsemide, exert their action at the thick ascending loop of Henle. Loop diuretics are not filtered through the glomerulus, but instead undergo active transport into the tubular lumen via the organic acid pathway. As a result, drugs that compete for this active transport (e.g., probenecid and organic by-products of uremia) can lower efficacy of loop diuretics. Loop diuretics increase sodium and water excretion and induce a prostaglandin-mediated increase in renal blood flow which contributes to their natriuretic effect. Unlike thiazides, they retain their diuretic ability in patients with poor renal function. The various loop diuretics are equally effective when used at equipotent doses, although there are intrinsic differences in pharmacokinetics and pharmacodynamics (Table 3–6).[5] The choice of which loop diuretic to use and the route of administration depends on clinical factors, such as presence of intestinal edema and rapidity of desired effect. Oral diuretic efficacy may vary based on differing bioavailability, which is almost complete for torsemide and bumetanide, but averages only 50% for furosemide. Therefore, oral torsemide can be considered an alternative to the intravenous route of administration for patients who do not respond to oral furosemide in the setting of profound edema. The onset of effect is slightly delayed after oral administration but occurs within a few minutes with intravenous dosing. Consequently, bioequivalent doses of intravenous furosemide are half the oral dose, whereas bumetanide and torsemide intravenous doses are generally equivalent to the oral doses.

In patients with evidence of mild to moderate volume overload, diuretics should be initiated at a low dose and titrated to achieve a weight loss of up to 2 pounds (0.91 kg) per day. Patients with severe volume overload should be managed in an inpatient setting. Once diuretic therapy is initiated, dosage adjustments are based on symptomatic improvement and daily body weight. As body weight changes are a sensitive marker of fluid retention or loss, patients should continue to weigh themselves daily. Once a patient reaches a euvolemic state, diuretics may be cautiously tapered and then withdrawn in appropriate patients. In stable, educated, and compliant patients, another option is self-adjusted diuretic dosing. Based on daily body weight, patients may temporarily increase their diuretic regimen in order to reduce the incidence of overt edema. This also avoids overuse of diuretics and possible complications of over-diuresis such as hypotension, fatigue, and renal impairment.

TABLE 3–6. Loop Diuretics Used in Heart Failure

	Furosemide	Bumetanide	Torsemide
Usual daily dose (oral)	20–160 mg	0.5–4 mg	10–80 mg
Ceiling dose:			
Normal renal function	80–160 mg	1–2 mg	20–40 mg
CrCL 20–50 mL/minute	160 mg	2 mg	40 mg
CrCL less than 20 mL/minute	400 mg	8–10 mg	100 mg
Bioavailability	10–100% (average 50%)	80–90%	80–100%
Affected by food	Yes	Yes	No
Half-life	0.3–3.4 hours	0.3–1.5 hours	3–4 hours

CrCL, creatinine clearance.

The maximal response to diuretics is reduced in HF, creating a "ceiling dose" above which there is limited added benefit. This diuretic resistance is due to a compensatory increase in sodium reabsorption in the proximal and distal tubules, which decreases the effect of blocking sodium reabsoption in the loop of Henle.[17] In addition, there is a simultaneous increase in the reabsorption of sodium from the proximal tubule, allowing less to reach the site of action for loop diuretics. Apart from increasing diuretic doses, strategies to improve diuretic efficacy include increasing the frequency of dosing to two or three times daily, utilizing a continuous infusion of a loop diuretic, and/or combining a loop diuretic with a thiazide diuretic.[17,18] The latter strategy theoretically prevents sodium and water reabsorption at both the loop of Henle and the compensating distal convoluted tubule. Metolazone is used most often for this purpose, as it retains its activity in settings of a low creatinine clearance. Metolazone can be dosed daily or as little as once weekly. This combination is usually maintained until the patient reaches his or her baseline weight.

Diuretics cause numerous adverse effects and metabolic abnormalities, with severity linked to diuretic potency. A particularly worrisome adverse effect in the setting of HF is

hypokalemia. Low serum potassium can predispose patients to arrhythmias and sudden death. Hypomagnesemia often occurs concomitantly with diuretic-induced hypokalemia, and therefore both should be assessed and replaced in patients needing correction of hypokalemia. Magnesium is an essential co-factor for movement of potassium intracellularly to restore body stores. Patients taking diuretics are also at risk for renal insufficiency due to overdiuresis and reflex activation of the renin-angiotensin system. The potential reduction in renal blood flow and glomerular pressure is amplified by concomitant use of ACE inhibitors or ARBs.

Neurohormonal Blocking Agents

❽ *Agents with proven benefits in improving symptoms, slowing disease progression, and improving survival in chronic HF target neurohormonal blockade. These include ACE inhibitors, ARBs, β-adrenergic blockers, and aldosterone antagonists.*

Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors are the cornerstone of treatment for HF. ACE inhibitors decrease neurohormonal activation by blocking the conversion of angiotensin I (AT_1) to angiotensin II (AT_2), a potent mediator of vasoconstriction and cardiac remodeling. The breakdown of bradykinin is also reduced. Bradykinin enhances the release of vasodilatory prostaglandins and histamines. These effects result in arterial and venous dilatation, and a decrease in myocardial workload through reduction of both preload and afterload. ACE inhibitors demonstrate favorable effects on cardiac hemodynamics, such as long-term increases in **cardiac index** (CI), stroke work index, and SV index, as well as significant reductions in LV filling pressure, SVR, mean arterial pressure, and HR.

There is extensive clinical experience with ACE inhibitors in systolic HF. Numerous clinical studies show ACE inhibitor therapy is associated with improvements in clinical symptoms, exercise tolerance, NYHA functional class, LV size and function, and quality of life as compared with placebo.[18–21] ACE inhibitors significantly reduce hospitalization rates and mortality regardless of underlying disease severity or etiology. ACE inhibitors are also effective in preventing HF development in high-risk patients. Studies in acute MI patients show a reduction in new-onset HF and death with ACE inhibitors whether they are initiated early (within 36 hours) or started later. In addition, ACE inhibition decreases the risk of HF hospitalization and death in patients with asymptomatic LV dysfunction. The exact mechanisms for decreased HF progression and mortality are postulated to involve both the hemodynamic improvement and the inhibition of angiotensin II's growth promoting and remodeling effects. All patients with documented LV systolic dysfunction, regardless of existing HF symptoms, should receive ACE inhibitors unless a contraindication or intolerance is present.

There is no evidence to suggest that one ACE inhibitor is preferred over another. ACE inhibitors should be initiated using low doses and titrated up to target doses over several weeks depending on tolerability (adverse effects and blood pressure). The ACC/AHA 2005 guidelines advocate using the doses that were proven to decrease mortality in clinical trials as the target doses (Table 3–7).[1] If the target dose cannot be attained in a given patient, the highest tolerated dose should be used chronically. Although there is incremental benefit with higher doses of ACE inhibitors, it is accepted that lower doses provide substantial if not the majority of the effect.[22] Since ACE inhibitors are only one component of a mortality-reducing treatment plan in HF, targeting a high ACE inhibitor dose should not interfere with starting a β-blocker or aldosterone antagonist. Specifically, higher ACE inhibitor dosing may accentuate the hypotensive effects. Higher ACE inhibitor dosing may also limit tolerability of a regimen which also includes β-blockers and aldosterone antagonists.

Despite their clear benefits, ACE inhibitors are still underutilized in HF. One reason is undue concern or confusion regarding absolute versus relative contraindications for their use. Absolute contraindications include a history of angioedema, bilateral renal artery stenosis, and pregnancy. Relative contraindications include unilateral renal artery stenosis, renal insufficiency, hypotension, hyperkalemia, and cough. Relative contraindications provide a warning that close monitoring is required, but they do not necessarily preclude their use.

Clinicians are especially concerned about the use of ACE inhibitors in patients with renal insufficiency. It is important to recognize that ACE inhibitors can potentially contribute to preservation or decline in renal function depending on the clinical scenario. Through preferential efferent arteriole vasodilation, ACE inhibitors can reduce intraglomerular pressure. Reduced glomerular pressures are renoprotective chronically; however, in situations of reduced or fixed renal blood flow, this leads to a reduction in filtration. In general, ACE inhibitors can be used in patients with serum creatinine less than 2.5 to 3 mg/dL (221 to 265 μmol/L). In HF, their addition can result in improved renal function through an increase in CO and renal perfusion. Some data suggest that ACE inhibitors are especially beneficial in those with renal dysfunction. Although a small increase in serum creatinine (less than 0.5 mg/dL [44 μmol/L]) is possible with the addition of an ACE inhibitor, it is usually transient or becomes the patient's new serum creatinine baseline level. However, ACE inhibition can also worsen renal function since glomerular filtration is maintained in the setting of reduced CO through angiotensin II's constriction of the efferent arteriole. Patients most dependent on angiotensin II for maintenance of glomerular filtration pressure, and hence most susceptible to ACE inhibitor worsening of renal function, include those with hyponatremia, severely depressed LV function, or dehydration. It is important to note that the most common reason for creatinine elevation in a patient without a history of renal dysfunction is overdiuresis. Therefore, clinicians should consider decreasing or holding diuretic doses if an elevation in serum creatinine occurs concomitantly with a rise in blood urea nitrogen.

TABLE 3–7. Dosing and Monitoring for Neurohormonal Blocking Agents

Drug	Initial Daily Dose	Target or Maximum Daily Dose	Monitoring
ACE Inhibitors			
Captopril	6.25 mg 3 times	50 mg 3 times	BP
Enalapril	2.5 mg twice	10–20 mg twice	Electrolytes (K^+, BUN, SCr) at baseline, 2 weeks, and after dose titration, CBC periodically
Fosinopril	5–10 mg once	40 mg once	
Lisinopril	2.5–5 mg once	20–40 mg once	
Perindopril	2 mg once	8–16 mg once	
Quinopril	5 mg once	20 mg twice	Adverse effects: cough, angioedema
Ramipril	1.25–2.5 mg once	10 mg once	
Trandolapril	1 mg once	4 mg once	
Angiotensin Receptor Blockers			
Candesartan	4–8 mg once	32 mg once	BP
Losartan	25–50 mg once	50–100 mg once	Electrolytes (K^+, BUN, SCr) at baseline, 2 weeks, and after dose titration, CBC periodically
Valsartan	20–40 mg once	160 mg twice	Adverse effects: cough, angioedema
Aldosterone Antagonists			
Spironolactone	12.5–25 mg once	25 mg once or twice	BP
Eplerenone	25 mg once	50 mg once	Electrolytes (K^+) at baseline and within 1 week of initiation and dose titration
			Adverse effects: gynecomastia or breast tenderness, menstrual changes, hirsutism
β-Blockers			
Bisoprolol	1.25 mg once	10 mg once	BP, HR baseline and after each dose titration, ECG
Carvedilol	3.125 mg twice	25 mg twice (50 mg twice for patients greater than 85 kg or 187 lbs)	Adverse effects: worsening HF symptoms (edema, SOB, fatigue), depression, sexual dysfunction
Metoprolol succinate	12.5–25 mg once	200 mg once	

BP, blood pressure; BUN, blood urea nitrate; CBC, complete blood cell count; ECG, electrocardiogram; HF, heart failure; HR, heart rate; K^+, potassium; SCr, serum creatinine; SOB, shortness of breath.

Hypotension occurs commonly at the initiation of therapy or with dosage increases but may happen anytime during therapy. Hypotension can manifest as dizziness, lightheadedness, presyncope, or syncope. The risk of hypotension due to possible volume depletion increases when ACE inhibitors are initiated or used concomitantly in patients on high diuretic doses. Therefore, in euvolemic patients, diuretic doses may often be decreased or withheld during ACE inhibitor dose titration. Initiating at a low dose and titrating slowly can also minimize hypotension. It may be advisable to initiate therapy with a short-acting ACE inhibitor, such as captopril, and subsequently switch to a longer-acting agent, such as lisinopril or enalapril, once the patient is stabilized.

Hyperkalemia results from reduced angiotensin II–stimulated aldosterone release. The risk of hyperkalemia with ACE inhibitors is also increased in HF due to a propensity for impaired renal function and additive effects with aldosterone antagonists. To minimize hyperkalemia, patients should be counseled to avoid foods high in potassium such as certain salt substitutes. ACE inhibitor dose may need to be decreased or held if serum potassium increases above 5 mEq/L (5 mmol/L). Persistent hyperkalemia in the setting of renal insufficiency may preclude the use of an ACE inhibitor.

Cough is commonly seen with ACE inhibitors (5% to 15%) and may be related to accumulation of tissue bradykinins.[5] It can be challenging to distinguish an ACE inhibitor–induced cough from cough caused by pulmonary congestion. A productive or wet cough usually signifies congestion, whereas a dry, hacking cough is more indicative of a drug-related etiology. If a cough is determined to be ACE inhibitor–induced, its

severity should be evaluated before deciding on a course of action. If the cough is truly bothersome, a trial with a different ACE inhibitor or switching to an ARB is warranted.

Angiotensin Receptor Blockers

Angiotensin receptor blockers selectively antagonize the effects of angiotensin II directly at the AT_1 receptor. AT_1 receptor stimulation is associated with vasoconstriction, release of aldosterone, and cellular growth promoting effects, while angiotensin receptor type 2 (AT_2) stimulation causes vasodilation. By selectively blocking AT_1 but leaving AT_2 unaffected, ARBs block the detrimental AT_1 effects on cardiac function while allowing AT_2-mediated vasodilation and inhibition of ventricular remodeling. Angiotensin receptor blockers are considered an equally effective replacement for ACE inhibitors in patients who are intolerant or have a contraindication to an ACE inhibitor.

It was hoped that the more complete blockade of angiotensin II's AT_1 effects would confer greater long-term efficacy with ARBs compared to ACE inhibitors. However, prospective, randomized trials suggest that the clinical efficacy of ARBs is similar to that of ACE inhibitors for reduction of hospitalizations for HF, sudden cardiac death, and all cause mortality.[23–25] Despite poorer suppression of AT_2, comparable efficacy of ACE inhibitors may be due to the additional effects on the kallikrein-kinin system. Although ARBs produce hemodynamic and neurohormonal effects similar to those of ACE inhibitors, they are considered second-line therapy due to the overwhelming clinical trial experience with ACE inhibitors.

Since the mechanism for long-term benefit appears different for ACE inhibitors and ARBs, the combination has been studied for additive benefits. One study evaluated the addition of the ARB candesartan versus placebo in three distinct groups of HF patients: systolic dysfunction intolerant to an ACE inhibitor, systolic dysfunction currently on ACE inhibitor therapy, and patients with preserved systolic function.[25] Candesartan reduced the combined incidence of cardiovascular death and hospitalization for HF in all three groups, with the greatest benefit being seen in those not on an ACE inhibitor. Candesartan significantly decreased mortality compared to placebo when all three groups were combined. Based on this study, the addition of an ARB to ACE inhibitor therapy can be considered in patients with evidence of disease progression despite optimal ACE inhibitor therapy.[1] This study also demonstrates the importance of having some form of angiotensin II antagonism as part of a treatment regimen.

Angiotensin receptor blockers show similar tolerability to ACE inhibitors with regard to hypotension and hyperkalemia, but they do not induce cough since ARBs do not cause an accumulation of bradykinin. Angiotensin receptor blockers can be considered in patients with ACE inhibitor–induced angioedema, but they should be initiated cautiously, as cross-reactivity has been reported. Many of the other considerations for the use of ARBs are similar to those of ACE inhibitors, including the need for monitoring renal function, blood pressure, and potassium. Bilateral renal artery stenosis is an absolute contraindication to ARB therapy unless it has been corrected. Neither ACE inhibitors nor ARBs should be used in patients who are pregnant or actively trying to become pregnant because of associated teratogenicity. In patients truly intolerant or contraindicated to ACE inhibitors or ARBs, the combination of hydralazine and isosorbide dinitrate should be considered.

Hydralazine and Isosorbide Dinitrate

Complementary hemodynamic actions originally led to the combination of nitrates with hydralazine. Nitrates reduce preload by causing primarily venous vasodilation through activating guanylate cyclase and a subsequent increase in cyclic guanosine monophosphate (cGMP) in vascular smooth muscle. Hydralazine reduces afterload through direct arterial smooth muscle relaxation via an unknown mechanism. More recently, nitric oxide has been implicated in modulating numerous pathophysiologic processes in the failing heart, including inflammation, cardiac remodeling, and oxidative damage. Supplementation of nitric oxide via administration of nitrates has also been proposed as a mechanism for benefit from this combination therapy. The beneficial effect of an external nitric oxide source may be more apparent in the African-American population, which appears to be predisposed to having an imbalance in nitric oxide production. In addition, hydralazine may reduce the development of nitrate tolerance when nitrates are given chronically.

The combination of hydralazine and isosorbide dinitrate was the first therapy shown to improve long-term survival in patients with systolic HF, but has largely been supplanted by angiotensin II antagonist therapy (ACE inhibitors and ARBs).[27,28] Therefore, until recently, this combination therapy was reserved for patients intolerant to ACE inhibitors or ARBs secondary to renal impairment, angioedema, or hyperkalemia. New insight into the pathophysiologic role of nitric oxide has reinvigorated research into this combination therapy.

The nitrate-hydralazine combination was first shown to improve survival compared to placebo.[27] Subsequently, the combination of isosorbide dinitrate 40 mg and hydralazine 75 mg, both given four times daily, was compared to the ACE inhibitor enalapril.[28] Enalapril produced a 28% greater decrease in mortality. Therefore, the combination is considered a third-line vasodilatory option for patients truly intolerant of ACE inhibitors and ARBs.

More recently, the value of adding the combination of isosorbide dinitrate 40 mg and hydralazine 75 mg three times daily to therapy including ACE inhibitors, β-blockers, digoxin, and diuretics was evaluated in a prospective, randomized trial.[26] The study enrolled only African-American patients and demonstrated a significant reduction in mortality, as well as first hospitalization for HF. Quality-of-life scores were also improved over placebo. ❾ *Combination therapy with hydralazine and isosorbide dinitrate is an appropriate substitute for angiotensin II antagonism*

in those unable to tolerate an ACE inhibitor or ARB or as add-on therapy in African-Americans. The ACC/AHA HF guidelines now recommend considering the addition of isosorbide dinitrate and hydralazine in African-Americans already on ACE inhibitors or ARBs.[1] Combination therapy with isosorbide dinitrate and hydralazine should be initiated and titrated as are other neurohormonal agents such as ACE inhibitors and β-blockers. Low doses are used to initiate therapy with subsequent titration of the dose toward target doses based on tolerability. Adverse effects such as hypotension and headache cause frequent discontinuations in patients taking this combination, and full doses often cannot be tolerated. Patients should be monitored for headache, hypotension, and tachycardia. Hydralazine is also associated with a dose-dependent risk for lupus.

The frequent dosing of isosorbide dinitrate (e.g. 3–4 times daily) is not conducive to patient adherence; therefore, a once-daily isosorbide mononitrate is commonly substituted for isosorbide dinitrate to simplify the dosing regimen. A nitrate-free interval is still required when using nitrates for HF.

Beta-Adrenergic Antagonists

Beta-adrenergic antagonists, or β-blockers, competitively block the influence of the SNS at β-adrenergic receptors. As recently as 15 years ago, β-adrenergic blockers were thought to be detrimental in HF due to their negative inotropic actions, which could potentially worsen symptoms and cause acute decompensations. Since then, the benefits of inhibiting the SNS have been recognized as far outweighing the acute negative inotropic effects. Chronic β-blockade reduces ventricular mass, improves ventricular shape, and reduces LV end-systolic and diastolic volumes.[6,8] β-Blockers also exhibit antiarrhythmic effects, slow or reverse catecholamine-induced ventricular remodeling, decrease myocyte death from catecholamine-induced necrosis or apoptosis, and prevent myocardial fetal gene expression. Consequently, β-blockers improve EF, reduce all-cause and HF-related hospitalizations, and decrease all-cause mortality in patients with systolic HF.[29–33]

The ACC/AHA recommends that β-blockers be initiated in all patients with NYHA FC I to IV or ACC/AHA stages B through D heart failure if clinically stable.[1] To date, only three β-blockers have been shown to reduce mortality in systolic HF, including the selective β_1-antagonists bisoprolol and metoprolol succinate, and the non-selective β_1-, β_2-, and α_1-antagonist carvedilol.[29–33] The positive findings should not be extrapolated to be indicative of a class effect, as bucindolol did not exhibit a beneficial effect on mortality when studied for HF, and there is limited information with propranolol and atenolol.

Controversy surrounds the selection of a β-blocker for HF management. First, although metoprolol and carvedilol are the most commonly used β-antagonists in HF, it remains controversial as to whether one agent should be considered first-line. Carvedilol exhibits several pharmacologic properties that theoretically would confer superior efficacy, since carvedilol: (1) provides blockade at multiple adrenergic receptors, which translates into vasodilatory effects and theoretically more complete antagonism of sympathetic stimulation, and (2) has in vitro antioxidant activity that could reduce vascular and cardiac oxidative damage. Several smaller studies and a meta-analysis suggested that carvedilol increased left ventricular ejection fraction (LVEF), improved cardiac hemodynamics, and slowed remodeling to a greater extent than metoprolol tartrate. To compare their relative effects on patient outcomes, one study compared immediate-release metoprolol tartrate to carvedilol in 3,000 patients with mild to severe HF.[33] Carvedilol lowered all-cause mortality significantly more than metoprolol tartrate. However, the controversy remains, as proponents for metoprolol question: (1) the validity of using immediate-release metoprolol tartrate as the comparison agent in this study, and (2) the low average dose of metoprolol tartrate achieved in the study. It also remains controversial as to whether metoprolol tartrate should be used in HF since the only trial demonstrating a mortality benefit with metoprolol used the sustained-release succinate dosage form.

The key to utilizing β-blockers in systolic HF is initiation with low doses and slow titration to target doses over weeks to months. It is important that the β-blocker be initiated when a patient is clinically stable and euvolemic. Volume overload at the time of β-blocker initiation increases the risk for worsening symptoms. β-Blockade should begin with the lowest possible dose (Table 3–7), after which the dose may be doubled every 2 to 4 weeks depending on patient tolerability. β-Blockers may cause an acute decrease in LVEF and short-term worsening of HF symptoms upon initiation and at each dosage titration. After each dose titration, if the patient experiences symptomatic hypotension, bradycardia, orthostasis, or worsening symptoms, further increases in dose should be withheld until the patient stabilizes. After stabilization, attempts to increase the dose should be reinstituted. If mild congestion ensues as a result of the β-blocker, an increase in diuretic dose may be warranted. If moderate or severe symptoms of congestion occur, a reduction in β-blocker dose should be considered along with an increase in diuretic dose. Dose titration should continue until target clinical trial doses are achieved (Table 3–7) or until limited by repeated hemodynamic or symptomatic intolerance. Patient education regarding the possibility of acutely worsening symptoms but improved long-term function and survival is essential to ensure adherence.

Apart from possible clinical differences between the β-blockers approved for HF, selection of a β-blocker may also be affected by pharmacologic differences. Carvedilol exhibits a more pronounced blood pressure lowering effect and thus causes more frequent dizziness and hypotension as a consequence of its α_1-receptor blocking activity. Therefore, in patients predisposed to symptomatic hypotension, such as those with advanced LV dysfunction (LVEF less than 20%) who normally exhibit low systolic blood pressures, metoprolol succinate may be the most desirable first-line β-blocker. In patients with uncontrolled hypertension, carvedilol may provide additional antihypertensive efficacy.

β-Blockers may be used by those with reactive airway disease or peripheral vascular disease, but should be used with considerable caution or avoided if patients display active respiratory symptoms. Care must also be used in interpreting shortness of breath in these patients, as the etiology could be either cardiac or pulmonary. A selective β_1-blocker such as metoprolol is a reasonable option for patients with reactive airway disease. The risk versus benefit of using any β-blocker in peripheral vascular disease must be weighed based on the severity of the peripheral disease.

Both metoprolol and carvedilol are metabolized by the liver through cytochrome P-450 (CYP450)2D6 and undergo extensive first-pass metabolism. Bisoprolol is not as commonly used since it is not Food and Drug Administration (FDA)-approved for this use.

Aldosterone Antagonists

Currently, the aldosterone antagonists available are spironolactone and eplerenone. Both agents are inhibitors of aldosterone that produce weak diuretic effects while sparing potassium concentrations. Eplerenone is selective for the mineralocorticoid receptor and hence does not exhibit the endocrine adverse-effect profile commonly seen with spironolactone. The initial rationale for specifically targeting aldosterone for treatment of HF was based on the knowledge that ACE inhibitors do not suppress the chronic production and release of aldosterone. Aldosterone is a key pathologic neurohormone which exerts multiple detrimental effects in HF. Through the kidneys, aldosterone promotes fluid retention and electrolyte abnormalities. Aldosterone is another neurohormone known to mediate pathologic ventricular remodeling by causing increased extracellular matrix collagen deposition and cardiac fibrosis. Aldosterone potentially contributes to disease progression via sympathetic potentiation and ventricular remodeling. In addition, the combination of these multiple effects is likely responsible for the increased risk of sudden cardiac death attributed to aldosterone. Similar to norepinephrine and angiotensin II, aldosterone levels are increased in HF and have been shown to correlate with disease severity and patient outcomes.

Each agent (spironolactone and eplerenone) has been studied in a defined population of patients with HF. One study established efficacy with low-dose spironolactone in NYHA FC III and IV heart failure patients in reducing HF hospitalizations, improving functional class, reducing sudden cardiac death, and improving all-cause mortality.[34] Another study investigated the use of eplerenone in patients within 14 days of MI and LVEF less than 40%.[35] Eplerenone was found to decrease mortality as well as cardiovascular death and related hospitalization, mainly due to reducing occurrence of sudden cardiac death. Based on these two studies, the ACC/AHA guidelines recommend that the addition of spironolactone be considered in NYHA FC III and IV (ACC/AHA stages C and D) patients, and eplerenone in directly post-MI patients with evidence of LV dysfunction.[1]

The major risk related to aldosterone antagonists is hyperkalemia. Therefore, the decision for use of these agents should balance the benefit of decreasing death and hospitalization from HF and the potential risks of life-threatening hyperkalemia. Before and within one week of initiating therapy, two parameters must be assessed: serum potassium and creatinine clearance (or serum creatinine). Aldosterone antagonists should not be initiated in patients with potassium concentrations greater than 5.5 mEq/L (5.5 mmol/L). Likewise, these agents should not be given when creatinine clearance is less than 30 mL/minute or serum creatinine is greater than 2.5 mg/dL (221 μmol/L).

In patients without contraindications, spironolactone is initiated at a dose of 12.5 to 25 mg daily, or occasionally on alternate days for patients with baseline renal insufficiency. Eplerenone is used at a dose of 25 mg daily, with the option to titrate up to 50 mg daily. Doses should be halved or switched to alternate-day dosing if creatinine clearance falls below 50 mL/minute. Potassium supplementation is often decreased or stopped after aldosterone antagonists are initiated, and patients should be counseled to avoid high-potassium foods. At any time after initiation of therapy, if potassium concentrations exceed 5.5 mEq/L (5.5 mmol/L), the dose of the aldosterone antagonist should be reduced or discontinued. Patients receiving concomitant potassium supplements should have these discontinued. In addition, worsening renal function dictates consideration for stopping the aldosterone antagonist. Other adverse effects observed mainly with spironolactone include gynecomastia for men and breast tenderness and menstrual irregularities for women. Gynecomastia leads to discontinuation in up to 10% of patients on spironolactone. Eplerenone is a CYP3A4 substrate and should not be used concomitantly with strong inhibitors of 3A4.

Digoxin

Digoxin has been used for several decades in the treatment of HF. Traditionally, it was considered useful for its positive inotropic effects, but more recently its benefits are thought to be related to neurohormonal modulation. Digoxin exerts positive inotropic effects through binding to sodium- and potassium-activated adenosine triphosphate (ATP) pumps, leading to increased intracellular sodium concentrations and subsequently more available intracellular calcium during systole. The mechanism of digoxin's neurohormonal blocking effect is less well understood, but may be related to restoration of baroreceptor sensitivity and reduced central sympathetic outflow.[5]

The exact role of digoxin in therapy remains controversial largely due to disagreement on the risk versus benefit of routinely using this drug in patients with systolic HF. Digoxin was shown to decrease HF-related hospitalizations but did not decrease HF progression or improve survival.[36] Moreover, digoxin was associated with an increased risk for concentration related toxicity and numerous adverse effects. Post-hoc study analyses demonstrated a clear relationship between digoxin plasma concentration and outcomes. Concentrations below 1.2 mg/dL (1.5 nmol/L) were associated with no apparent

adverse effect on survival, whereas higher concentrations increased the relative risk of mortality.[37,38]

Current recommendations are for the addition of digoxin for patients who remain symptomatic despite an optimal HF regimen consisting of an ACE inhibitor or ARB, β-blocker, and diuretic. In patients with concomitant atrial fibrillation, digoxin may be added to slow ventricular rate regardless of HF symptomology.

Digoxin is initiated at a dose of 0.125 to 0.25 mg daily depending on age, renal function, weight, and risk for toxicity. The lower dose should be used if the patient satisfies any of the following criteria: over 65 years of age, creatinine clearance less than 60 mL/minute, or ideal body weight less than 70 kg (154 lb). The 0.125 mg daily dose is adequate in the majority of patients. The desired concentration range for digoxin is 0.5 to 1.2 ng/mL (0.64 to 1.5 nmol/L), preferably with concentrations at or less than 0.8 ng/mL (1 nmol/L). Routine monitoring of serum drug concentrations is not required but recommended in those with changes in renal function, suspected toxicity, or after addition or subtraction of an interacting drug.

Digoxin toxicity may manifest as non-specific findings such as fatigue or weakness, and other CNS effects such as confusion, delirium, and psychosis. Gastrointestinal manifestations include nausea, vomiting, or anorexia, and visual disturbances may occur such as halos, photophobia, and color perception problems (red-green or yellow-green vision). Cardiac findings include numerous types of arrhythmias related to enhanced automaticity, slowed or accelerated conduction, or delayed afterdepolarizations. These include ventricular tachycardia and fibrillation, atrioventricular nodal block, and sinus bradycardia. Risk of digoxin toxicity, in particular the cardiac manifestations, are increased with electrolyte disturbances such as hypokalemia, hypercalcemia, and hypomagnesemia. To reduce the proarrhythmic risk of digoxin, serum potassium and magnesium should be monitored closely to ensure adequate concentrations (potassium greater than 4.0 mEq/L [4.0 mmol/L] and magnesium greater than 2.0 mEq/L [1 mmol/L]). In patients with life-threatening toxicity due to cardiac or other findings, administration of digoxin-specific Fab antibody fragments usually reverses adverse effects within an hour in most cases.

Calcium Channel Blockers

Treatment with nondihydropyridine calcium channel blockers (diltiazem and verapamil) may worsen HF and increase the risk of death in patients with advanced LV dysfunction due to their negative inotropic effects. Conversely, dihydropyridine calcium channel blockers, although negative inotropes in vitro, do not appear to decrease contractility in vivo. Amlodipine and felodipine are the two most extensively studied dihydropyridine calcium channel blockers for systolic HF.[39,40] These two agents have not been shown to affect patient survival, either positively or negatively. As such, they are not routinely recommended as part of a standard HF regimen; however, amlodipine and felodipine can safely be used in HF patients to treat uncontrolled hypertension or angina once all other appropriate drugs are maximized.

Antiplatelets and Anticoagulation

Patients with HF are at an increased risk of thromboembolic events secondary to a combination of hypercoagulability, relative stasis of blood, and endothelial dysfunction. However, the role of antiplatelets and anticoagulants remains debatable due to a lack of prospective clinical trials.

Aspirin is generally used in HF patients with an underlying ischemic etiology, a history of ischemic heart disease, or other compelling indications such as history of embolic stroke. Routine use in non-ischemic cardiomyopathy patients is currently discouraged because of a lack of data supporting any long-term benefit, as well as the potential negative drug-drug interaction with ACE inhibitors and ARBs. If aspirin is indicated, the preference is to use a low dose (81 mg daily).[41] Although no data are available with clopidogrel, it may become the antiplatelet agent of choice in HF because it has not been shown to adversely affect the actions of ACE inhibitors or ARBs.

Current consensus recommendations support the use of warfarin in patients with reduced LV systolic dysfunction and a compelling indication such as atrial fibrillation or prosthetic heart valves.[42] In addition, warfarin is empirically used in patients with echocardiographic evidence of a mural thrombus or severely depressed (LVEF less than 20%) LV function.[43] However, there are no prospective data and only limited observational data supporting the use of empiric warfarin based on these echocardiographic findings. Patients with HF often have difficulty maintaining a therapeutic International Normalized Ratio (INR) due to fluctuating volume status and varying drug absorption. Therefore, the benefit of using warfarin should be evaluated in the context of the risk for major and minor bleeding.

Heart Failure with Preserved Left Ventricular Ejection Fraction

It is now recognized that a significant number of patients exhibiting HF symptoms have normal systolic function or preserved LVEF (40% to 60%). It is believed that the primary defect in these patients is impaired ventricular relaxation and filling, commonly referred to as diastolic dysfunction or diastolic HF. Heart failure with preserved EF is more prevalent in older women and is closely associated with hypertension or diabetes, and to a lesser extent, CAD and atrial fibrillation.[44] Morbidity in HF patients with preserved EF is comparable to those with depressed EF, as both are characterized by frequent, repeated hospitalizations.[44] However, HF with preserved EF is associated with better survival. The diagnosis is based on findings of typical signs and symptoms of HF, in conjunction with echocardiographic evidence of normal LV systolic function and no valvular disease.

Unlike systolic HF, few prospective trials have evaluated the safety and efficacy of various cardiac medications in patients with diastolic HF or preserved ejection fraction. The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) study demonstrated that angiotensin receptor blockade with candesartan resulted in beneficial effects on HF morbidity in patients with preserved LVEF similar to those seen in depressed LV function.[25]

In the absence of more landmark clinical studies, the current treatment approach for diastolic dysfunction or preserved LVEF is: (1) correction or control of underlying etiologies (including optimal treatment of hypertension and CAD and maintenance of normal sinus rhythm); (2) reduction of cardiac filling pressures at rest and during exertion; and (3) increased diastolic filling time. Diuretics, ACE inhibitors, and ARBs are frequently used to control congestion. Angiotensin receptor blockers may also slow disease progression. β-Blockers and calcium channel blockers can theoretically improve ventricular relaxation through negative inotropic and chronotropic effects. Unlike in systolic HF, nondihydropyridine calcium channel blockers (diltiazem and verapamil) may be especially useful in improving diastolic function by limiting the availability of calcium that mediates contractility. The role of digoxin for symptom management and HR control in these patients is not well established.

Special Populations and Patients with Concomitant Disorders

Ethnic and Genetic Considerations

Heart failure is more prevalent and associated with a worse prognosis in African-Americans compared to the general population.[1] Unfortunately, deficiencies in disease prevention, detection, and access to treatment are well documented in minority populations. African-Americans and other races are underrepresented in clinical trials, compromising the extrapolation of results from these studies to ethnic subpopulations. The influence of race on efficacy and safety of medications used in HF treatment has received additional attention with the advent of pharmacogenomics (the influence of genetics on drug response). The application of race and genetics to pharmacotherapeutic decision making for HF is in the early stages. However, these concepts are being applied to the use of hydralazine and isosorbide dinitrate in African-American patients.[26] It is anticipated that further investigation will lead to better insight relating to the clinical applicability of genetic variations to drug responses.

Peripartum Cardiomyopathy and Pregnancy

Peripartum cardiomyopathy (PPCM) is currently defined as clinical and echocardiographic evidence for new-onset HF occurring during pregnancy and up to 6 months after delivery, with other etiologies excluded. Although PPCM is not well understood, it manifests in pregnant women of all ages, but the risk is elevated in women older than 30 years of age.[45] The true incidence of idiopathic PPCM is debatable, with reported rates for peripartum HF at 1 case per 100 to 4,000 deliveries.[46] The leading hypothesis for PPCM pathogenesis is myocarditis caused by a viral infection or an abnormal immune response to pregnancy. Heart failure may persist after delivery but can be reversible (with partial or full recovery of cardiac function) in many cases.[45]

The clinical presentation of peripartum HF is indistinguishable from that of other types of HF. Initial treatment is also similar, with the exception of ACE inhibitors and ARBs being contraindicated during the antepartum period. Treatment includes reducing preload by sodium restriction and diuretics, afterload reduction with vasodilators, and sometimes inotropic support with digoxin. Hydralazine is utilized frequently in pregnancy and is classified as FDA pregnancy category C. Labetalol is used for acute parenteral control of blood pressure, but long-term β-blocker use corresponds with low birth weight infants. Management of the cardiomyopathy after delivery includes use of ACE inhibitors and β-blockers, although these treatment guidelines have been extrapolated from studies in patients with idiopathic dilated cardiomyopathy rather than specific trials in PPCM. Patients with PPCM also have a high rate of thromboembolism. Treatment options during pregnancy are limited to unfractionated heparin and low-molecular-weight heparin since warfarin is contraindicated. After delivery, anticoagulation is recommended in patients with LVEF less than 20%.[46]



Patient Encounter, Part 3

Based on the information presented and your problem-based assessment, create a care plan for BE's heart failure. Your plan should include:

- Nonpharmacologic treatment options.
- Acute and chronic treatment plans to address BE's symptoms and prevent disease deterioration.
- Monitoring plan for acute and chronic treatments.

OUTCOME EVALUATION OF CHRONIC HEART FAILURE

- The evaluation of therapy is influenced by the ability of treatment to successfully reduce symptoms, improve quality of life, decrease frequency of hospitalizations for AHF, reduce disease progression, and prolong survival (Fig. 3–1).
- The major outcome parameters focus on: (1) volume status; (2) exercise tolerance; (3) overall symptoms/quality of life; (4) adverse drug reactions; and (5) disease progression and

cardiac function. Assess quality of life by evaluating patients' ability to continue their activities of daily living.

- Assess symptoms of HF such as dyspnea on exertion, orthopnea, weight gain, and edema, and abdominal manifestations such as nausea, bloating, and loss of appetite.
- If diuretic therapy is warranted, monitor for therapeutic response by assessing weight loss and improvement of fluid retention, as well as exercise tolerance and presence of fatigue.
- Once therapy for preventing disease progression is initiated, monitoring for symptomatic improvement continues.
- It is important to keep in mind that patients' symptoms of HF can worsen with β-blockers, and it may take weeks or months before patients notice improvement.
- Monitor blood pressure to evaluate for hypotension caused by drug therapy.
- To assess for prevention of disease progression, practitioners may utilize serial echocardiograms every 6 months to assess cardiac function and evaluate the effects of drug therapy.
- Occasional exercise testing is conducted in order to ascertain disease prognosis or suitability for heart transplant. Even though these tests can demonstrate improvement in heart function and therefore slowed disease progression, patient symptoms may not improve.

ACUTE AND ADVANCED HEART FAILURE

Clinical Presentation and Diagnosis of Acute Heart Failure

Patients with acute heart failure (AHF) present with symptoms of worsening fluid retention or decreasing exercise tolerance and fatigue (typically worsening of symptoms presented in the chronic heart failure clinical presentation text box). These symptoms reflect congestion behind the failing ventricle and/or hypoperfusion. Patients can be categorized into hemodynamic subsets based on assessment of physical signs and symptoms of congestion and/or hypoperfusion.[47] Patients can be described as "wet" or "dry" depending on volume status, as well as "warm" or "cool" based on adequacy of tissue perfusion. "Wet" refers to patients with volume/fluid overload [e.g., edema and jugular venous distention (JVD)], whereas "dry" refers to euvolemic patients. "Warm" refers to patients with adequate CO to perfuse peripheral tissues (and hence the skin will be warm to touch), whereas "cool" refers to patients with evidence of hypoperfusion (skin cool to touch with diminished pulses). Additionally, invasive hemodynamic monitoring can be used to provide

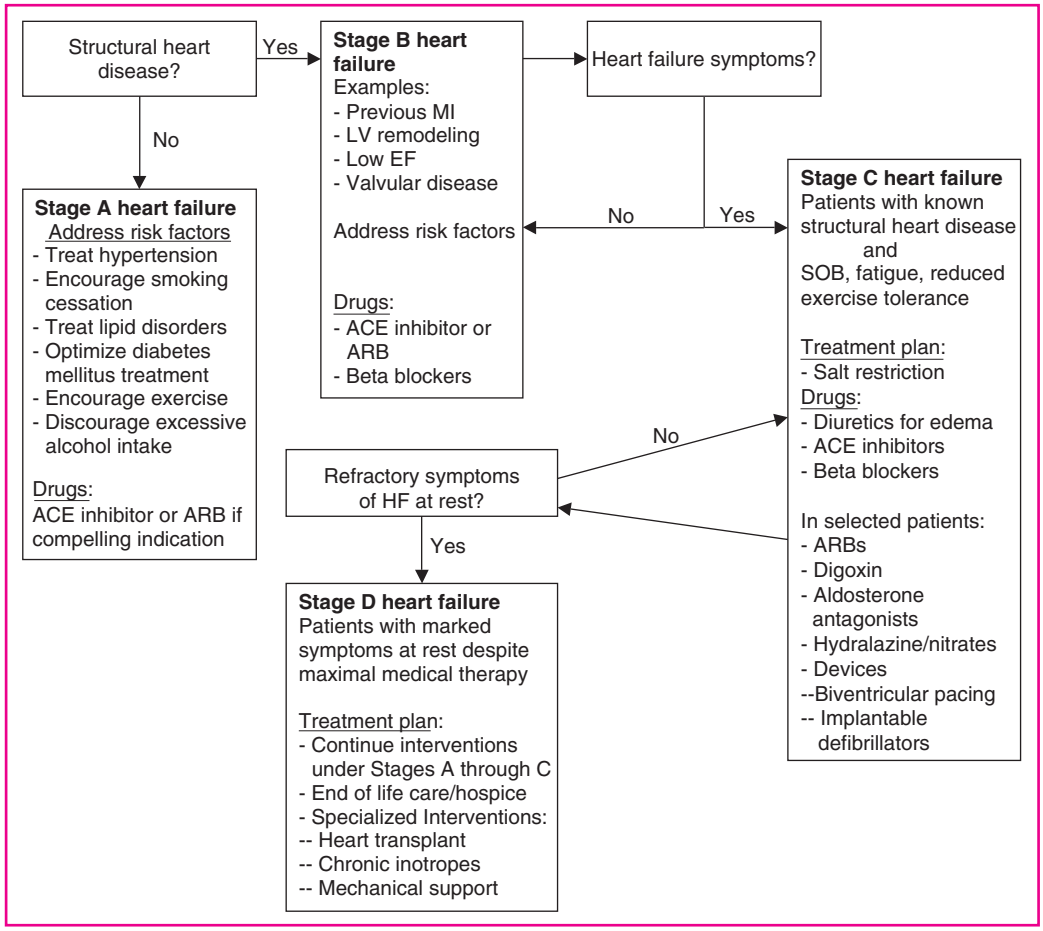


FIGURE 3–1. Treatment algorithm for chronic heart failure. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; EF, ejection fraction; HF, heart failure; LV, left ventricular; MI, myocardial infarction; SOB: shortness of breath. Table 3–5 describes staging of heart failure.

objective data for assessing volume status [pulmonary capillary wedge pressure (PCWP)] and perfusion (CO). A CI below 2.2 L/minute per square meter is consistent with hypoperfusion and reduced contractility, and a PCWP above 18 mm Hg correlates with congestion and an elevated preload. The four possible hemodynamic subsets a patient may fall into are: "warm and dry," "warm and wet," "cool and dry," or "cool and wet."



Clinical Presentation of Acute Heart Failure

Subset I (Warm and Dry)
- Cardiac index (CI) *greater than* 2.2 L/minute per square meter, pulmonary capillary wedge pressure (PCWP) *less than* 18 mm Hg
- Patients considered well compensated and perfused, without evidence of congestion
- No immediate interventions necessary except optimizing oral medications and monitoring

Subset II (Warm and Wet)
- CI *greater than* 2.2 L/minute per square meter, PCWP *greater than* or equal to 18 mm Hg
- Patients adequately perfused and display signs and symptoms of congestion
- Main goal is to reduce preload (PCWP) carefully with loop diuretics and vasodilators

Subset III (Cool and Dry)
- CI *less than* 2.2 L/minute per square meter, PCWP *less than* 18 mm Hg
- Patients are inadequately perfused and not congested
- Hypoperfusion leads to increased mortality, elevating death rates four-fold compared to those who are adequately perfused
- Treatment focuses on increasing CO with positive inotropic agents and/or replacing intravascular fluids
- Fluid replacement must be performed cautiously, as patients can rapidly become congested

Subset IV (Cool and Wet)
- CI *less than* 2.2 L/minute per square meter, PCWP *greater than* 18 mm Hg
- Patients are inadequately perfused and congested
- Classified as the most complicated clinical presentation of AHF with the worst prognosis
- Most challenging to treat; therapy targets alleviating signs and symptoms of congestion by increasing CI as well as reducing PCWP, while maintaining adequate mean arterial pressure
- Treatment involves a delicate balance between diuretics, vasodilators, and inotropic agents
- Use of vasopressors is sometimes necessary to maintain blood pressure

Clinical Assessment and Diagnosis

Precipitating Factors

❸ *It is important for the clinician to identify the cause(s) of AHF in order to maximize treatment efficacy and reduce future disease exacerbations. Cardiovascular, metabolic, and lifestyle factors can all precipitate AHF.* The most common precipitating factors for acute decompensation and how they contribute pathophysiologically are listed in Table 3–3.

Laboratory Assessment

Routine laboratory testing of patients with AHF includes electrolytes and blood glucose, as well as serum creatinine and blood urea nitrogen to assess renal function. Complete blood cell count is measured to determine if anemia or infection is present. Creatine kinase and/or troponin concentrations are used to diagnose ischemia, and hepatic transaminases are measured to help rule out hepatic congestion (in other words, until it is determined that it is not hepatic congestion). Thyroid function tests are measured to assess hyperthyroidism or hypothyroidism as causes of AHF. A urinalysis is attained in patients with an unknown history of renal disease to rule out nephrotic syndrome. Lastly, a toxicology screen is obtained in patients in whom use of illicit drugs is suspected.

Assays measuring BNP and its degradation product NT-proBNP have been developed and are being used with greater frequency in clinical practice.[10] B-type natriuretic peptide is synthesized, stored, and released from the ventricles in response to increased ventricular filling pressures. Hence, plasma levels of BNP can be used as a marker for volume overload. The most widely accepted indication for BNP measurement is as an adjunctive aid for diagnosing a cardiac etiology for dyspnea.[10] Although there is evidence to support a prognostic role for BNP concentrations in HF and MI, widespread clinical application has yet to occur. Current trials are also testing whether serial BNP monitoring can be used to guide therapy.

The current values for ruling out a cardiac etiology for dyspnea are a BNP less than 100 pg/mL (100 ng/L) or an NT-proBNP less than 300 pg/mL (300 ng/L or 35.4 pmol/L). BNP measurements require cautious interpretation, as numerous conditions can also elevate BNP concentrations. These include older age, renal dysfunction, pulmonary embolism, and chronic pulmonary disease. Nesiritide, a recombinant BNP drug, has an identical structure to native BNP and will interfere with the commercial BNP assay, resulting in a falsely elevated level. Therefore, blood for BNP determination should be obtained 2 hours after the end of a nesiritide infusion, or alternatively the NT-proBNP assay should be utilized.

Other diagnostic tests should also be obtained in order to rule out precipitating factors (chest radiograph) and to evaluate cardiac function (ECG).

Invasive hemodynamic monitoring in patients with HF entails placement of a right heart or pulmonary artery catheter (PAC). The catheter is inserted percutaneously through a central vein and advanced through the right side of the heart to the

TABLE 3–8. Hemodynamic Monitoring: Normal Values

Hemodynamic Variable	Normal Value
Central venous (right atrial) pressure, mean	Less than 5 mm Hg
Right ventricular pressure	25/0 mm Hg
Pulmonary artery pressure	25/10 mm Hg
Pulmonary artery pressure, mean	Less than 18 mm Hg
Pulmonary artery occlusion pressure, mean	Less than 12 mm Hg
Systemic arterial pressure	120/80 mm Hg
Mean arterial pressure	90–120 mm Hg
Cardiac index	2.8–4.2 L/minute per square meter
Stroke volume index	30–65 mL/beat per square meter
Systemic vascular resistance	900–1.400 dyn·s·m^{-5}
Pulmonary vascular resistance	150–250 dyn·s·m^{-5}
Arterial oxygen content	20 mL/dL
Mixed venous oxygen content	15 mL/dL
Arteriovenous oxygen content difference	3–5 mL/dL

pulmonary artery. Inflation of a balloon proximal to the end port allows the catheter to "wedge," yielding the PCWP, which estimates pressures in the left ventricle during diastole. Additionally, CO can be estimated and SVR calculated (Table 3–8).

There are no universally accepted guidelines dictating when invasive monitoring in HF is required. The use of a PAC remains an essential component of management and monitoring of patients in cardiogenic shock; however, the use of inotropic agents does not mandate invasive monitoring. Invasive hemodynamic monitoring is most commonly used to aid in the assessment of hemodynamics when there is disagreement between signs and symptoms and clinical response. In addition, invasive monitoring is helpful in guiding ongoing therapy for AHF. Invasive monitoring offers the advantage of immediate hemodynamic assessment of an intervention, allowing for prompt adjustments. Risks with PACs include infection, bleeding, thrombosis, catheter malfunction, and ventricular ectopy. A recent randomized trial of PAC use in HF demonstrated a neutral effect on patient mortality.

TREATMENT OF ACUTE HEART FAILURE

Desired Therapeutic Outcomes

The goals of therapy for AHF are to: (1) correct the underlying precipitating factor(s); (2) relieve the patient's symptoms; (3) improve hemodynamics; (4) optimize a chronic oral medication regimen; and (5) educate the patient, reinforcing adherence to lifestyle modifications and the drug regimen. The ultimate goal for a patient hospitalized for AHF is the return to a compensated HF state and discharge to the outpatient setting on oral medications. Only through aggressive management to achieve all of these goals will a patient's prognosis be improved and future hospitalizations for acute decompensations prevented.

Removal or control of precipitating factors is essential for an optimal response to pharmacologic therapy. Relief of symptoms should occur rapidly to minimize length of hospitalization. Although a rapid discharge from the hospital is desirable, a patient should not be discharged before ensuring that he or she is in a euvolemic, or nearly euvolemic, state with a body weight and functional capacity similar to before the acute decompensation. Oral agents such as β-blockers, ACE inhibitors or ARBs, and aldosterone antagonists should be initiated as soon as possible during the hospitalization. These chronic oral medications not only improve mortality and prevent readmissions, acutely they also contribute to improvement in hemodynamics. Patient education prior to discharge from the hospital is recommended to assist in minimizing adverse effects and non-adherence. Dissemination of written information, in addition to verbal information, is helpful for patient comprehension and retention. This can include therapy goals, lifestyle modifications, drug regimen, dosage information, and relevant adverse effects, as well as symptom and diary cards.

Pharmacologic Approaches to Treatment

⑩ *Treatment of AHF targets relief of congestion and optimization of CO utilizing oral or intravenous diuretics, intravenous vasodilators, and when appropriate inotropes, based on presenting hemodynamics. Current treatment strategies in AHF target improving hemodynamics while preserving organ function.* A specific treatment approach is formulated depending on the patient's symptoms (congestion versus hypoperfusion) and hemodynamic indices (CI and PCWP).[48,49] If the patient primarily exhibits signs and symptoms of congestion, treatment entails use of diuretics as first-line agents to decrease PCWP. Additionally, intravenous vasodilators are added to provide rapid relief of congestion and additional reductions in PCWP. By reducing congestion in the heart, cardiac contractile function may improve, which results in an increase in SV and CO, and hence perfusion to vital organs. For patients primarily displaying symptoms of hypoperfusion, treatment relies on use of agents that increase cardiac contractility, known as positive inotropes. Some patients display both symptoms of congestion as well as hypoperfusion and thus require use of combination therapies. One of the current challenges to the treatment of AHF is achieving hemodynamic improvement without adversely affecting organ function. In the case of inotropes, the increased contractility occurs at the expense of an increase in cardiac workload and proarrhythmia. In addition, high-dose diuretic therapy is associated with worsened renal function and possibly neurohormonal activation.

Diuretics

Loop diuretics, including furosemide, bumetanide, and torsemide are the diuretics of choice in the management of

TABLE 3–9. Intravenous Diuretics Used to Treat Heart Failure–Related Fluid Retention

	Onset of Action (minutes)	Duration of Action (hours)	Relative Potency	Intermittent Bolus Dosing (mg)	Continuous Infusion Dosing (bolus/infusion)
Furosemide	2–5	6	40	20–200+	20–40/2.5–10
Torsemide	Less than 10	6–12	20	10–100	20/2–5
Bumetanide	2–3	4–6	0.5	1–10	1–4/0.5–1
Ethacrynic acid	5–15	2–7		0.5–1 mg/kg per dose up to 100 mg/dose	

AHF. Furosemide is the most commonly used agent. Diuretics decrease preload by functional venodilation within 5 to 15 minutes of administration and subsequently by an increase in sodium and water excretion. This provides rapid improvement in symptoms of pulmonary congestion. Diuretics reduce PCWP but do not increase CI like positive inotropes and arterial vasodilators. Patients who have significant volume overload often have impaired absorption of oral loop diuretics because of intestinal edema or altered transit time. Therefore, doses are usually administered via intravenous boluses, given either at the same dose as the home oral dose for those taking diuretics regularly or at lower doses for diuretic-naïve patients (Table 3–9). Higher doses may be required for patients with renal insufficiency due to decreased drug delivery to the site of action in the loop of Henle.

There is a paucity of clinical trial evidence comparing the benefit of diuretics to other therapies for symptom relief or long-term outcomes. Additionally, excessive preload reduction can lead to a decrease in CO resulting in reflex increase in sympathetic activation, renin release, and the expected consequences of vasoconstriction, tachycardia, and increased myocardial oxygen demand. Careful use of diuretics is recommended to avoid overdiuresis. Monitor serum electrolytes such as potassium, sodium, and magnesium frequently to identify and correct imbalances. Monitor serum creatinine and blood urea nitrogen daily at a minimum to assess volume depletion and renal function.

Occasionally, patients with HF do not respond to a diuretic, defined as failure to achieve a weight reduction of at least 0.5 kg (or negative net fluid balance of at least 500 mL) after several increasing bolus doses.[17]

Several strategies are employed to overcome diuretic resistance. These include using larger oral doses, converting to intravenous dosing, or increasing the frequency of administration. Small studies using low-dose continuous infusions of furosemide and torsemide have shown an increase in urine output compared to intermittent bolus dosing.[50] Continuous infusions may provide a theoretical advantage of continuous presence of high drug levels within the tubular lumen, causing a sustained natriuresis. Most regimens include a bolus dose followed by a maintenance infusion (Table 3–9).[51] Another useful strategy is to combine two diuretics with different sites of action within the nephron. The most common combination is the use of a loop diuretic with a thiazide diuretic such as metolazone. Combining diuretics should be used with caution due to an increased risk for cardiovascular collapse due to rapid intravascular volume depletion. Strict monitoring of electrolytes, vital signs, and fluid balance is warranted.

Finally, poor CO may contribute to diuretic resistance. In these patients, it may become necessary to add vasodilators or inotropes to enhance perfusion to the kidneys. Care must be taken, as vasodilators can decrease renal blood flow despite increasing CO through dilation of central and peripheral vascular beds.

Vasodilators

Intravenous vasodilators cause a rapid decrease in arterial tone, resulting in a decrease in SVR and a subsequent increase in SV and CO. Additionally, vasodilators reduce ventricular filling pressures (PCWP) within 24 to 48 hours, reduce myocardial oxygen consumption, and decrease ventricular workload. Vasodilators are commonly used in patients presenting with AHF accompanied by moderate to severe congestion. This class includes nitroglycerin, nitroprusside, and nesiritide. Hemodynamic effects and dosages for these agents are included in Tables 3–10 and 3–11, respectively. Although vasodilators are generally safe and effective, identification of the proper patient for use is important to minimize the risk of

TABLE 3–10. Usual Hemodynamic Effects of Commonly Used Intravenous Agents for Treatment of Acute or Severe Heart Failure

Drug	CO	PCWP	SVR	BP	HR
Diuretics	↑/↓/0	↓		↓	0
Nitroglycerin	↑	↓↓	↓	↓↓	↑/0
Nitroprusside	↑	↓↓↓	↓↓↓	↓↓↓	↑
Nesiritide	↑	↓↓	↓↓	↓↓	0
Dobutamine	↑↑	↓/0	↓/0	↓/0	↑↑
Milrinone	↑↑	↓↓	↓	↓	↑

BP, blood pressure; CO, cardiac output; HR, heart rate; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance; ↑, increase; ↓, decrease; 0, no or little change.

TABLE 3–11. Usual Doses and Monitoring of Commonly Used Hemodynamic Medications

Drug	Dose	Monitoring Variables[a]
Dopamine	0.5–10+ mcg/kg per minute	BP, HR, urinary output and kidney function, ECG, extremity perfusion (higher doses only)
Dobutamine	2.5–20 mcg/kg per minute	BP, HR urinary output and function, ECG
Milrinone	0.375–0.75 mcg/kg per minute	BP, HR, urinary output and function, ECG, changes in ischemic symptoms (e.g., chest pain), electrolytes
Nitroprusside	0.25–3 mcg/kg per minute	BP, HR, liver and kidney function, blood cyanide and/or thiocyanate concentrations if toxicity suspected (nausea, vomiting, altered mental function)
Nitroglycerin	5–200+ mcg/kg per minute	BP, HR, ECG, changes in ischemic symptoms
Nesiritide	Bolus: 2 mcg/kg; Infusion: 0.01 mcg/kg per minute	BP, HR, urinary output and kidney function, blood BNP concentrations

[a] In addition to pulmonary capillary wedge pressure and cardiac output.

BNP, B-type natriuretic peptide; BP, blood pressure; ECG, electrocardiogram; HR, heart rate.

significant hypotension. In addition, vasodilators are contraindicated in patients whose cardiac filling (and hence CO) depends on venous return or intravascular volume, as well as patients who present with shock.

Nitroglycerin

Nitroglycerin acts as a source of nitric oxide, which induces smooth muscle relaxation in venous and arterial vascular beds. Nitroglycerin is primarily a venous vasodilator at lower doses, but exerts potent arterial vasodilatory effects at higher doses. Thus, at lower doses, nitroglycerin causes decreases in preload (or filling pressures) and improved coronary blood flow. At higher doses (greater than 100 mcg/minute), additional reduction in preload is achieved, along with a decrease in afterload and subsequent increase in SV and CO. Intravenous nitroglycerin is primarily used as a preload reducer for patients exhibiting pulmonary congestion or in combination with inotropes for congested patients with severely reduced CO.[52]

Continuous infusions of nitroglycerin should be initiated at a dose of 5 to 10 mcg/minute and increased every 5 to 10 minutes until symptomatic or hemodynamic improvement. Effective doses range from 35 to 200 mcg/minute. The most common adverse events reported are headache, dose-related hypotension, and tachycardia. A limitation to nitroglycerin's use is the development of tachyphylaxis, or tolerance to its effects, which can be evident within 12 hours after initiation of continuous infusion and necessitate additional titrations to higher doses.

Nitroprusside

Nitroprusside, like nitroglycerin, causes the formation of nitric oxide and vascular smooth muscle relaxation. In contrast to nitroglycerin, nitroprusside is both a venous and arterial vasodilator regardless of dosage. Nitroprusside causes a pronounced decrease in PCWP, SVR, and blood pressure, with a modest increase in CO. Nitroprusside has been studied to a limited extent in AHF and no studies have evaluated its effects on mortality.[48] Nitroprusside is initiated at 0.1 to 0.25 mcg/kg per minute, followed by dose adjustments in 0.1 to 0.2 mcg/kg per minute increments if necessary to achieve desired effect. Because of its rapid onset of action and metabolism, nitroprusside is administered as a continuous infusion that is easy to titrate and provides predictable hemodynamic effects. Nitroprusside requires strict monitoring of blood pressure and HR. Nitroprusside's use is limited in AHF due to recommended hemodynamic monitoring with an arterial line and mandatory intensive care unit admission at many institutions. Abrupt withdrawal of therapy should be avoided, as rebound neurohormonal activation may occur. Therefore, the dose should be tapered slowly. Nitroprusside has the potential to cause cyanide and thiocyanate toxicity, especially in patients with renal insufficiency. Toxicity is most common with use longer than 3 days and with higher doses. Nitroprusside should be avoided in patients with active ischemia, because its powerful afterload-reducing effects within the myocardium can "steal" coronary blood flow from myocardial segments that are supplied by epicardial vessels with high-grade lesions.

Nesiritide

B-type natriuretic peptide is an endogenous neurohormone that is synthesized and released from the ventricles in response to chamber wall stretch or increased filling pressures. Recombinant BNP, or nesiritide, is the newest compound developed for AHF. Nesiritide binds to guanylate cyclase receptors in vascular smooth muscle and endothelial cells, causing an increase in cGMP concentrations leading to vasodilation (venous and arterial) and natriuresis. Nesiritide also antagonizes the effects of the RAAS and endothelin. Nesiritide reduces PCWP, right atrial pressure, and SVR. Consequently, it also increases SV and CO without affecting heart rate. Continuous infusions result in sustained effects for 24 hours without tachyphylaxis, although experience with its use beyond 72 hours is limited.

Nesiritide has been shown to improve symptoms of dyspnea and fatigue. In a randomized clinical trial, the safety and efficacy of adding nesiritide to standard care was compared to placebo and nitroglycerin.[53] Nesiritide was found to significantly decrease PCWP more than nitroglycerin and placebo over 3 hours. Nesiritide improved patients' self-reported

dyspnea scores compared to placebo at 3 hours, but there was no difference compared to nitroglycerin. There are no prospective mortality studies with nesiritide in AHF.

Currently, nesiritide is indicated for patients with AHF exhibiting dyspnea at rest or with minimal activity. The recommended dose regimen is a bolus of 2 mcg/kg, followed by a continuous infusion for up to 24 hours of 0.01 mcg/kg per minute. Because nesiritide's effects are predictable and sustained at the recommended dosage, titration of the infusion rate (maximum of 0.03 mcg/kg per minute) is not commonly required nor is invasive hemodynamic monitoring. Nesiritide should be avoided in patients with systolic blood pressure less than 90 mm Hg. Although nesiritide's place in AHF therapy is not firmly defined, it is used as one of the first-line agents (in combination with diuretics) for the majority of patients presenting in moderate to severe decompensation, mainly due to its proven benefits and unique mechanism of action. One potential disadvantage compared to other vasodilators is its longer half-life. If hypotension occurs, the effect can be prolonged (2 hours). There are also concerns relating to elevations in serum creatinine observed with nesiritide; however, whether this effect is clinically relevant remains unanswered.

Inotropic Agents

Currently available positive inotropic agents act via increasing intracellular cyclic adenosine monophosphate (cAMP) concentrations through different mechanisms. β-Agonists activate adenylate cyclase through stimulation of β-adrenergic receptors, which subsequently catalyzes the conversion of adenosine triphosphate (ATP) to cAMP. In contrast, phosphodiesterase inhibitors reduce degradation of cAMP. The resulting elevation in cAMP levels leads to enhanced phospholipase activity, which then increases the rate and extent of calcium influx during systole, thereby enhancing contractility. Additionally, during diastole, cAMP promotes uptake of calcium by the sarcoplasmic reticulum which improves cardiac relaxation. The inotropes approved for use in AHF are discussed in the following sections.

Dobutamine

Dobutamine has historically been the inotrope of choice for AHF. As a synthetic catecholamine, it acts as an agonist mainly on β_1- and β_2-receptors and minimally on α_1-receptors. The resulting hemodynamic effects are due to both receptor- and reflex-mediated activities. These effects include: increased contractility and HR through β_1- (and β_2-) receptors and vasodilation through a relatively greater effect on β_2- than α_1-receptors. Dobutamine can increase, decrease, or cause little change in mean arterial pressure depending on whether the resulting increase in CO is enough to offset the modest vasodilation. Although dobutamine displays a half life of approximately 2 minutes, its positive hemodynamic effects can be observed for several days to months after administration. The use of dobutamine is supported by several small studies documenting improved hemodynamics, but large-scale clinical trials in AHF are lacking.[54]

Dobutamine is initiated at a dose of 2.5 to 5 mcg/kg per minute, which can be gradually titrated to 20 mcg/kg per minute based on clinical response. There are several practical considerations to dobutamine therapy in AHF. First, owing to its vasodilatory potential, monotherapy with dobutamine is reserved for patients with systolic blood pressures greater than 90 mm Hg. However, it is commonly used in combination with vasopressors in patients with lower systolic blood pressures. Second, due to down-regulation of β_1-receptors or uncoupling of β_2- receptors from adenylate cyclase with prolonged exposure to dobutamine, attenuation of hemodynamic effects has been reported to occur as early as 48 hours after initiation of a continuous infusion, although tachyphylaxis is more evident with use spanning longer than 72 hours. Full sensitivity to dobutamine's effects can be restored 7 to 10 days after the drug is withdrawn. Third, many patients with AHF will be taking β-blockers on a chronic basis. Because of β-blockers' high affinity for β-receptors, the effectiveness of β-agonists such as dobutamine will be reduced. In patients on β-blocker therapy, it is recommended that consideration be given to the use of phosphodiesterase inhibitors such as milrinone, which are not dependent on β-receptors for effect.[55,56] Although commonly practiced, use of high doses of dobutamine to overcome the β-blockade should be discouraged, as this negates any of the protective benefits of the β-blocker.

Dopamine

Dopamine is most commonly reserved for patients with low systolic blood pressures and those approaching cardiogenic shock. It may also be used in low doses (less than 3 mcg/kg per minute) to improve renal function in a patient with inadequate urine output despite high filling pressures and volume overload, although this indication is controversial.

Dopamine exerts its effects through direct stimulation of adrenergic receptors, as well as release of norepinephrine from adrenergic nerve terminals. Dopamine produces hemodynamic effects that differ based on dosing. At lower doses, dopamine stimulates dopamine type 1 (D1) receptors and thus increases renal perfusion. Positive inotropic effects are more pronounced at doses of 3 to 10 mcg/kg per minute. Cardiac index is increased due to increased SV and HR. At doses higher than 10 mcg/kg per minute, chronotropic and α_1-mediated vasoconstriction effects are evident. This causes an increase in mean arterial pressure due to higher CI and SVR. The ultimate effect on cardiac hemodynamics will depend largely on the dosage prescribed and must be individually tailored to the patient's clinical status. Dopamine is generally associated with an increase in CO and blood pressure, with a concomitant increase in PCWP. Dopamine increases myocardial oxygen demand and may decrease coronary blood flow through vasoconstriction and increased wall tension. As with other inotropes, dopamine is associated with a risk for arrhythmias.

Phosphodiesterase Inhibitors

Milrinone and inamrinone work by inhibiting phosphodiesterase III, the enzyme responsible for the breakdown of cAMP. The increase in cAMP levels leads to increased intracellular calcium concentrations and enhanced contractile force generation. Milrinone has replaced inamrinone as the phosphodiesterase inhibitor of choice due to the higher frequency of thrombocytopenia seen with inamrinone.

Milrinone has both positive inotropic and vasodilating properties and as such is referred to as an "inodilator." Its vasodilating activities are especially prominent on venous capacitance vessels and pulmonary vascular beds, although a reduction in arterial tone is also noted. Intravenous administration results in an increase in SV and CO, and usually only minor changes in heart rate. Milrinone also lowers PCWP through venodilation. Routine use of milrinone during acute decompensations in NYHA FC II to IV HF is not recommended, and milrinone use remains limited to patients who require inotropic support.[57]

Dosing recommendations for milrinone include a loading dose of 50 mcg/kg, followed by an infusion beginning at 0.5 mcg/kg per minute (range 0.23 mcg/kg per minute for patients with renal failure up to 0.75 mcg/kg per minute). A loading dose is not necessary if immediate hemodynamic effects are not required or if patients have low systolic blood pressures (less than 90 mm Hg). Decreases in blood pressure during an infusion may necessitate dose reductions as well.

Milrinone is a good option for patients requiring an inotrope who are also chronically receiving β-blockers, as the inotropic effects are achieved independent of β-adrenergic receptors. However, milrinone exhibits a long distribution and elimination half-life compared to β-agonists, thus requiring a loading dose when an immediate response is desired. Potential adverse effects include hypotension, arrhythmias, and less commonly, thrombocytopenia. Milrinone should not be used in patients in whom vasodilation is contraindicated.

Mechanical, Surgical, and Device Therapies

Implantable Cardioverter Defibrillators

Implantable cardioverter defibrillators (ICDs) are the most effective modality for primary and secondary prevention of sudden cardiac death in patients with LV dysfunction. Studies universally demonstrate greater efficacy compared to antiarrhythmic therapy and a significant reduction in mortality compared to placebo.[58–60] Recent studies have expanded the eligible patient populations beyond classic indications, such as prior MI and non-sustained ventricular tachycardia or non-suppressible ventricular tachycardia during an electrophysiologic study. A clear advantage of implanting ICDs in all symptomatic patients with LVEF less than 35% regardless of etiology or other cardiac parameters has been demonstrated.[60] Since ICD implantation and follow-up is associated with a significant economic burden, the cost-effectiveness of widespread ICD use continues to be debated. Defining subgroups that



Patient Encounter, Part 4

After 6 months, BE returns to clinic complaining of extreme SOB with any activity, including dressing and showering, as well as at rest. She sleeps sitting up due to severe orthopnea, is unable to eat without nausea, and states she has gained 22 lb (10 kg) from her baseline weight. She also states that she does not feel her furosemide therapy is working, She is admitted to the cardiology unit.

SH

BE admits to resuming smoking after quitting for 2 months; additionally, she has been eating out in restaurants more often in the past 2 weeks.

Meds

Lisinopril 10 mg once daily
Furosemide 80 mg twice daily
Nitroglycerin 0.4 mg sublingual (SL) as needed
Multivitamin daily
Aspirin 325 mg daily

VS: blood pressure 146/94 mm Hg, pulse 102 bpm and regular, respiratory rate 22/minute, temperature 37°C (98.6°F), Wt 271 lb (123 kg), BMI 41.2

Lungs: There are rales present bilaterally

CV: Regular rate and rhythm with normal S_1 and S_2; there is an S_3 and an S_4; a 4/6 systolic ejection murmur is present and heard best at the left lower sternal border; point of maximal impulse is displaced laterally; jugular veins are distended, JVP is 11 cm above sternal angle; a positive HJR is observed

Abd: Hard, tender, and bowel sounds are absent; 3+ pitting edema of extremities is observed

CXR: Bilateral pleural effusions and cardiomegaly

Echo: EF = 20%

Pertinent labs

BNP 740 pg/mL (740 ng/L), K: 4.2 mEq/L (4.2 mmol/L), BUN 64 mg/dL (23 mmol/L), SCr 2.4 mg/dL (212 mmol/L), Mg 1.8 mEq/L (0.9 mmol/L)

A pulmonary catheter is placed, revealing the following: PCWP 37 mm Hg; cardiac index 2.2 L/minute per square meter

- What NYHA functional class, ACC/AHA stage, and hemodynamic subset is BE currently in?
- What are your initial treatment goals?
- What pharmacologic agents are appropriate to use at this time?
- Identify a monitoring plan to assess for efficacy and toxicity of the recommended drug therapy.
- Once BE's symptoms are improved, how would you optimize her oral medication therapy for heart failure?

would derive the greatest benefit and determining the optimal ICD configuration will aid in improving the potential costs compared to benefits.

Cardiac Resynchronization Therapy

Dyssynchronous contraction, as a reflection of intra- and interventricular conduction delays between chambers of the heart, is common in advanced HF patients. Dyssynchrony contributes to diminished cardiac function and unfavorable myocardial energetics through altered filling times, valvular dysfunction, and wall motion defects. Cardiac resynchronization therapy (CRT) with biventricular pacing devices improves cardiac function, quality of life, and mortality in patients with NYHA FC III or IV HF, evidence of intraventricular conduction delay (QRS greater than 120 ms), depressed LV function (LVEF less than 35%), and on an optimal pharmacologic regimen. A recent study also showed that the addition of an ICD to CRT with biventricular pacing further reduced hospitalizations and mortality.[61]

Intra-aortic Balloon Counterpulsation

Intra-aortic balloon counterpulsation (IABC) or intra-aortic balloon pumps (IABPs) are one of the most widely used mechanical circulatory assistance devices for patients with cardiac failure who do not respond to standard therapies. An IABP is placed percutaneously into the femoral artery and advanced to the high descending thoracic aorta. Once in position, the balloon is programmed to inflate during diastole and deflate during systole. Two main beneficial mechanisms are: (1) inflation during diastole increases aortic pressure and perfusion of the coronary arteries, and (2) deflation just prior to the aortic valve opening reduces arterial impedence (afterload). As such, IABC increases myocardial oxygen supply and decreases oxygen demand. This device has many indications, including cardiogenic shock, high-risk unstable angina in conjunction with percutaneous interventions, preoperative stabilization of high-risk patients prior to surgery, and in patients who cannot be weaned from cardiopulmonary bypass. Possible complications include infection, bleeding, thrombosis, limb ischemia, and device malfunction. The device is typically useful for short-term therapy due to the invasiveness of the device, the need for limb immobilization, and the requirement for full anticoagulation.

Ventricular Assist Device

The ventricular assist device (VAD) is a surgically implanted pump that reduces or replaces the work of the right, left, or both ventricles. Ventricular assist devices are currently indicated for short-term support in patients refractory to pharmacologic therapies, as long-term bridge therapy (a temporary transition treatment) in patients awaiting cardiac transplant, or in some instances, as the destination therapy (treatment for patients in lieu of cardiac transplant for those who are not appropriate candidates for transplantation).[1] The most common complications are infection and thromboembolism. Other adverse effects include bleeding, air embolism, device failure, and multiorgan failure.

Surgical Therapy

Heart transplantation represents the final option for refractory, end-stage HF patients who have exhausted medical and device therapies. Heart transplantation is not a cure, but should be considered a trade between a life-threatening syndrome and the risks associated with the operation and long-term immunosuppression. Assessment of appropriate candidates includes comorbid illnesses, psychosocial behavior, available financial and social support, and patient willingness to adhere to lifelong therapy and close medical follow-up.[1] Overall, the transplant recipient's quality of life may be improved, but not all patients receive this benefit. Posttransplant survival continues to improve due to advances in immunosuppression, treatment and prevention of infection, and optimal management of patient comorbidities.

Investigational Therapies

Clinical trials are currently investigating new agents for the treatment of AHF. These compounds offer unique mechanisms of action by targeting different neurohormonal receptors (vasopressin, endothelin, atrial natriuretic peptide, and adenosine) or through completely novel pharmacologic profiles (levosimendan). Some agents or drug classes being studied include: tolvaptan, a V_2-selective vasopressin antagonist; various ET-A selective and non-selective antagonists; and an adenosine-1 receptor agonist.

OUTCOME EVALUATION OF ACUTE HEART FAILURE

- Focus on: (1) acute improvement of symptoms and hemodynamics due to intravenous therapies; (2) criteria for a safe discharge from the hospital; and (3) optimization of oral therapy.
- Initially, monitor patients for rapid relief of symptoms related to the chief complaint on admission. This includes improvement of dyspnea, oxygenation, fatigue, JVD, and other markers of congestion or distress.
- Monitor for adequate perfusion of vital organs through assessment of mental status, creatinine clearance, liver function tests, and a stable HR between 50 and 100 beats per minute. Additionally, adequate skin and muscle blood perfusion and normal pH is desirable.
- Monitor changes in hemodynamic variables if available. Cardiac index should increase, with a goal to maintain it above 2.2 L/minute per square meter. Pulmonary capillary wedge pressure should decrease in volume overloaded patients to a goal of less than 18 mm Hg.
- Closely monitor blood pressures and renal function while decreasing preload with diuretics and vasodilators.

- Ensure patients are euvolemic or nearly euvolemic prior to discharge.
- Since oral therapies can both improve symptoms and prolong survival, optimizing outpatient HF management is a priority when preparing a patient for hospital discharge. Ensure that the patient's regimen includes a vasodilator, β-blocker, a diuretic at an adequate dose to maintain euvolemia, and digoxin or aldosterone antagonist if indicated.



Patient Care and Monitoring

1. Assess the severity and duration of the patient's symptoms including limitations in activity. Rule out potential exacerbating factors.
2. Obtain a thorough history of prescription, nonprescription, and herbal medication use. Is the patient taking any medications that can exacerbate HF?
3. Review available diagnostic information from the chest radiograph, ECG, and echocardiogram.
4. Review the patient's lifestyle habits including salt and alcohol intake, tobacco product use, and exercise routine.
5. If unknown, investigate the patient's underlying etiology of HF. Verify that comorbidities that lead to or worsen HF are optimally managed with appropriate drug therapy.
6. Educate the patient on lifestyle modifications such as salt restriction (maximum 2 to 4 grams per day), fluid restriction if appropriate, limitation of alcohol, tobacco cessation, participation in a cardiac rehabilitation and exercise program, and proper immunizations such as the pneumococcal vaccine and yearly influenza vaccine.
7. Develop a treatment plan to alleviate symptoms and maintain euvolemia with diuretics. Daily weights to assess fluid retention are recommended.
8. Develop a medication regimen to slow the progression of HF with the use of neurohormonal blockers such as vasodilators (ACE inhibitors, ARBs, or hydralazine/isosorbide dinitrate), β-blockers, and aldosterone antagonists. Utilize digoxin if the patient remains symptomatic despite optimization of the above therapies.
   - Is the patient at goal or maximally tolerated doses of vasodilator and β-blocker therapy?
   - Are aldosterone antagonists utilized in appropriate patients with proper electrolyte and renal function monitoring?
9. Stress the importance of adherence to the therapeutic regimen and lifestyle changes for maintenance of a compensated state and slowing of disease progression.
10. Evaluate the patient for presence of adverse drug reactions, drug allergies, and drug interactions.
11. Provide patient education with regard to disease state and drug therapy, and reinforce self-monitoring for symptoms of HF that necessitate follow-up with a health care practitioner.

ABBREVIATIONS

ACC/AHA:	American College of Cardiology/American Heart Association
ACE:	angiotensin-converting enzyme
AHF:	acute heart failure
ANP:	atrial natriuretic peptide
ARB:	angiotensin receptor blocker
AT_1:	angiotensin type 1
AT_2:	angiotensin type 2
ATP:	adenosine triphosphate
BMI:	body mass index
BNP:	B-type natriuretic peptide
BP:	blood pressure
bpm:	beats per minute
BUN:	blood urea nitrogen
CAD:	coronary artery disease
cAMP:	cyclic adenosine monophosphate
CBC:	complete blood cell count
cGMP:	cyclic guanosine monophosphate
CHARM:	Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity
CI:	cardiac index
CNS:	central nervous system
CO:	cardiac output
CrCL:	creatinine clearance
CRT:	cardiac resynchronization therapy
CXR:	chest x-ray
CYP450:	cytochrome P-450 isoenzyme
D1:	dopamine receptor type 1
ECG:	electrocardiogram
EF:	ejection fraction
ET-1:	endothelin-1
ET-A:	endothelin-A
ET-B:	endothelin-B
FDA:	Food and Drug Administration
HF:	heart failure
HJR:	hepatojugular reflux
HR:	heart rate
IABC:	intra-aortic balloon counterpulsation
IABP:	intra-aortic balloon pump
ICD:	implantable cardioverter defibrillator
iNOS:	inducible nitric oxide synthetase
INR:	international normalized ratio
JVD:	jugular venous distention
JVP:	jugular venous pressure
LV:	left ventricular
LVEF:	left ventricular ejection fraction
LVF:	left ventricular failure
MI:	myocardial infarction
MVO_2:	myocardial oxygen consumption
NSAID:	non-steroidal anti-inflammatory drug
NT-proBNP:	N-terminal proBNP
NYHA FC:	New York Heart Association Functional Class
PAC:	pulmonary artery catheter
PCWP:	pulmonary capillary wedge pressure
PE:	physical exam
PND:	paroxysmal nocturnal dyspnea
PPCM:	peripartum cardiomyopathy
QRS:	ventricular depolarization

RAAS:	renin-angiotensin-aldosterone system
RVF:	right ventricular failure
SCr:	serum creatinine
SL:	sublingual
SNS:	sympathetic nervous system
SOB:	shortness of breath
SV:	stroke volume
SVR:	systemic vascular resistance
TNF-α:	tumor necrosis factor-α
V_{1a}:	vasopressin type 1a
V_2:	vasopressin type 2
VAD:	ventricular assist device

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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4 Ischemic Heart Disease

Larisa H. Cavallari and Robert J. DiDomenico



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Identify risk factors for the development of ischemic heart disease.
2. Recognize the symptoms and diagnostic criteria of ischemic heart disease in a specific patient.
3. Differentiate between the pathophysiology of chronic stable angina and acute coronary syndromes.
4. Identify the treatment goals of ischemic heart disease and appropriate lifestyle modifications and pharmacologic therapy to address each goal.
5. Design an appropriate therapeutic regimen for the management of ischemic heart disease based on patient-specific information.
6. Formulate a monitoring plan to assess effectiveness and adverse effects of an ischemic heart disease drug regimen.

Key Concepts

❶ Ischemic heart disease results from an imbalance between myocardial oxygen demand and oxygen supply that is most often due to coronary atherosclerosis. Common clinical manifestations of ischemic heart disease include chronic stable angina and the acute coronary syndromes of unstable angina, non–ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction.

❷ Early detection and aggressive modification of risk factors is one of the primary strategies for delaying ischemic heart disease progression and preventing ischemic heart disease–related events including death.

❸ Patients with chest pressure or heaviness that is provoked by activity and relieved with rest should be assessed for ischemic heart disease. Sharp pain is not a typical symptom of ischemic heart disease. Some patients may experience discomfort in the neck, jaw, shoulder, or arm rather than, or in addition to, the chest. Pain may be accompanied by nausea, vomiting, or diaphoresis.

❹ The major goals for the treatment of ischemic heart disease are to prevent acute coronary syndromes and death, alleviate acute symptoms of myocardial ischemia, prevent recurrent symptoms of myocardial ischemia, and avoid or minimize adverse treatment effects.

❺ Both 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) and angiotensin-converting enzyme inhibitors are believed to provide vasculoprotective effects, and in addition to antiplatelet agents, have been shown to reduce the risk of acute coronary events as well as mortality in patients with ischemic heart disease. Angiotensin receptor blockers may be used in patients who cannot tolerate angiotensin-converting enzyme inhibitors because of side effects (e.g., chronic cough). β-Blockers have been shown to decrease morbidity and improve survival in patients who have suffered a myocardial infarction.

❻ Antiplatelet therapy with aspirin should be considered for all patients without contraindications, particularly in patients with a history of myocardial infarction. Clopidogrel may be considered in patients with allergies or intolerance to aspirin. In some patients, combination antiplatelet therapy with aspirin and clopidogrel may be used.

❼ To control risk factors and prevent major adverse cardiac events, statin therapy should be considered in all patients with ischemic heart disease, particularly in those with elevated low-density lipoprotein cholesterol. In the absence of contraindications, angiotensin-converting enzyme inhibitors should be considered in ischemic heart disease patients who also have diabetes mellitus, left ventricular dysfunction, history of myocardial infarction, or any combination of these. Angiotensin receptor blockers

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may be used in patients who cannot tolerate angiotensin-converting enzyme inhibitors because of side effects.

8 All patients with a history of angina should have sublingual nitroglycerin tablets or spray to relieve acute ischemic symptoms. Patients should be instructed to use one dose (tablet or spray) every 5 minutes until pain is relieved and to call 911 if pain is unimproved or worsens 5 minutes after the first dose.

9 β-Blockers are first-line therapy for preventing ischemic symptoms, particularly in patients with a history of myocardial infarction. Long-acting calcium channel blockers and long-acting nitrates may be added for refractory symptoms or substituted if a β-blocker is not tolerated.

10 Patients should be monitored to assess for drug effectiveness, adverse drug reactions, and potential drug-drug interactions. Patients should be assessed for adherence to their pharmacotherapeutic regimens and lifestyle modifications.

Ischemic heart disease (IHD) is also called coronary heart disease (CHD) or coronary artery disease. The term "ischemic" refers to a decreased supply of oxygenated blood, in this case to the heart muscle. Ischemic heart disease is caused by the narrowing of one or more of the major coronary arteries that supply blood to the heart, most commonly by atherosclerotic plaques. Atherosclerotic plaques may impede coronary blood flow to the extent that cardiac tissue distal to the site of the coronary artery narrowing is deprived of sufficient oxygen in the face of increased oxygen demand. 1 *Ischemic heart disease results from an imbalance between myocardial oxygen supply and oxygen demand (Fig. 4–1). Common clinical manifestations of IHD include chronic stable angina and the* ***acute coronary syndromes*** *(ACS) of unstable angina, non–ST-segment elevation myocardial infarction (MI), and ST-segment elevation MI.*

Angina pectoris, or simply angina, is the most common symptom of IHD. Angina is discomfort in the chest that occurs when the blood supply to the myocardium is compromised. Chronic stable angina is defined as a chronic and predictable occurrence of chest discomfort due to transient myocardial ischemia with physical exertion or other conditions that increase oxygen demand. The primary focus of this chapter is on the management of chronic stable angina. However, some information is also provided related to ACS, given the overlap between the two disease states. The American College of Cardiology and the American Heart Association have jointly published practice guidelines for the management of patients with chronic stable angina, and the reader is referred to these guidelines for further information.[1]

EPIDEMIOLOGY AND ETIOLOGY

Ischemic heart disease affects over 13 million Americans and is the leading cause of death for both men and women in the United States.[2] The incidence of IHD is higher in middle-aged men compared to women. However, the rate of IHD increases

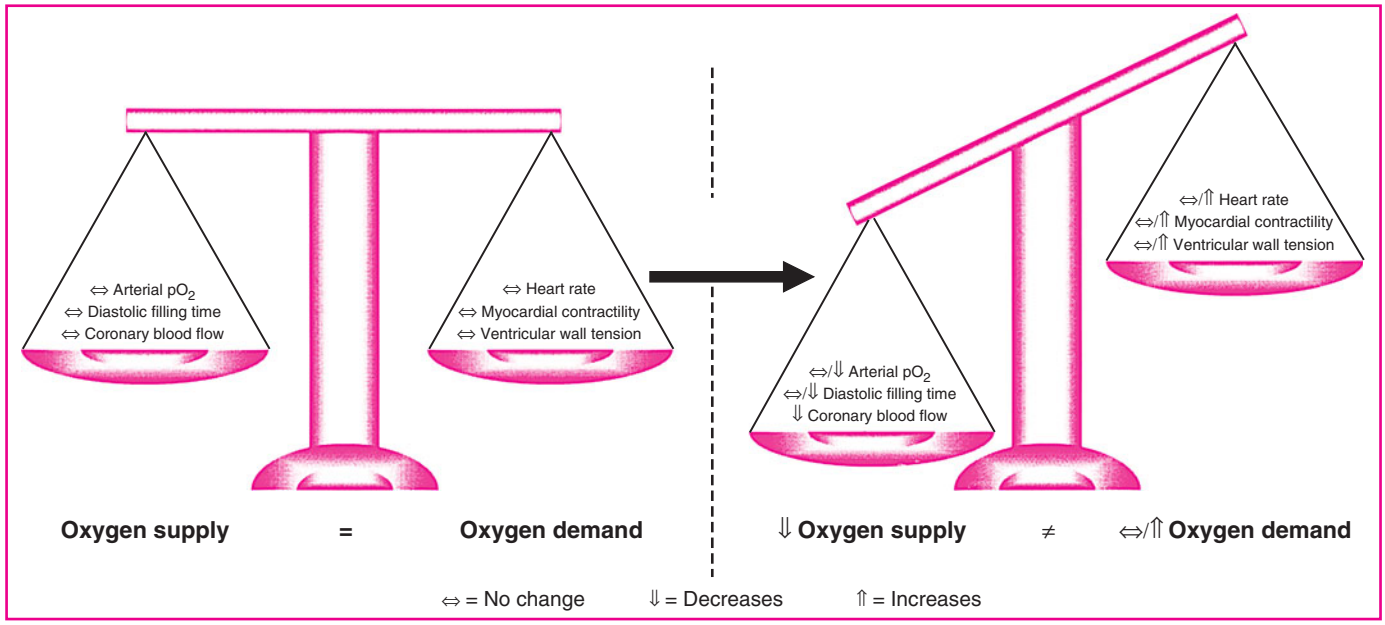


FIGURE 4–1. This illustration depicts the balance between myocardial oxygen supply and demand and the various factors that affect each. It should be noted that diastolic filling time is not an independent predictor of myocardial oxygen supply per se, but rather a determinant of coronary blood flow. On the left is myocardial oxygen supply and demand under normal circumstances. On the right is the mismatch between oxygen supply and demand in patients with ischemic heart disease. In patients without ischemic heart disease, coronary blood flow increases in response to increases in myocardial oxygen demand. However, in patients with ischemic heart disease, coronary blood flow cannot sufficiently increase (and may decrease) in response to increased oxygen demand resulting in angina. IHD, ischemic heart disease; pO_2, partial pressure of oxygen.

two- to three-fold in women after menopause. Chronic stable angina is the initial manifestation of IHD in about 50% of patients. In other patients, unstable angina or MI is the first sign of IHD. Chronic stable angina is associated with considerable patient morbidity, with many affected patients eventually requiring hospitalization for ACS.[3] In addition, chronic stable angina has a major negative impact on health-related quality of life.[4] Thus, in patients with chronic stable angina, it is important to optimize pharmacotherapy to reduce symptoms, improve quality of life, slow disease progression, and prevent ACS.

Conditions Associated with Angina

Figure 4–2 shows the anatomy of the coronary arteries. The major epicardial coronary arteries are the left main, left anterior descending, left circumflex, and right coronary arteries. **Atherosclerosis** involving one or more of the major coronary arteries or their principal branches is the major cause of angina. **Vasospasm** at the site of an atherosclerotic plaque may contribute to angina by further restricting blood supply to the distal myocardium. Less commonly, vasospasm in coronary arteries with no or minimal atherosclerotic disease can produce angina and even precipitate ACS. This type of vasospasm is referred to as variant or **Prinzmetal's angina**.

Non-ischemic cardiac conditions, such as aortic dissection (tear in the wall of the aorta leading to bleeding into the media layer of vessel and separation or dissecting of media from the outer layer of the aorta) and **pericarditis**, can cause chest discomfort that resembles angina. Non-cardiac conditions involving the pulmonary, gastrointestinal, and psychological systems can also cause angina-like symptoms. Table 4–1 lists specific conditions other than atherosclerosis that can precipitate angina-like symptoms. It is important to differentiate the etiology of chest discomfort since treatment varies depending on the underlying disease process.

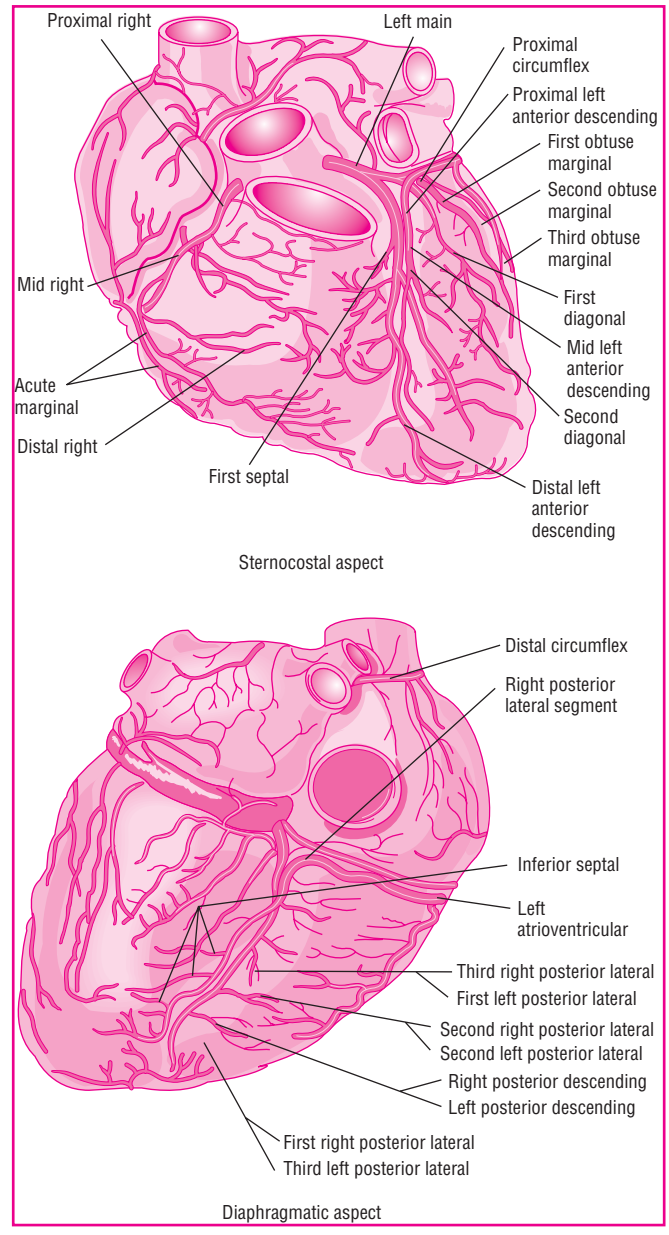


FIGURE 4–2. Coronary artery anatomy with sternocostal and diaphragmatic views. (Reproduced from Talbert RL. Ischemic heart disease. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 263, with permission.)

Risk Factors

Factors that predispose an individual to IHD are listed in Table 4–2. Hypertension, diabetes, **dyslipidemia**, and cigarette smoking are associated with endothelial dysfunction and potentiate atherosclerosis of the coronary arteries. The risk for IHD increases two-fold for every 20 mm Hg increment in systolic blood pressure and up to eight-fold in the presence of diabetes.[5,6] Physical inactivity and obesity independently increase the risk for IHD, in addition to predisposing individuals to other cardiovascular risk factors (e.g., hypertension, dyslipidemia, and diabetes).

Patients with multiple risk factors, particularly those with diabetes, are at the greatest risk for IHD. Metabolic syndrome is a constellation of cardiovascular risk factors related to hypertension, abdominal obesity, dyslipidemia, and insulin resistance. The risk of developing IHD and related complications is two-fold higher in patients with metabolic syndrome.[7] Therefore, detection and appropriate management of these patients is important. While there are several criteria used to diagnose metabolic syndrome, those endorsed by the National Cholesterol Education Program are probably the most widely

TABLE 4–1. Non-atherosclerotic Conditions that Can Cause Angina-like Symptoms

Organ System	Condition
Cardiac	Aortic dissection, coronary artery vasospasm, pericarditis, valvular heart disease
Non-cardiac	Anemia, anxiety disorders, carbon monoxide poisoning, cocaine use, esophageal reflux, peptic ulcer, pleuritis, pneumonia, **pneumothorax**, pulmonary embolus, pulmonary hypertension, **thyrotoxicosis**

accepted.[8] To diagnose metabolic syndrome, patients must meet at least three of the following criteria:

- Increased waist circumference (greater than 40 inches or 102 cm in males and greater than 35 inches or 89 cm in females).
- Triglycerides of 150 mg/dL (1.70 mmol/L) or greater or active treatment to lower triglycerides.
- Low high-density lipoprotein (HDL) cholesterol (less than 40 mg/dL or 1.04 mmol/L in males and less than 50 mg/dL or 1.3 mmol/L in females) or active treatment to raise HDL cholesterol.
- Blood pressure of 130/85 mm Hg or greater or active treatment with antihypertensive therapy.
- Fasting blood glucose of 100 mg/dL (5.55 mmol/L) or greater or active treatment for diabetes.

❷ *Early detection and aggressive modification of risk factors are among the primary strategies for delaying IHD progression and preventing IHD-related events including death.*

PATHOPHYSIOLOGY

The determinants of oxygen supply and demand are shown in Fig. 4–1. Increases in heart rate, left ventricular wall tension, and cardiac contractility increase the rate of myocardial oxygen consumption (MVO_2). Left ventricular wall tension is a function of blood pressure, left ventricular end-diastolic volume, and ventricular wall thickness. Physical exertion increases heart rate, blood pressure, and cardiac contractility, and commonly precipitates ischemia and symptoms of angina in patients with significant coronary atherosclerosis. Medications that reduce heart rate, cardiac contractility, and/or ventricular wall tension are commonly prescribed to prevent ischemic symptoms in patients with chronic stable angina.

TABLE 4–2. Major Risk Factors for Ischemic Heart Disease

Modifiable	Non-modifiable
Cigarette smoking	Age 45 years or greater for males, age 55 years or greater for females
Dyslipidemia	Gender (men and postmenopausal women)
• Elevated LDL or total cholesterol	Family history of premature cardiovascular disease, defined as cardiovascular disease in a male first-degree relative (i.e., father or brother) younger than 55 years old or a female first-degree relative (i.e., mother or sister) younger than 65 years
• Reduced HDL cholesterol	
Diabetes mellitus	
Hypertension	
Physical inactivity	
Obesity (body mass index greater than or equal to 30 kg/m^2)	

HDL, high-density lipoprotein; LDL, low-density lipoprotein

Reductions in coronary blood flow (secondary to atherosclerotic plaques, vasospasm, or **thrombus** formation) and arterial oxygen content (secondary to hypoxia) decrease myocardial oxygen supply. Because the coronary arteries fill during diastole, decreases in diastolic filling time (e.g., tachycardia) can also reduce coronary perfusion and myocardial oxygen supply. In chronic stable angina, atherosclerotic plaques are the most common cause of coronary artery narrowing and reductions in coronary blood flow. In contrast, in ACS, disruption of an atherosclerotic plaque with subsequent thrombus (blood clot) formation causes abrupt reductions in coronary blood flow and oxygen supply. Anemia, carbon monoxide poisoning, and cyanotic congenital heart disease are examples of conditions that reduce the oxygen-carrying capacity of the blood, potentially causing ischemia in the face of adequate coronary perfusion. Interventional procedures to compress or bypass atherosclerotic plaques are effective methods of improving myocardial oxygen supply in patients with IHD.

Coronary Atherosclerosis

The normal arterial wall consists of the intima, media, and adventitia, as illustrated in Fig. 4–3A. The endothelium is located in the intima and consists of a layer of endothelial cells that line the lumen of the artery and form a selective barrier between the vessel wall and blood contents. The internal elastic lamina separates the intima and media, where vascular smooth muscle cells are found. The vascular adventitia comprises the artery's outer layer. Atherosclerotic lesions form in the subendothelial space between the endothelial cells and internal elastic lamina.

Dysfunction of the endothelium allows lipoproteins, predominantly low-density lipoprotein (LDL) cholesterol, and inflammatory cells, namely monocytes and T lymphocytes, to migrate from the plasma to the sub-endothelial space. Monocyte-derived macrophages ingest lipoproteins to form foam cells. Macrophages also secrete growth factors that promote smooth muscle cell migration from the media to the intima. A fatty streak consists of lipid-laden macrophages and smooth muscle cells and is the earliest type of atherosclerotic lesion.

Lipid-laden macrophages, smooth muscle cells, and necrotic debris from the death of foam cells accumulate in the subendothelial space, leading to enlargement of the fatty streak. A collagen matrix forms a fibrous cap that covers the lipid core of the lesion to establish a fibrous plaque called an atherosclerotic plaque. Initially, the diameter of the coronary artery lumen is

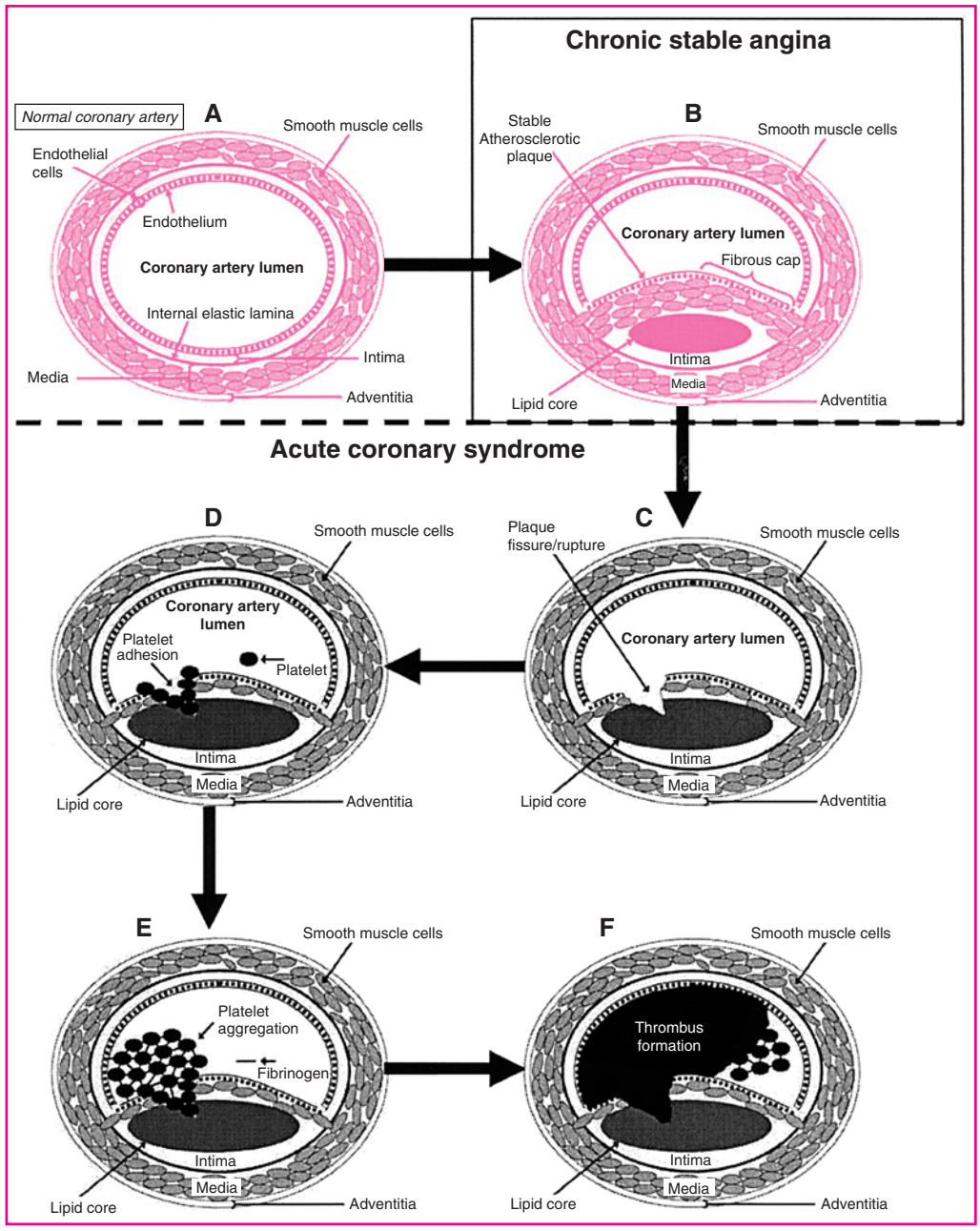


FIGURE 4–3. Pathophysiology of chronic stable angina versus acute coronary syndromes. Panel A depicts the cross-section of a normal coronary artery. Panel B depicts the cross-section of a coronary artery with a stable atherosclerotic plaque. Note that the lipid core is relatively small in size and the fibrous cap is made up of several layers of smooth muscle cells. Panel C depicts an unstable atherosclerotic plaque with a larger lipid core, and a thin fibrous cap comprised of a single layer of smooth muscle cells with a fissure or rupture. Panel D depicts platelet adhesion in response to the fissured plaque. Platelet activation may ensue leading to platelet aggregation as fibrinogen binds platelets to one another to form a meshlike occlusion in the coronary lumen (Panel E). At this stage, patients may experience symptoms of acute coronary syndrome. If endogenous anticoagulant proteins fail to halt this process, platelet aggregation continues and fibrinogen is converted to fibrin, resulting in an occlusive thrombus (Panel F).

maintained as the plaque grows outward (external to the lumen) in a process referred to as arterial remodeling.[9] However, with significant plaque progression, the atherosclerotic plaque begins to protrude into the artery lumen and impede blood flow. When the plaque occludes 70% or more of the artery, the patient may begin to experience angina during activities that increase myocardial oxygen demand (i.e., chronic stable angina).

Stable versus Unstable Atherosclerotic Plaques

The hallmark feature in the pathophysiology of chronic stable angina is an established atherosclerotic plaque that impedes coronary blood flow to the extent that myocardial oxygen supply can no longer meet increases in myocardial oxygen demand. Over time, an established plaque may become unstable and rupture, leading to an ACS. Atherosclerotic plaque rupture with subsequent thrombus formation is the hallmark feature in the pathophysiology of unstable angina and MI and is depicted in Fig. 4–3. Plaque rupture refers to fissuring or erosion of the fibrous cap that covers the lipid core and exposure of the plaque contents to elements in the blood. Plaque composition, rather than the degree of coronary stenosis, determines the stability of the plaque and the likelihood of plaque rupture and ACS. Specifically, a stable lesion consists of

a small lipid core that is surrounded by a thick fibrous cap that protects the lesion from the shear stress of blood flow (Fig. 4–3B). In contrast, an unstable plaque consists of a thin, weak cap in combination with a large, rich lipid core that renders the plaque vulnerable to rupture (Fig. 4–3C). The transformation of a stable plaque into an unstable plaque involves the degradation of the fibrous cap by substances released from macrophages and other inflammatory cells. An unstable plaque often produces minimal occlusion of the coronary vessel, and the patient remains asymptomatic until the plaque ruptures. In fact, the majority of MIs arise from vulnerable plaques that occlude less than 50% of the coronary lumen.[10] As a result, unstable angina or MI is the initial manifestation of IHD in about one-half of affected patients.

Atherosclerotic Plaque Rupture

Following plaque rupture, exposure of the blood to the thrombogenic contents of the plaque stimulates platelet adhesion and activation of the coagulation cascade. Platelets adhere to the site of rupture, aggregate, and generate thrombin (Fig. 4–3D, E, and F). Thrombin converts fibrinogen to fibrin to form a fibrin clot. Coronary thrombi extend into the vessel lumen, where they either partially or completely occlude blood flow, resulting in unstable angina or MI.

Coronary Artery Vasospasm

Prinzmetal's or variant angina results from spasm (or contraction) of a normal or diseased coronary artery. In contrast to chronic stable angina, diseased arteries in variant angina contain lesions that do not obstruct blood flow. While vasospasm is generally transient, in some instances vasospasm may persist long enough to infarct the myocardium. Variant angina usually occurs at rest, especially in the early morning hours. Patients with variant angina are typically younger than those with chronic stable angina and often do not possess the classic risk factors for IHD. The cause of variant angina is unclear but appears to involve endothelial dysfunction and paradoxical response to agents that normally cause vasodilation. Precipitants of variant angina include cigarette smoking, cocaine use, hyperventilation, and exposure to cold temperatures. The management of variant angina differs from that of classic angina, and thus it is important to distinguish between the two.

CLINICAL PRESENTATION AND DIAGNOSIS

History

The evaluation of a patient with suspected IHD begins with a detailed history of anginal symptoms. The five components commonly used to characterize chest pain are quality, location, duration of pain, factors that provoke pain, and factors



❸Clinical Presentation and Diagnosis of Ischemic Heart Disease

General

- Patients with chronic stable angina will generally be in no acute distress. In patients presenting in acute distress, the clinician should be suspicious of ACS.

Symptoms of Angina Pectoris

- Patients typically describe pain as a sensation of pressure, heaviness, or squeezing in the anterior chest area. Sharp pain is not a typical symptom of IHD.
- Pain may radiate to the neck, jaw, shoulder, back, or arm.
- Pain may be accompanied by dyspnea, nausea, vomiting, or **diaphoresis.**
- Symptoms are often provoked by exertion (e.g., walking, climbing stairs, and doing yard or house work) or emotional stress and relieved within minutes by rest or nitroglycerin. Other precipitating factors include exposure to cold temperatures and heavy meals. Pain that occurs at rest (without provocation) or that is prolonged and unrelieved by nitroglycerin is indicative of an ACS. Some patients, most commonly women and patients with diabetes, present with atypical symptoms of ischemia including indigestion, gastric fullness, and shortness of breath.

Signs

- Findings on the physical exam are often normal in patients with chronic stable angina. However, during episodes of ischemia, patients may present with abnormal heart sounds, such as paradoxical splitting of the second heart sound, a third heart sound, or a loud fourth heart sound.

Laboratory Tests

- Biochemical markers (creatine kinase [CK], CK-MB fraction, troponin I and troponin T) are elevated in MI (ST-segment elevation MI and non–ST-segment elevation MI), but normal in chronic stable angina and unstable angina.

Other Diagnostic Tests

- A 12-lead electrocardiogram (ECG) recorded during rest is often normal in patients with chronic stable angina in the absence of active ischemia. Significant Q waves indicate prior MI. ST-segment or T-wave changes during symptoms of angina support the diagnosis of IHD. ST-segment depression or T-wave inversion is typically observed in chronic stable angina, unstable angina, and non–ST-segment elevation MI, whereas ST-segment elevation occurs with ST-segment elevation MI and Prinzmetal's (variant) angina.
- Treadmill or bicycle exercise ECG, commonly referred to as a "stress test," is considered positive for IHD if the ECG shows at least a 1 mm deviation of the ST-segment (depression or elevation).
- Wall motion abnormalities or left ventricular dilation with stress echocardiography are indicative of IHD.
- Stress myocardial perfusion imaging with the radionuclides technetium-99m sestamibi or thallium-201 allows for the identification of multivessel disease and assessment of myocardial viability.

(*Continued*)

- Coronary angiography detects the location and degree of coronary atherosclerosis and is used to evaluate the potential benefit from revascularization procedures. Stenosis of at least 70% of the diameter of at least one of the major epicardial arteries on coronary angiography is indicative of significant IHD.

that relieve pain. The classic presentation of angina is described in the Clinical Presentation and Diagnosis box. In some cases, ischemia may not produce any symptoms and is termed "silent ischemia." Patients with diabetes may experience associated symptoms, such as dyspnea and diaphoresis, without having any of the classic chest pain symptoms.

Non-cardiac conditions, such as gastroesophageal reflux disease, may cause chest pain that is difficult to distinguish from angina. A detailed history and risk factor assessment may help to clarify the diagnosis. For example, pain that is sharp or stabbing, occurs randomly (not provoked by exertion or stress), is tender to palpation, changes with position or respiration, responds variably to nitroglycerin, or lasts for hours is atypical of angina and suggestive of a non-cardiac etiology. The diagnosis of IHD is also less likely in a patient with atypical symptoms who has no known risk factors for IHD.

The Canadian Cardiovascular Society Classification System

The Canadian Cardiovascular Society Classification System (Table 4–3) is commonly used to assess the degree of disability resulting from IHD. Patients are categorized into one of four classes depending on the extent of activity that produces angina. Grouping patients according to this or a similar method is commonly used to assess changes in IHD severity over time and the effectiveness of pharmacologic therapy.



Patient Encounter, Part 1

RJ is a 47-year-old man with a history of hypertension who presents to your clinic complaining of chest pain that occurred several times over the past few weeks. RJ describes his chest pain as "a heaviness." He states that it first occurred while he was mowing the grass. He later felt the same heavy sensation while raking leaves and again while carrying some boxes. The pain was located in the substernal area and radiated to his neck. The pain resolved after about 5 minutes of rest.

- Are RJ's symptoms consistent with angina?
- What tests would be beneficial in establishing a diagnosis?
- What additional objective information do you need in order to create a treatment plan for this patient?

TABLE 4–3. The Canadian Cardiovascular Society Classification System of Angina[49]

Class	Description
I	Able to perform ordinary physical activity (e.g., walking and climbing stairs) without symptoms. Strenuous, rapid, or prolonged exertion causes symptoms.
II	Symptoms slightly limit ordinary physical activity. Walking rapidly or for more than two blocks, climbing stairs rapidly or climbing more than one flight of stairs causes symptoms.
III	Symptoms markedly limit ordinary physical activity. Walking less than two blocks or climbing one flight of stairs causes symptoms.
IV	Angina may occur at rest. Any physical activity causes symptoms.

Distinguishing Characteristics of Chronic Stable Angina and Unstable Angina

Chronic stable angina should be distinguished from unstable angina since the latter is associated with a greater risk for MI and death and requires more aggressive treatment. Because the pathophysiology of chronic stable angina is due primarily to increases in oxygen demand, not acute changes in oxygen supply, symptoms are typically reproducible and reversible. Specifically, a patient will generally experience a similar pattern of discomfort (i.e., same quality, location, and accompanying symptoms) with a similar level of exertion with each angina attack. Chronic stable angina is usually relieved within minutes by rest or sublingual nitroglycerin. In contrast, unstable angina is due to an acute decrease in coronary blood flow leading to insufficient oxygen supply. Consequently, unstable angina is marked by prolonged symptoms (greater than or equal to 20 minutes) or an escalation in the frequency or severity of angina over a short period of time. Unstable angina frequently occurs at rest without any precipitating factors, whereas chronic stable angina usually occurs with exertion. Unstable angina may be less responsive to rest or medication. The presentation of unstable angina is described in greater detail in Table 4–4.

Physical Findings and Laboratory Analysis

A thorough medical history and physical exam are necessary to ascertain cardiovascular risk factors and to exclude non-ischemic

TABLE 4–4. Presentations of Unstable Angina[50]

- Angina at rest that is prolonged in duration, usually lasting over 20 minutes.
- Angina of recent onset (within 2 months) that markedly limits usual activity.
- Angina that increases in severity (i.e., by Canadian Cardiovascular Society Classification System Class of one level or greater), frequency, or duration, or that occurs with less provocation over a short time period (i.e., within 2 months).

and non-cardiac conditions that could cause angina-like symptoms. Cardiac findings on the physical exam are often normal in patients with chronic stable angina. However, findings such as **carotid** bruits or abnormal peripheral pulses would indicate atherosclerosis in other vessel systems and raise the suspicion for IHD.

Laboratory analysis and cardiac testing are other important components of the evaluation of the patient with chest pain. Usual laboratory tests include hemoglobin, fasting glucose, and fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) to assess for cardiovascular risk factors and comorbid conditions. Biochemical markers of myocardial necrosis (i.e., cardiac enzymes), including creatine kinase (CK)-MB fraction and cardiac troponin (I or T), are acutely elevated after MI but normal in chronic stable angina and unstable angina. Therefore serial measurements of cardiac enzymes (usually three measurements within 24 hours) are used to exclude the diagnosis of MI.

Diagnostic Tests

A resting ECG is indicated in all patients with angina-like symptoms. A 12-lead ECG should be done within 10 minutes of presentation to the emergency department in patients with symptoms of ischemia. Electrocardiographic findings indicative of myocardial ischemia include ST-segment elevation, ST-segment depression, and T-wave abnormalities in two or more contiguous leads. It is important to promptly identify patients with ST-segment elevation, as these patients are at the highest risk of death and need interventions to restore blood flow to the myocardium as quickly as possible. In patients without ST-segment elevation, biochemical markers are used to distinguish between unstable angina and non–ST-segment elevation MI.

Exercise ECG testing using either a treadmill (most commonly) or bicycle ergometer is a common non-invasive test to evaluate the patient with suspected IHD. "Stress" testing increases myocardial oxygen demand and often precipitates angina in patients with IHD. Approximately 50% of patients with IHD who have a normal ECG at rest will develop ECG changes with exercise. Pharmacologic stressors are used for patients who are unable to exercise. Dobutamine is commonly used with stress echocardiography, whereas adenosine or dipyridamole are used for nuclear imaging studies. Coronary angiography (also referred to as a cardiac catheterization or "cardiac cath") is considered the gold standard for the diagnosis of IHD and is indicated when stress testing results are abnormal or symptoms of angina are poorly controlled. Angiography involves catheter insertion, usually into the femoral artery, and advancement into the aorta and into the coronary arteries. Contrast medium is injected through the catheter into the coronary arteries allowing visualization of the coronary anatomy by fluoroscopy.



Patient Encounter, Part 2: Medical History, Physical Exam, and Diagnostic Tests

PMH
Hypertension, diagnosed 7 years ago

FH
Father with coronary artery disease, had a myocardial infarction at age 50 years
Mother alive and well

SH
Smokes $^1/_2$ to 1 pack per day
Denies alcohol and illicit drug use
No regular exercise program

Meds
Hydrochlorothiazide 25 mg PO once daily
Nifedipine XL 60 mg PO once daily
No known drug allergies

PE
VS: Blood pressure = 154/90 mm Hg
Heart rate = 84 beats per minute, respirations = 16
Temperature = 37°C (98.6°F)
Height = 5′10″ (178 cm), weight = 230 lb (104.6 kg)
Cardiovascular: Regular rate and rhythm, normal S_1 and S_2, no S_3 or S_4; no murmurs, rubs, gallops
Lungs: Clear to auscultation and percussion
Abd: Nontender, nondistended, + bowel sounds

Labs
Fasting lipid profile: total cholesterol 233 mg/dL (6.03 mmol/L), HDL cholesterol 30 mg/dL (0.78 mmol/L), LDL cholesterol 165 mg/dL (4.27 mmol/L), triglycerides 188 mg/dL (2.12 mmol/L); other labs within normal limits

Exercise treadmill test: positive for ischemia

- Identify RJ's risk factors for ischemic heart disease.
- How might RJ's current drug regimen adversely affect his ischemic heart disease?
- What therapeutic alternatives are available to manage RJ's ischemic heart disease?

TREATMENT

Desired Outcomes

Once the diagnosis of IHD is established in a patient, the clinician should provide counseling on lifestyle modifications, institute appropriate pharmacologic therapy, and evaluate the need for surgical revascularization. ❹ *The major goals for the treatment of IHD are to:*

- *Prevent acute coronary syndromes and death;*
- *Alleviate acute symptoms of myocardial ischemia;*

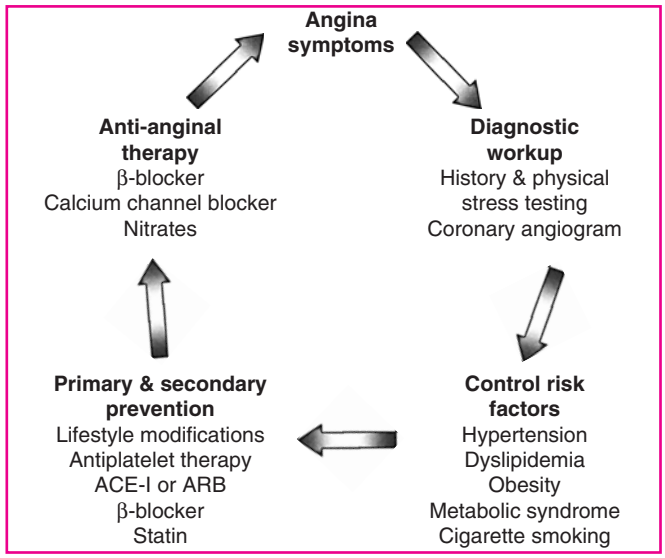


FIGURE 4–4. General treatment strategies for angina follow in clockwise fashion from the top center. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

- *Prevent recurrent symptoms of myocardial ischemia; and*
- *Avoid or minimize adverse treatment effects.*

The treatment approach to address these goals is illustrated in Fig. 4–4.

General Approach to Treatment

The primary strategies for preventing ACS and death are to:

- Modify cardiovascular risk factors;
- Slow the progression of coronary atherosclerosis; and
- Stabilize existing atherosclerotic plaques.

The treatment algorithm in Fig. 4–5 summarizes the appropriate management of IHD. Risk factor modification is accomplished through lifestyle changes and pharmacologic therapy. ❺ *Both 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMG-CoA reductase inhibitors or statins) and angiotensin-converting enzyme (ACE) inhibitors are believed to provide vasculoprotective effects (properties that are generally protective of the vasculature, which may include anti-inflammatory effects, antiplatelet effects, improvement in endothelial function, and improvement in arterial compliance and tone), and in addition to aspirin, have been shown to reduce the risk of acute coronary events as well as mortality in patients with IHD. Angiotensin receptor blockers (ARBs) may be used in patients who cannot tolerate ACE inhibitors because of side effects (e.g., chronic cough). β-Blockers have been shown to decrease morbidity and improve survival in patients who have suffered an MI.*

Therapies to alleviate and prevent angina are aimed at improving the balance between myocardial oxygen demand and supply. Since angina usually results from increased myocardial oxygen demand in the face of a relatively fixed reduction in oxygen supply, drug treatment is primarily aimed at reducing oxygen demand. Short-acting nitrates are indicated to acutely relieve angina. β-Blockers, calcium channel blockers (CCBs), and long-acting nitrates are traditionally used to reduce the frequency of angina and improve exercise tolerance. In most patients with IHD, the most effective treatments to improve myocardial oxygen supply are invasive mechanical interventions: **percutaneous coronary intervention (PCI)** and **coronary artery bypass graft (CABG) surgery**. Percutaneous coronary intervention involves the threading of a catheter to the site of an atherosclerotic lesion in a coronary artery. Then, either a balloon on the tip of the catheter is inflated to compress the plaque against the arterial wall (balloon angioplasty) or a device is used to cut away the plaque. Often, a stent (a wire mesh tube resembling a spring) is placed at the site of balloon angioplasty to hold the vessel open. Coronary artery bypass graft surgery involves using a leg vein or mammary artery to form a conduit around an atherosclerotic plaque.

Adverse treatment effects can largely be averted by avoiding drug interactions and the use of drugs that may have unfavorable effects on comorbid diseases. For example, β-blockers may exacerbate preexisting bronchospasm. β-Blockers are not absolutely contraindicated in bronchospastic disease, but should be avoided in patients with poorly controlled symptoms. While patients often require combination anti-anginal therapy, there is a potential pharmacodynamic drug interaction with the concurrent use of β-blockers and nondihydropyridine calcium channel blockers. Since both drug classes slow electrical conduction through the atrioventricular (AV) node, serious bradycardia or heart block may result with their concomitant use. Appropriate drug dosing and monitoring also reduces the risk for adverse treatment effects. Drugs should be initiated in low doses, with careful up-titration as necessary to control symptoms of angina and cardiovascular risk factors.

Lifestyle Modifications

Lifestyle modifications include smoking cessation, dietary modifications, increased physical activity, and weight loss. Lifestyle modifications reduce cardiovascular risk factors, slow the progression of IHD, and decrease the risk for IHD-related complications. Cigarette smoking is the single most preventable cause of IHD. Smoking cessation substantially reduces the risk of death from IHD.[11] The clinician should ascertain smoking status on the patient's initial clinic visit and provide counseling on the importance of smoking cessation at each subsequent visit for patients who continue to smoke. There are several pharmacologic aids for smoking cessation. Transdermal nicotine replacement therapy has been shown to be safe in patients with IHD.[12]

Weight loss, through caloric restriction and increased physical activity, should be encouraged in patients who have a body mass index greater than 25 kg/m^2. Dietary modification is important for risk factor management, and dietary counseling

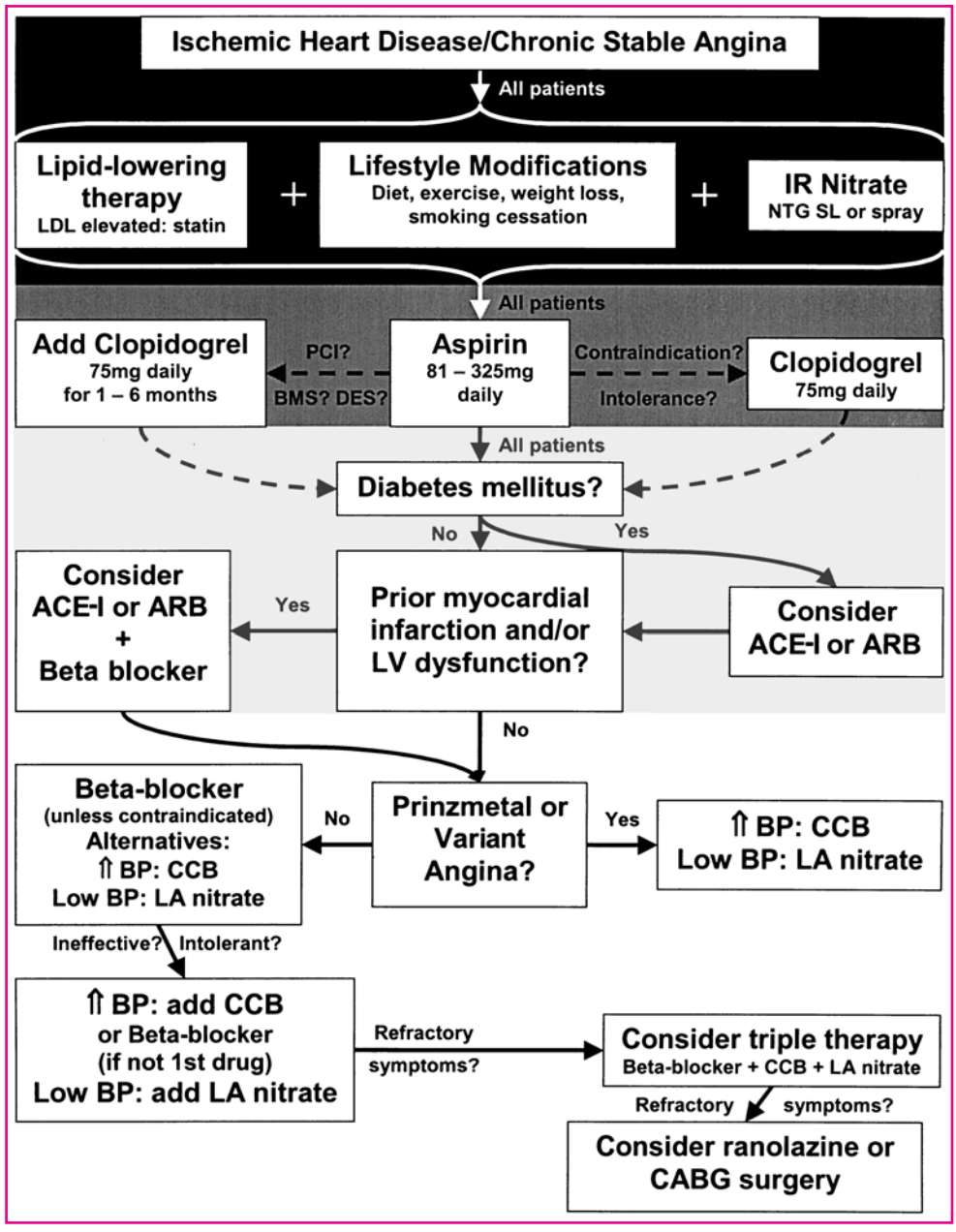


FIGURE 4–5. The treatment algorithm for ischemic heart disease. It begins at the top (black section), which suggests risk factor modifications as the first treatment modality. Moving down to the dark gray section, appropriate antiplatelet therapy is selected. The light gray section identifies patients at high-risk for major adverse cardiac events and suggests appropriate drug therapy to decrease cardiovascular risk. The white section at the bottom recommends appropriate anti-anginal therapy. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMS, bare metal stent; BP, blood pressure; CABG, coronary artery bypass graft; CCB, calcium channel blocker; DES, drug-eluting stent; IR, immediate-release; LA, long-acting; LDL, low-density lipoprotein; LV, left ventricular; NTG, nitroglycerin; PCI, percutaneous coronary intervention; SL, sublingual.

should be provided to all patients with newly diagnosed angina regardless of weight. The American Heart Association recommends a diet that includes a variety of fruits, vegetables, grains, low-fat or non-fat dairy products, fish, legumes, poultry, and lean meats.[13] Fatty fish, such as salmon and herring, are high in omega-3 fatty acids, which have been shown to reduce triglyceride concentrations and slow atherosclerotic plaque progression.[13] A Mediterranean diet rich in fish in addition to fruit, cooked and raw vegetables, and olive oil has been shown to reduce mortality after MI.[14] Specific dietary recommendations for patients with IHD should include the following:[13]

- Limit fat intake to less than 30% of total caloric consumption.
- Limit cholesterol intake to less than 200 mg per day.
- Limit consumption of saturated fat found in fatty meats, full-fat dairy products, and hydrogenated vegetable oils to less than 7% of total calories.
- Consume at least two servings of fish per week.
- Consume at least six servings of grains, five servings of fruits and vegetables, and two servings of non-fat or low-fat dairy products per day.
- Limit daily sodium intake to 2.4 grams (6 grams of salt) for blood pressure control.

Exercise facilitates both weight loss and blood pressure reduction. In addition, regular exercise improves functional capacity and symptoms in chronic stable angina.[1] Once drug therapy for IHD is instituted, patients should be encouraged

to begin a low level of exercise for 20 to 30 minutes at a time, with increases in exercise duration and intensity as symptoms allow.[15]

Interventional Approaches

Percutaneous Coronary Intervention

When drug therapy fails or if extensive coronary atherosclerosis is present, PCI is often performed to restore coronary blood flow, relieve symptoms, and prevent major adverse cardiac events. Patients with one or more critical coronary stenoses (i.e., greater than 70% occlusion of the coronary lumen) detected during coronary angiography may be candidates for PCI. Several catheter-based interventions may be used during PCI, including:

- Percutaneous transluminal coronary angioplasty (PTCA);
- Intracoronary bare metal stent placement;
- Intracoronary drug-eluting stent placement; and
- Rotational atherectomy.

During PCI, a catheter is advanced into the blocked coronary artery, as described for cardiac catheterization. If PTCA (i.e., balloon angioplasty) is performed, a balloon at the end of the catheter is inflated inside the artery at the site of the critical stenosis. When inflated, this balloon catheter displaces the atherosclerotic plaque out of the lumen of the artery, restoring normal myocardial blood flow. In addition to angioplasty, most PCI procedures involve the insertion of an intracoronary stent. In this case, a special balloon catheter containing a small wire stent (similar in size and shape to the spring at the tip of a ball point pen) is used. When the balloon is inflated, the wire stent (bare metal stent) is deployed in the wall of the coronary artery, forming a sort of bridge to maintain normal coronary blood flow. While bare metal stents are very effective in restoring coronary blood flow, restenosis (re-narrowing of the coronary artery after a PCI to improve coronary blood flow) at the site of stent deployment is common, requiring additional PCI. Drug-eluting stents have thus been developed to reduce the incidence of restenosis and are commonly used in patients undergoing PCI. These stents are impregnated with low concentrations of antiproliferative medications, such as paclitaxel or sirolimus, which are slowly released locally within the coronary artery over several weeks. The antiproliferative effects of these drugs significantly inhibit restenosis, decreasing the need for repeated PCI procedures. Despite the effectiveness of both bare metal and drug-eluting stents, acute thrombotic occlusion is still possible. Therefore, following PCI with either type of stent, combination antiplatelet therapy (discussed later) is required for at least 1 month and perhaps indefinitely to reduce this risk. Lastly, rotational atherectomy may be performed wherein a special catheter is used to essentially cut away the atherosclerotic plaque, restoring coronary blood flow.

Coronary Artery Bypass Graft Surgery

As an alternative to PCI, CABG surgery, or open-heart surgery, may be performed if the patient is found to have extensive coronary atherosclerosis (generally greater than 70% occlusion of three or more coronary arteries) or is refractory to medical treatment. In the former case, CABG surgery has been shown to reduce mortality from IHD. During CABG surgery, veins from the leg or arteries on the inside of the chest wall (i.e., internal mammary arteries) are surgically removed. In the case of venous conduits, one end of the removed blood vessel is attached to the aorta, and the other end is attached to the coronary artery distal to the atherosclerotic plaque. However, when internal mammary arteries are used, the distal end of the artery is detached from the chest wall and anastomosed to the coronary artery distal to the plaque. A median sternotomy, in which an incision the length of the sternum is made, is commonly required to gain access to the thoracic cavity and expose the heart. As the "new" blood vessels are being engrafted, the patient is typically placed on cardiopulmonary bypass (i.e., heart-lung machine) to maintain appropriate myocardial and systemic perfusion. Because of the extremely invasive nature of this surgery, CABG surgery is often a treatment of last resort in patients with IHD.

Pharmacologic Therapy

Pharmacotherapy to Prevent Acute Coronary Syndromes and Death

Antiplatelet Agents

Platelets play a major role in the pathophysiology of ACS. Specifically, platelets adhere to the site of atherosclerotic plaque rupture where they become activated, aggregate, and stimulate thrombus formation and ACS. Thromboxane is a potent platelet activator. Aspirin inhibits cyclooxygenase, an enzyme responsible for the production of thromboxane. Through its effects on thromboxane, aspirin inhibits platelet activation and aggregation. ❺ *In patients with stable or unstable angina, aspirin has been consistently shown to reduce the risk of major adverse cardiac events, particularly MI.*[16–18] ❻ *Antiplatelet therapy with aspirin should be considered for all patients without contraindications, particularly in patients with a history of myocardial infarction.* Aspirin doses of 75 to 325 mg daily have been shown to be cardioprotective. If aspirin is contraindicated (e.g., aspirin allergy, active peptic ulcer disease, or active internal bleeding) or is not tolerated by the patient, other antiplatelet agents such as clopidogrel should be considered.

Recent studies have suggested that combination antiplatelet therapy may be synergistic in reducing the risk of IHD-related events. In patients with ACS, the combination of aspirin and clopidogrel 75 mg daily for up to 9 months was more effective than aspirin alone in decreasing the risk of

death, MI, and stroke.[19] This combination also prevents complications following PCI.[20] The American College of Chest Physicians recommends the combination of aspirin and clopidogrel for 9 to 12 months in patients with IHD who have undergone PCI.[21] For isolated PCI procedures, the recommended duration of combination aspirin and clopidogrel therapy is as follows:

- At least 2 weeks for bare metal stent placement.
- At least 2 to 3 months for sirolimus-eluting stent placement.
- At least 6 months following paclitaxel-eluting stent placement.

Statins

Over the last decade, several studies in tens of thousands of patients have revealed that lowering cholesterol, specifically lowering LDL cholesterol with statins, is effective for both primary and secondary prevention of IHD-related events. Statins shown to decrease morbidity and mortality associated with IHD include lovastatin, simvastatin, pravastatin, and atorvastatin.[22,23] A recent meta-analysis showed that the risk of major adverse cardiac events is reduced by 21% with the use of statins in patients at high risk for IHD-related events.[23]

Several studies have investigated whether statins possess pharmacologic properties in addition to their LDL cholesterol–lowering effect that may confer additional benefits in IHD.[24] These studies were prompted by evidence that patients with "normal" LDL cholesterol derived benefit from statins. Statins have been shown to modulate the following characteristics thought to stabilize atherosclerotic plaques and contribute to the cardiovascular risk reduction seen with these drugs:

- Shift LDL cholesterol particle size from predominantly small, dense, highly atherogenic particles to larger, less atherogenic particles.
- Improve endothelial function leading to more effective vasoactive response of the coronary arteries.
- Prevent or inhibit inflammation by lowering C-reactive protein and other inflammatory mediators thought to be involved in atherosclerosis.
- Possibly improving atherosclerotic plaque stability.

❼ *In summary, to control risk factors and prevent major adverse cardiac events, statin therapy should be considered in all patients with ischemic heart disease, particularly in those with elevated low-density lipoprotein cholesterol. Statins are potent lipid-lowering agents, possess non–lipid-lowering effects that may provide additional benefit to patients with IHD, and have been shown to reduce morbidity and mortality in patients with IHD. Based on these benefits, statins are generally considered the drugs of choice in patients with dyslipidemias. Moreover, based on evidence that statins improve outcomes in patients with IHD and "normal" LDL cholesterol concentration, statins should be considered in all patients with IHD at high risk of major adverse cardiac events, regardless of baseline LDL cholesterol.*

ACE Inhibitors and Angiotensin Receptor Blockers

Angiotensin II is a neurohormone produced primarily in the kidney. It is a potent vasoconstrictor and stimulates the production of aldosterone. Together, angiotensin II and aldosterone increase blood pressure and sodium and water retention (increasing ventricular wall tension), cause endothelial dysfunction, promote blood clot formation, and cause myocardial fibrosis.

Angiotensin-converting enzyme (ACE) inhibitors antagonize the effects of angiotensin II and have consistently been shown to decrease morbidity and mortality in patients with heart failure or a history of MI.[25,26] A recent meta-analysis of 22 clinical trials with ACE inhibitors in post-MI patients found that ACE inhibitors reduced 1-year mortality by 16% to 32% percent, and the mortality-reducing effects were sustained for up to 4 years.[25] In addition, there is evidence that ACE inhibitors reduce the risk of vascular events in patients with chronic stable angina or risk factors for IHD.[27,28] Specifically, in nearly 10,000 patients with vascular disease (including IHD) or risk factors for vascular disease, such as diabetes, ramipril reduced the risk of death, acute MI, and stroke by 22% compared to placebo after an average of 5 years of treatment.[27] Similar results have been demonstrated with perindopril in patients with IHD.[28]

❼ *In the absence of contraindications, ACE inhibitors should be considered in ischemic heart disease patients who also have diabetes mellitus, left ventricular dysfunction, history of myocardial infarction, or any combination of these.[1] In addition, they should also be considered in all patients with IHD and in patients at high-risk for developing IHD based on findings from the studies summarized above. Angiotensin receptor blockers may be used in patients who cannot tolerate ACE inhibitors due to side effects (e.g., chronic cough).* Angiotensin receptor blockers also antagonize the effects of angiotensin II. In one large trial, valsartan was as effective as captopril at reducing morbidity and mortality in post-MI patients.[26] However, there are far more data supporting the use of ACE inhibitors in IHD. Therefore, ACE inhibitors should remain first-line in patients with a history of MI, diabetes, or left ventricular dysfunction. The ACE inhibitors and ARBs with indications for patients with or at risk for IHD or IHD-related complications are listed in Table 4–5.

Control of Risk Factors

A major component of any IHD treatment plan is control of modifiable risk factors, including dyslipidemia, hypertension, and diabetes. Treatment strategies for dyslipidemia and hypertension in the patient with IHD are summarized in the following paragraphs. Visit chapters in this textbook on the management of hypertension and dyslipidemia for further information.

Because lipoprotein metabolism and the pathophysiology of atherosclerosis are closely linked, treatment of dyslipidemias is critical for both primary and secondary prevention of IHD-related cardiac events. In 2001, the Adult Treatment Panel III of the National Cholesterol Education Program

TABLE 4–5. Doses of ACE inhibitors and Angiotensin Receptor Blockers Indicated in Ischemic Heart Disease (IHD).

Drug	Indications	Usual Dosage in IHD
Angiotensin-Converting Enzyme Inhibitors		
Captopril	HTN, HF, post-MI, diabetic nephropathy	6.25–50 mg 3 times daily
Enalapril	HTN, HF	2.5–40 mg daily in 1–2 divided doses
Fosinopril	HTN, HF	10–80 mg daily in 1–2 divided doses
Lisinopril	HTN, HF, post-MI	2.5–40 mg daily
Perindopril	HTN, IHD	4–8 mg daily
Quinapril	HTN, HF, post-MI	5–20 mg twice daily
Ramipril	HTN, high-risk for IHD, HF, post-MI	2.5–10 mg daily in 1–2 divided doses
Trandolapril	HTN, HF, post-MI	1–4 mg daily
Angiotensin Receptor Blockers		
Candesartan	HTN, HF	4–32 mg daily
Valsartan	HTN, HF, post-MI	80–320 mg daily in 1–2 divided doses

HF, heart failure; HTN, hypertension; MI, myocardial infarction.

issued guidelines for the management of dyslipidemia and recommended an LDL cholesterol goal of less than 100 mg/dL (2.59 mmol/L) for patients with documented IHD or IHD risk equivalents such as diabetes or other vascular disease.[8] Statins are the preferred drugs to achieve this goal based on their potency in lowering LDL cholesterol and efficacy in preventing cardiac events. Since the publication of these guidelines, new evidence from several primary and secondary prevention trials suggests that there are additional clinical benefits from further reduction in LDL cholesterol.[29] In response to this evidence, more aggressive cholesterol-lowering goals were established for patients at *very high risk* for developing IHD-related events.[29] Patients with both known IHD and at least one of the following are considered very high risk:

- Multiple major risk factors for IHD, especially diabetes.
- Severe and poorly controlled risk factors, particularly smoking.
- Multiple risk factors of the metabolic syndrome.
- Patients with ACS.

The following modifications were made to the National Cholesterol Education Program treatment guidelines in patients at high or very high risk for IHD-related events:

- If LDL cholesterol is 100 mg/dL (2.59 mmol/L) or greater, statin or other LDL-lowering therapy is indicated along with lifestyle modifications.
- Intensity of LDL-lowering therapy should be sufficient to decrease LDL cholesterol by 30% to 40%.
- Goal LDL cholesterol in patients at very high risk may be decreased to less than 70 mg/dL (1.81 mmol/L).

Like dyslipidemia, hypertension is a major, modifiable risk factor for the development of IHD and related complications. Unfortunately, awareness, treatment, and control of blood pressure are not nearly enough.[30] Aggressive identification and control of hypertension is warranted in patients with IHD to minimize the risk of major adverse cardiac events. Goal blood pressure in patients with IHD is less than 140/90 mm Hg or less than 130/80 mm Hg in patients with diabetes. Because of their cardioprotective benefits, β-blockers and ACE inhibitors (or ARBs in ACE-inhibitor-intolerant patients), either alone or in combination, are appropriate for most patients with both hypertension and IHD.

Nitroglycerin to Relieve Acute Symptoms

Short-acting nitrates are first-line treatment to terminate acute episodes of angina. ❽ *All patients with a history of angina should have sublingual nitroglycerin tablets or spray to relieve acute ischemic symptoms.* Nitrates undergo biotransformation to nitric oxide. Nitric oxide activates soluble guanylate cyclase and leads to increased intracellular concentrations of cyclic guanosine monophosphate, and ultimately, to smooth muscle relaxation. Nitrates primarily cause venodilation, leading to reductions in preload. The resultant decrease in ventricular volume and wall tension leads to a reduction in myocardial oxygen demand. In higher doses, nitrates may also cause arterial dilation and reduce afterload. In addition to reducing oxygen demand, nitrates increase myocardial oxygen supply by dilating the epicardial coronary arteries and collateral vessels, as well as relieving vasospasm.

Short-acting nitrates are available in tablet and spray formulations for sublingual administration. Sublingual nitroglycerin tablets are most commonly used to alleviate angina and are less expensive than the spray. However, the spray is preferred for patients who have difficulty opening the tablet container or produce insufficient saliva for rapid dissolution of sublingual tablets. ❽ *At the onset of an angina attack, a 0.3 to 0.4 mg dose of nitroglycerin (tablet or spray) should be administered sublingually, and repeated every 5 minutes until symptoms resolve. Sitting or standing enhances venous pooling and the effectiveness of nitroglycerin. Sublingual nitroglycerin can also be used to prevent effort-induced angina (i.e., angina that occurs with exertion). In this case, the patient should use sublingual nitroglycerin 2 to 5 minutes prior to an activity known to cause angina, with the effects persisting for approximately 30 minutes.* Isosorbide dinitrate, also available in a sublingual form, has a longer half-life with anti-anginal effects lasting up to 2 hours. The use of short-acting nitrates alone, without concomitant long-acting anti-anginal therapy, may be acceptable for patients who experience angina symptoms once every few days. However, for patients with more frequent attacks, long-acting anti-anginal therapy with β-blockers, calcium channel blockers, or long-acting nitrates is recommended.

Phosphodiesterase type 5 inhibitors are commonly prescribed for erectile dysfunction and include sildenafil, vardenafil,

and tadalafil. Phosphodiesterase degrades cyclic guanosine monophosphate (GMP), which is responsible for the vasodilatory effects of nitrates. Concomitant use of nitrates and phosphodiesterase type 5 inhibitors enhances cyclic GMP-mediated vasodilation and can result in serious hypotension and even death. Therefore, the use of nitrates within 24 hours of sildenafil or vardenafil and within 48 hours of tadalafil is contraindicated.

All patients with IHD should receive a prescription for short-acting nitrates and education regarding their use. Points to emphasize when counseling a patient on nitroglycerin use include:

- The seated position is generally preferred when using nitroglycerin since the drug may cause dizziness.
- Call 911 if symptoms are unimproved or worsen 5 minutes after the first dose.
- Keep nitroglycerin tablets in the original glass container and close the cap tightly after use.
- Nitroglycerin should not be stored in the same container as other medications since this may reduce nitroglycerin's effectiveness.
- Repeated use of nitroglycerin is not harmful or addictive and does not result in any long-term side effects. Patients should not hesitate to use nitroglycerin whenever needed.
- Nitroglycerin should not be used within 24 hours of taking sildenafil or vardenafil or within 48 hours of taking tadalafil because of the potential for life-threatening hypotension.

Pharmacotherapy to Prevent Recurrent Ischemic Symptoms

The overall goal of anti-anginal therapy is to allow patients with IHD to resume normal activities without symptoms of angina and to experience minimal to no adverse drug effects. The drugs traditionally used to prevent ischemic symptoms are β-blockers, calcium channel blockers, and nitrates. These drugs exert their anti-anginal effects by improving the balance between myocardial oxygen supply and demand, with specific effects listed in Table 4–6. β-Blockers, calcium channel blockers, and nitrates decrease the frequency of angina and delay the onset of angina during exercise. However, there is no evidence that any of these agents prevent ACS or improve survival in patients with chronic stable angina. Recently, the Food and Drug Administration (FDA) approved ranolazine, a new molecular entity, for the treatment of chronic stable angina in patients unresponsive to traditional anti-anginal medications. Combination therapy with two or three anti-anginal drugs is often needed.

TABLE 4–6. Effects of Anti-anginal Medications on Myocardial Oxygen Demand and Supply

	Oxygen Demand			
Anti-anginal Agent	Heart Rate	Wall Tension	Cardiac Contractility	Oxygen Supply
β-Blockers	↓	↔ or ↑	↓	↔
Calcium channel blockers				
Verapamil, diltiazem	↓	↓	↓	↑
Dihydropyridines	↔ or ↑	↓	↓	↑
Nitrates	↑	↓	↔	↑

↓, decreases; ↔, no change; ↑, increases.

Beta-Blockers

Stimulation of the β_1- and β_2-adrenergic receptors in the heart increases heart rate and cardiac contractility. β-Blockers antagonize these effects and decrease myocardial oxygen demand. β-Blockers may also reduce oxygen demand by lowering blood pressure and ventricular wall tension. However, with marked reductions in heart rate, β-blockers may actually increase ventricular wall tension. This is because slower heart rates allow the ventricle more time to fill during diastole, leading to increased left ventricular volume, end diastolic pressure, and wall tension. However, the net effect of β-blockade is usually a reduction in myocardial oxygen demand. β-Blockers do not improve myocardial oxygen supply.

The properties and recommended doses of various β-blockers are summarized in Table 4–7. β-Blockers with intrinsic sympathomimetic activity have partial β-agonist effects and cause lesser reductions in heart rate at rest. As a result, β-blockers with intrinsic sympathomimetic activity may produce lesser reductions in myocardial oxygen demand and should be avoided in patients with IHD. Other β-blockers appear equally effective at controlling symptoms of angina. The frequency of dosing and drug cost should be taken into consideration when choosing a particular drug. Agents that can be dosed once or twice daily are preferred. Most β-blockers are available in inexpensive generic versions. β-Blockers should be initiated in doses at the lower end of the usual dosing range, with titration according to symptom and hemodynamic response. The β-blocker dose is commonly titrated to achieve the following:

- Resting heart rate between 50 and 60 beats per minute.
- Maximum heart rate with exercise of 100 beats per minute or less or 20 beats per minute above the resting heart rate.

❾ *β-Blockers are first-line therapy for preventing ischemic symptoms, particularly in patients with a history of myocardial infarction. In the absence of contraindications, β-blockers are preferred for several reasons. First, β-blockers may prevent cardiac arrhythmias by decreasing the rate of spontaneous depolarization of ectopic pacemakers. Second, in several large randomized trials, β-blockers were shown to prevent target organ damage, particularly stroke and heart failure, in patients with hypertension.*[31] *Finally, while the long-term effects of β-blockers on morbidity and mortality in patients with chronic stable angina are largely unknown, certain β-blockers have been shown to decrease the risk for reinfarction and improve survival in patients who have suffered*

TABLE 4–7. Properties and Dosing of β-Blockers in Ischemic Heart Disease

Drug	Receptor Affinity	Intrinsic Sympathomimetic Activity	Usual Dose Range
Acebutolol	β_1-Selective	Yes	100–400 mg twice daily
Atenolol	β_1-Selective	No	25–100 mg once daily
Betaxolol	β_1-Selective	No	5–20 mg once daily
Bisoprolol	β_1-Selective	No	2.5–10 mg once daily
Carvedilol	α_1, β_1, and β_2	No	6.25–25 mg twice daily
Labetalol	α_1, β_1, and β_2	Yes, at β_2-receptors	100–400 mg twice daily
Metoprolol	β_1-Selective	No	50–100 mg twice daily (once daily for extended-release)
Nadolol	β_1 and β_2	No	40–120 mg once daily
Penbutolol	β_1 and β_2	Yes	10–40 mg once daily
Pindolol	β_1 and β_2	Yes	10–40 mg twice daily
Propranolol	β_1 and β_2	No	20–80 mg twice daily (60–180 mg once daily for long-acting formulation)
Timolol	β_1 and β_2	No	10–20 mg twice daily

an MI.[32] Specific β-blockers associated with mortality reductions in clinical trials include metoprolol, propranolol, and carvedilol.[32,33] In a meta-analysis of 82 clinical trials investigating the use of β-blockers in patients following MI, the relative risk of death was reduced by 23% in patients treated with β-blockers compared to control subjects.[32] Long-term therapy (for at least 6 months) was associated with greater mortality benefit compared to short-term β-blockade (6 weeks or less).

β-Blockers are contraindicated in patients with severe bradycardia (heart rate less than 50 beats per minute) or AV conduction defects in the absence of a pacemaker. β-Blockers should be used with particular caution in combination with other agents that depress AV conduction (e.g., digoxin, verapamil, and diltiazem) because of increased risk for bradycardia and heart block. Relative contraindications include asthma, bronchospastic disease, severe depression, and peripheral vascular disease. β_1-Selective blockers are preferred in patients with asthma or chronic obstructive pulmonary disease. However, selectivity is dose dependent, and β_1-selective agents may induce bronchospasm in higher doses. Calcium channel blockers are preferred in patients with severe peripheral vascular disease who experience symptoms at rest.

There are several precautions to consider with the use of β-blockers in patients with diabetes or heart failure. All β-blockers may mask the tachycardia and tremor (but not sweating) that commonly accompany episodes of hypoglycemia in diabetes. In addition, non-selective β-blockers may alter glucose metabolism and slow recovery from hypoglycemia in insulin-dependent diabetes. β_1-Selective agents are preferred because they are less likely to prolong recovery from hypoglycemia. Importantly, β-blockers should not be avoided in patients with IHD and diabetes, particularly in patients with a history of MI who are at a high risk for recurrent cardiovascular events. β-Blockers are negative inotropes (i.e., they decrease cardiac contractility). Cardiac contractility is impaired in patients with left ventricular dysfunction. Therefore, β-blockers may worsen symptoms of heart failure in patients with left ventricular dysfunction (i.e., ejection fraction less than 35%). When used for management of IHD in a patient with heart failure, β-blockers should be initiated in very low doses with slow up-titration to avoid worsening heart failure symptoms.

Other potential adverse effects from β-blockers include fatigue, sleep disturbances, malaise, depression, and sexual dysfunction. Abrupt β-blocker withdrawal may increase the frequency and severity of angina, possibly because of increased receptor sensitivity to catecholamines after long-term β-blockade. If the decision is made to stop β-blocker therapy, the dose should be tapered over several days to weeks to avoid exacerbating angina.

Calcium Channel Blockers

Calcium channel blockers (CCBs) inhibit calcium entry into vascular smooth muscle and cardiac cells, resulting in the inhibition of the calcium-dependent process leading to muscle contraction. Inhibition of calcium entry into the vascular smooth muscle cells leads to systemic vasodilation and reductions in afterload. Inhibition of calcium entry into the cardiac cells leads to reductions in cardiac contractility. Thus, CCBs reduce myocardial oxygen demand by lowering both wall tension (through reductions in afterload) and cardiac contractility. In addition, the nondihydropyridine CCBs verapamil and diltiazem further decrease myocardial oxygen demand by slowing cardiac conduction through the AV nodes and lowering heart rate. In contrast, dihydropyridine calcium channel blockers, nifedipine in particular, are potent vasodilators that can cause baroreflex-mediated increases in sympathetic tone and heart rate. Because of their negative **chronotropic** effects, verapamil and diltiazem are generally more effective anti-anginal agents than the dihydropyridine CCBs. In addition to decreasing myocardial oxygen demand, all CCBs increase myocardial oxygen supply by dilating coronary arteries, thus increasing coronary blood flow and relieving vasospasm.

In randomized, controlled, clinical trials, calcium channel blockers were as effective as β-blockers at preventing ischemic symptoms. ❾ *Calcium channel blockers are recommended as initial treatment in IHD when β-blockers are contraindicated or not tolerated. In addition, CCBs may be used in combination with β-blockers when initial treatment is unsuccessful.* However, the combination of a β-blocker with either verapamil or diltiazem should be used with extreme caution since all of these drugs decrease AV nodal conduction, increasing the risk for severe bradycardia or AV block when used together. If combination therapy is warranted, a long-acting dihydropyridine CCB is preferred. β-Blockers will prevent reflex increases in sympathetic tone and heart rate with the use of calcium channel blockers with potent vasodilatory effects.

There are several precautions to consider with the use of CCBs. Since verapamil and diltiazem slow conduction through the AV node, these agents are contraindicated in patients with bradycardia and preexisting conduction disease. Verapamil and diltiazem should also be used with particular caution in combination with β-blockers as well as with digoxin, which also depresses AV nodal conduction, since the combination may cause bradycardia or heart block. Calcium channel blockers have negative **inotropic** effects that may be deleterious in patients with preexisting left ventricular systolic dysfunction. However, the degree of negative inotropy varies among agents. Amlodipine and felodipine possess less negative inotropic effects and appear to be safe in patients with left ventricular systolic dysfunction.[34,35] However, other calcium channel blockers may cause or exacerbate heart failure in patients with systolic dysfunction and should be avoided in this population. Finally, there is some evidence that short-acting calcium channel blockers (particularly short-acting nifedipine and nicardipine) may increase the risk of cardiovascular events.[31] Therefore, short-acting agents should be avoided in the management of IHD.

Long-Acting Nitrates

Nitrate products are available in both oral and transdermal formulations for chronic use. Commonly used products are listed in Table 4–8. All nitrate products are equally effective at preventing the recurrence of angina when used appropriately.

The major limitation of nitrate therapy is the development of tolerance with continuous use. The loss of anti-anginal effects may occur within the first 24 hours of continuous nitrate therapy. While the cause of tolerance is unclear, several mechanisms have been proposed. These include depletion of the sulfhydryl groups necessary for the conversion of nitrates to nitric oxide, activation of neurohormonal systems, increased intravascular volume, and generation of free radicals that degrade nitric oxide. The most effective method to avoid tolerance and maintain the anti-anginal efficacy of nitrates is to allow a daily nitrate-free interval of at least 8 to 12 hours. Nitrates do not provide protection from ischemia during the nitrate-free period. Therefore, the nitrate-free interval should occur when the patient is least likely to experience angina. Generally, angina is less common during the nighttime hours when the patient is sleeping and myocardial oxygen demand is reduced. Thus, it is common to dose long-acting nitrates so that the nitrate-free interval begins in the evening. For example, isosorbide dinitrate is typically dosed on awakening and again 7 hours later.

TABLE 4–8. Nitrate Formulations and Dosing for Chronic Use

Formulation	Dose
Oral	
Nitroglycerin extended-release capsules	2.5 mg 3 times daily initially, with up-titration according to symptoms and tolerance; allow a 10–12 hour nitrate-free interval
Isosorbide dinitrate tablets	5–20 mg 2–3 times daily, with a daily nitrate-free interval of at least 14 hours
Isosorbide dinitrate slow-release capsules	40 mg 1–2 times daily, with a daily nitrate-free interval of at least 18 hours
Isosorbide mononitrate tablets	20 mg 2 times daily, with doses 7 hours apart
Isosorbide mononitrate extended-release tablets	30–120 mg once daily
Transdermal	
Nitroglycerin extended-release film	0.2–0.8 mg/hour, on for 12–14 hours, off for 10–12 hours

Monotherapy with nitrates for the prevention of ischemia should generally be avoided for a couple of reasons. First, reflex increases in sympathetic activity and heart rate, with resultant increases in myocardial oxygen demand, may occur secondary to nitrate-induced venodilation. Second, patients are unprotected from ischemia during the nitrate-free interval. β-Blockers and calcium channel blockers are dosed to provide 24-hour protection from ischemia. ❾ *Treatment with long-acting nitrates should be added to baseline therapy with either a β-blocker or calcium channel blocker or a combination of the two.* β-Blockers attenuate the increase in sympathetic tone and heart rate that occurs during nitrate therapy. In turn, nitrates attenuate the increase in wall tension during β-blocker therapy. As a result, the combination of β-blockers and nitrates is particularly effective at preventing angina and provides greater protection from ischemia than therapy with either agent alone. Monotherapy with nitrates may be appropriate in patients who have low blood pressure at baseline or who experience symptomatic hypotension with low doses of β-blockers or calcium channel blockers.

Common adverse effects of nitrates include postural hypotension, flushing, and headache secondary to venodilation. Headache often resolves with continued therapy and may be treated with acetaminophen. Hypotension is generally

of no serious consequence. However, in patients with hypertrophic obstructive cardiomyopathy or severe aortic valve stenosis, nitroglycerin may cause serious hypotension and syncope. Therefore, long-acting nitrates are relatively contraindicated in these conditions. Because life-threatening hypotension may occur with concomitant use of nitrates and phosphodiesterase type 5 inhibitors, nitrates should not be used within 24 hours of taking sildenafil or vardenafil or within 48 hours of taking tadalafil. Skin erythema and inflammation may occur with transdermal nitroglycerin administration and may be minimized by rotating the application site.

Ranolazine

Although the exact mechanism of action for ranolazine is unknown, it may be related to partial inhibition of fatty acid oxidation and enhanced generation of adenosine triphosphate. Ultimately, ranolazine may improve energy efficiency, thus reducing the amount of oxygen supply necessary to meet an increase in oxygen demand. In clinical trials, ranolazine at a dose of 750 to 1000 mg twice daily improved angina and increased exercise capacity when added to standard therapy with a β-blocker or calcium channel blocker.[36] Ranolazine has the potential to prolong the QT interval and increase the risk for the life-threatening arrhythmia, torsades de pointes. Therefore, ranolazine should be reserved for patients who do not respond to traditional anti-anginal medications. Common adverse effects with ranolazine include dizziness, headache, constipation, and nausea.

Pharmacotherapy with No Benefit or Potentially Harmful Effects

Hormone Replacement Therapy

Hormone replacement therapy (HRT) has favorable effects on lipoprotein cholesterol concentrations. Data from several observational studies suggested that HRT might reduce the risk of cardiovascular events in women with IHD. However, subsequent randomized controlled studies failed to demonstrate a benefit with HRT in postmenopausal women.[37–39] In fact, HRT appeared to be harmful in this patient population. In one randomized controlled trial with HRT, more women receiving HRT had thromboembolic events and developed gallbladder disease than those on placebo.[37] Similarly, the Women's Health Initiative study found no reduction in the risk for IHD in healthy postmenopausal women receiving either estrogen plus progesterone or estrogen alone.[38,39] In addition, compared to placebo, the risks of thromboembolic events and breast cancer were higher with estrogen plus progesterone. The risk for stroke was higher with estrogen alone. Based on these findings, current guidelines recommend against the use of hormone replacement therapy to reduce cardiovascular risk.[1] Furthermore, the clinician should consider discontinuing hormone replacement therapy in women who suffer an acute coronary event while receiving such therapy.

Antioxidants

Oxidization of LDL-cholesterol is believed to play a significant role in the atherosclerotic process. The antioxidant vitamins, vitamin E and vitamin C, protect LDL cholesterol from oxidation. Evidence from observational and animal studies suggested that increased intake of antioxidant vitamins might inhibit the formation of atherosclerotic lesions and decrease the risk for cardiovascular events.[40] However, several large, randomized, prospective studies found no beneficial effect of vitamin E or other antioxidants on cardiovascular outcomes in patients with IHD or IHD risk factors.[41,42] Based on this evidence, current guidelines do not recommend supplementation with vitamin E or other antioxidants for the sole purpose of preventing cardiovascular events.

Folic Acid

Elevated homocysteine concentrations have been associated with an increased risk for cardiovascular disease in both epidemiologic and clinical studies.[43] Several studies have evaluated the benefit of lowering homocysteine levels with folic acid supplementation. One study reported a reduction in major cardiac events with the combination of folic acid, vitamin B_{12}, and vitamin B_6 following PCI.[44] However, a more recent study found an increased risk of instent restenosis and the need for target-vessel revascularization with folate supplementation following coronary stent placement.[45] The role of folate in the management of IHD is currently unclear.

Herbal Supplements

Herbal products are widely used for their purported cardiovascular benefits; examples of such products include danshen, dong quai, feverfew, garlic, hawthorn, and hellebore.[46] However, strong evidence supporting their benefits in cardiovascular disease is generally lacking. While there are data from small randomized controlled trials supporting the benefits of some herbal supplements, the potential for drug interactions and the lack of product standardization limits the products' usefulness in clinical practice. Safety with herbal supplements in patients with IHD is a major concern. Unlike prescription and over-the-counter (OTC) medicines, the FDA does not require manufacturers of herbal products to submit proof of safety prior to product marketing. Numerous case reports of adverse cardiovascular events, including stroke, MI, and lethal cardiac arrhythmias with ephedra-based products (e.g., Ma huang) led the FDA to ban ephedra-containing products in 2004. However, other herbal supplements with potentially serious adverse cardiovascular effects remain easily accessible to the consumer. Some herbal supplements may interact with antiplatelet and antithrombotic therapy and increase bleeding risk. Others may reduce the effectiveness of anti-anginal medications. Thus, it is important to assess the use of herbal products in patients with IHD and to counsel patients about the potential for drug interactions and adverse events with herbal therapies.



Patient Encounter, Part 3: Creating a Care Plan

Based on the information presented, create a specific plan for the management of RJ's ischemic heart disease. Your plan should include: (1) the goals of therapy; (2) specific nonpharmacologic and pharmacologic interventions to address these goals; and (3) a plan for follow-up to assess drug tolerance and whether the therapeutic goals have been achieved.

Cyclooxygenase-2 (COX-2) Inhibitors and Non-steroidal Anti-Inflammatory Drugs (NSAIDs)

Recent data suggest that COX-2 inhibitors, including rofecoxib, valdecoxib, and celecoxib, may increase the risk for MI and stroke.[47] There is also some evidence that the non-selective NSAIDs may increase the risk for cardiovascular events.[47,48] Rofecoxib was withdrawn from the market in late 2004 because of safety concerns. The FDA requested the withdrawal of valdecoxib from the market in 2005. The FDA also asked the manufacturers of celecoxib and non-selective NSAIDs (prescription and over-the-counter) to include information about the potential adverse cardiovascular effects of these drugs in their product labeling. The cardiovascular risk with COX-2 inhibitors and NSAIDs may be greatest in patients with a history of, or with risk factors for, cardiovascular disease. The American Heart Association recommends that the use of COX-2 inhibitors be limited to low-dose, short-term therapy in patients for whom there is no appropriate alternative.[48] Patients with cardiovascular disease should consult a clinician before using over-the-counter NSAIDs.

SPECIAL POPULATIONS

Variant Angina

Vasospasm as the sole etiology of angina (Prinzmetal's or variant angina) is relatively uncommon. As a result, treatment options are not well studied. Nevertheless, based on the pharmacology of available drugs, several recommendations can be made. First, β-blockers should be avoided in patients with variant angina because of their potential to worsen vasospasm due to unopposed α-adrenergic receptor stimulation. In contrast, both calcium channel blockers and nitrates are effective in relieving vasospasm and are preferred in the management of variant angina. Nitrates have several limitations outlined above, most notably the need for an 8- to 12-hour nitrate-free interval. Therefore, the role of monotherapy with long-acting nitrates as prophylaxis for anginal attacks due to vasospasm is limited. However, immediate-release nitroglycerin is effective at terminating acute anginal attacks due to vasospasm. Therefore, all patients diagnosed with variant angina should be prescribed immediate-release nitroglycerin. Calcium channel blockers are effective for monotherapy of variant angina. Since short-acting calcium channel blockers have been associated with increased risk of adverse cardiac events, they should be avoided.[31] Long-acting nitrates may be added to CCB therapy if needed.

Elderly Patients with IHD

Elderly patients are more likely than younger patients to have other comorbidities that may influence drug selection for the treatment of angina. As a result, polypharmacy is more common in elderly patients, increasing the risk of drug-drug interactions, and perhaps decreasing medication adherence. Additionally, elderly patients are often more susceptible to adverse effects of anti-anginal therapies, particularly the negative chronotropic and inotropic effects of β-blockers and CCBs. Therefore, drugs should be initiated in low doses with close monitoring of elderly patients with IHD.

Acute Coronary Syndrome

The management of ACS is discussed in further detail in the chapter on acute coronary syndromes. It is important to educate patients with IHD on the signs of ACS and what to do if they appear. Importantly, patients should be instructed to seek emergent care if symptoms of angina last longer than 20 to 30 minutes, do not improve after 5 minutes of using sublingual nitroglycerin, or worsen after 5 minutes of using sublingual nitroglycerin. In patients with a history of ACS, it is crucial to select appropriate pharmacotherapy to prevent recurrent ACS and death. Appropriate pharmacotherapy for patients with a history of ACS includes aspirin, ACE inhibitors or ARBs, β-blockers, and statins. In addition, determining appropriate goals and instituting appropriate therapy to meet the goals for cardiovascular risk factors (e.g., dyslipidemia, hypertension, and diabetes) is critical.

OUTCOME EVALUATION

Assessing for Drug Effectiveness and Safety

- ⓫ *Monitor symptoms of angina at baseline and at each clinic visit for patients with IHD to assess the effectiveness of anti-anginal therapy. In particular, assess the frequency and intensity of anginal symptoms.* Determining the frequency of sublingual nitroglycerin use is helpful in making this assessment. If angina is occurring with increasing frequency or intensity, adjust anti-anginal therapy and refer the patient for additional

diagnostic testing (e.g., coronary angiography) and possibly for coronary interventions (e.g., PCI or CABG surgery).

- Assess the patient for IHD-related complications, such as heart failure. The presence of new comorbidities may indicate worsening IHD requiring additional workup or pharmacologic therapy.
- ⑩ *Hemodynamic parameters should be routinely monitored to assess drug tolerance. Assess blood pressure at baseline, after drug initiation and dose titration, then periodically thereafter in patients treated with β-blockers, CCBs, nitrates, ACE inhibitors, and/or ARBs.*
- Blood pressure reduction may be particularly pronounced after initiation and dose titration of β-blockers that also possess α-blocking effects (e.g., labetalol and carvedilol).
- Because of the potential for postural hypotension, warn patients that dizziness, presyncope, and even syncope may result from abrupt changes in body position during initiation or up-titration of drugs with α-blocking effects.
- ⑩ *Closely monitor heart rate in patients treated with drugs that have negative chronotropic effects (e.g., β-blockers, verapamil, or diltiazem) or drugs that may cause reflex tachycardia (e.g., nitrates or dihydropyridine CCBs).*
- Treatment with β-blockers, verapamil, or diltiazem can usually be continued in patients with asymptomatic bradycardia. However, reduce or discontinue treatment with these agents in patients who develop symptomatic bradycardia or serious conduction abnormalities.
- Control of existing risk factors and the presence of new risk factors for IHD should also be assessed regularly. Routine screening for the presence of metabolic syndrome will help in assessing the control of known major risk factors and identifying new risk factors. If new risk factors are identified and/or the presence of metabolic syndrome is detected, modify the pharmacotherapy regimen, as discussed previously, to control these risk factors and lower the risk of IHD and IHD-related adverse events.

Duration of Therapy

- Drugs that modify platelet activity, lipoprotein concentrations, and neurohormonal systems reduce the risk for coronary events and death. However, these therapies do not cure IHD.
- Treatment with antiplatelet (aspirin or clopidogrel), lipid-lowering, and neurohormonal-modifying therapy for IHD is generally lifelong. Similarly, anti-anginal therapy with a β-blocker, CCB, and/or nitrate is usually long-term.
- A patient with severe symptoms managed with combination anti-anginal drugs who undergoes successful coronary revascularization may be able to reduce anti-anginal therapy. However, treatment with at least one agent that improves the balance between myocardial oxygen demand and supply is usually warranted.



Patient Care and Monitoring

1. Assess the patient's symptoms to determine whether the patient should be evaluated by a physician.
   - Determine the quality, location, and duration of pain.
   - Determine factors that provoke and relieve pain.
   - Are symptoms characteristic of angina?
2. Identify risk factors for IHD.
   - Are there any modifiable risk factors?
3. Obtain a thorough history of prescription drug, nonprescription drug, and herbal product use.
   - Is the patient taking any medications/supplements that may exacerbate angina or interact with anti-anginal drug therapy?
4. Educate the patient on lifestyle modifications to control risk factors for IHD.
5. Is the patient taking appropriate drug therapy to prevent ACS and death? If not, why?
6. Is the patient taking appropriate anti-anginal therapy? If not, why?
7. Develop a plan to assess effectiveness of anti-ischemic therapy after 1 to 2 weeks.
8. Evaluate the patient to assess for adverse drug reactions, drug intolerance, and drug interactions.
9. Stress the importance of adherence with the therapeutic regimen, including lifestyle modifications.
10. Provide patient education regarding disease state, lifestyle modifications, and drug therapy:
    - What are the consequences of untreated IHD?
    - What lifestyle modifications should the patient follow?
    - When should the patient take his or her medications?
    - What potential adverse drug effects may occur?
    - Teach the patient how to monitor heart rate and blood pressure to assess tolerance to anti-anginal therapy.
    - Which drugs may interact with therapy or worsen IHD?
    - What should the patient do when chest pain or its equivalent occurs?
    - When should the patient seek emergent care?

ABBREVIATIONS

ACE:	angiotensin-converting enzyme
ACE-I:	angiotensin-converting enzyme inhibitor
ACS:	acute coronary syndrome
ARB:	angiotensin receptor blocker
AV:	atrioventricular
BMS:	bare metal stent
BP:	blood pressure
CABG:	coronary artery bypass graft
CCB:	calcium channel blocker

CHD:	coronary heart disease
CK:	creatinine kinase
CK-MB:	creatinine kinase, MB fraction
COX-2:	cyclooxygenase-2
DES:	drug-eluting stent
ECG:	electrocardiogram
FDA:	Food and Drug Administration
GMP:	guanosine monophosphate
HDL:	high-density lipoprotein
HF:	heart failure
HMG-CoA:	3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor
HRT:	hormone replacement therapy
HTN:	hypertension
IHD:	ischemic heart disease
IR:	immediate-release
LA:	long-acting
LV:	left ventricular
LDL:	low-density lipoprotein
MI:	myocardial infarction
MVO_2:	myocardial oxygen consumption
NSAID:	non-steroidal anti-inflammatory drug
NTG:	nitroglycerin
OTC:	over-the-counter
PCI:	percutaneous coronary intervention
PTCA:	percutaneous transluminal coronary angioplasty
SL:	sublingual

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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5 Acute Coronary Syndromes

Sarah A. Spinler and Simon de Denus



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Define the role of an atherosclerotic plaque, platelets, and coagulation system in an acute coronary syndrome.
2. Describe the onset, peak, and duration of elevation of troponin and creatine kinase myocardial band in acute myocardial infarction.
3. List key electrocardiographic and clinical features identifying a patient with non–ST-segment elevation acute coronary syndrome who is at high risk of myocardial infarction or death.
4. Devise a pharmacotherapy treatment plan for a patient undergoing primary percutaneous coronary intervention in ST-segment elevation myocardial infarction given patient-specific data.
5. Devise a pharmacotherapy treatment plan for a patient with ST-segment elevation myocardial infarction given patient-specific data.
6. List the quality indicators of care for myocardial infarction and explain the rationale behind each indicator.
7. Formulate a monitoring plan for a patient with ST-segment elevation acute coronary syndrome receiving fibrinolytics, aspirin, unfractionated heparin, intravenous nitroglycerin, intravenous β-blockers followed by oral β-blockers, an angiotensin-converting enzyme inhibitor, and a statin.
8. Devise a pharmacotherapy treatment and monitoring plan for a patient with non–ST-segment elevation acute coronary syndrome given patient-specific data.
9. Devise a pharmacotherapy and risk-factor modification treatment plan for secondary prevention of coronary heart disease events in a patient following myocardial infarction.

Key Concepts

❶ The cause of an acute coronary syndrome is the rupture of an atherosclerotic plaque with subsequent platelet adherence, activation, and aggregation, and the activation of the clotting cascade. Ultimately, a clot forms composed of fibrin and platelets.

❷ The American Heart Association and the American College of Cardiology recommend strategies, or guidelines, for acute coronary syndrome patient care for ST-segment and non–ST-segment elevation acute coronary syndrome.

❸ Patients with ischemic chest discomfort and suspected acute coronary syndrome are risk-stratified based upon a 12-lead electrocardiogram, past medical history, and results of the creatine kinase myocardial band and troponin tests. The diagnosis of myocardial infarction is confirmed based on the results of the creatine kinase myocardial band and troponin tests.

❹ Early reperfusion therapy with either primary percutaneous coronary intervention or administration of a fibrinolytic agent within 3 hours of symptom onset is the recommended therapy for patients presenting with ST-segment elevation acute coronary syndrome.

❺ The most recent non–ST-segment elevation American College of Cardiology/American Heart Association clinical practice guidelines recommend coronary angiography with either percutaneous coronary intervention or coronary artery bypass graft surgery revascularization as an early treatment (early invasive strategy) for high-risk and moderate-risk non–ST-segment elevation acute coronary syndrome patients.

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❻ According to the American College of Cardiology/American Heart Association ST-segment elevation acute coronary syndrome practice guidelines, in addition to reperfusion therapy, early pharmacotherapy of ST-segment elevation should include intranasal oxygen (if oxygen saturation is less than 90%), sublingual nitroglycerin followed by intravenous nitroglycerin, aspirin, an intravenous β-blocker, unfractionated heparin, and fibrinolysis in eligible candidates.

❼ According to the American College of Cardiology/American Heart Association non–ST-segment elevation acute coronary syndrome practice guidelines, in the absence of contraindications, early pharmacotherapy of non–ST-segment elevation should include intranasal oxygen (if oxygen saturation is low), sublingual nitroglycerin followed by intravenous nitroglycerin, aspirin, an intravenous β-blocker, and unfractionated heparin or low-molecular-weight heparin. Most patients should receive additional therapy with clopidogrel. High-risk patients should also receive a glycoprotein IIb/IIIa receptor blocker.

❽ Guidelines from the American College of Cardiology/American Heart Association suggest that, in the absence of contraindications, following myocardial infarction from either ST-segment elevation acute coronary syndrome or non–ST-segment elevation coronary syndrome, patients should receive indefinite treatment with aspirin, a beta-blocker, and an angiotensin-converting enzyme inhibitor.[2,3] For non–ST-segment elevation acute coronary syndrome, most patients should receive clopidogrel, in addition to aspirin, for up to 9 months. Most patients will receive a statin to reduce low-density lipoprotein cholesterol to less than 100 mg/dL.

❾ Secondary prevention of death, reinfarction, and stroke is more cost effective than primary prevention of coronary heart disease events.

Cardiovascular disease (CVD) is the leading cause of death in the United States and one of the major causes of death worldwide. **Acute coronary syndromes** (ACS), including unstable angina (UA) and myocardial infarction (MI), are a form of coronary heart disease (CHD) that comprises the most common cause of CVD death.[1] ❶ *The cause of an acute coronary syndrome is the rupture of an atherosclerotic plaque with subsequent platelet adherence, activation, and aggregation and the activation of the clotting cascade. Ultimately, a clot forms composed of fibrin and platelets.* ❷ *The American Heart Association (AHA) and the American College of Cardiology (ACC) recommend strategies, or guidelines, for ACS patient care for ST-segment and non–ST-segment elevation ACS.* These joint practice guidelines are based upon a review of available clinical evidence, have graded recommendations based upon evidence, and are updated periodically. These guidelines form the cornerstone for quality care of the ACS patient.[2,3]

EPIDEMIOLOGY

Each year, more than one million Americans will experience an ACS and 239,000 will die of an MI.[1] In the United States, more than 7.6 million living persons have survived an MI.[1] Chest discomfort is the most frequent reason for patient presentation to emergency departments, with up to 7 million, or approximately 3%, of all emergency department visits linked to chest discomfort and possible ACS. Coronary heart disease is the leading cause of premature, chronic disability in the United States. The risks of CHD events, such as death, recurrent MI, and stroke, are higher for patients with established CHD and a history of MI than for patients with no known CHD. The cost of CHD is high, with more than $10 billion being paid to Medicare beneficiaries in 1999, or more than $10,000 per MI hospital stay, with the average length of hospital stay for MI in 1999 being 5.6 days.[1]

In patients with **ST-segment elevation** (STE) ACS, in-hospital death rates are approximately 7% for patients who are treated with fibrinolytics and 16% for patients who do not receive reperfusion therapy. In patients with **non–ST-segment elevation** (NSTE) MI, in-hospital mortality is less than 5%. In-hospital and 1-year mortality rates are higher for women and elderly patients. In the first year following MI, 38% of women and 25% of men will die, most from recurrent **infarction**.[1] At 1 year, rates of mortality and reinfarction are similar between STE and NSTE MI.

Because reinfarction and death are major outcomes following ACS, therapeutic strategies to reduce morbidity and mortality, particularly utilization of coronary angiography, revascularization, and pharmacotherapy, will have a significant impact on the social and economic burden of CHD in the United States.

ETIOLOGY

Endothelial dysfunction, inflammation, and the formation of fatty streaks contribute to the formation of atherosclerotic coronary artery plaques, the underlying cause of coronary artery disease (CAD). ❶ *The predominant cause of ACS, in more than 90% of patients, is atheromatous plaque rupture, fissuring, or erosion of an unstable atherosclerotic plaque that occludes less than 50% of the coronary lumen prior to the event, rather than a more stable 70% to 90% stenosis of the coronary artery.*[3] Stable stenoses are characteristic of stable angina.

PATHOPHYSIOLOGY

Spectrum of Acute Coronary Syndromes

Acute coronary syndromes is a term that includes all clinical syndromes compatible with acute myocardial ischemia resulting from an imbalance between myocardial oxygen demand and supply.[3] In contrast to stable angina, an ACS results primarily from diminished myocardial blood flow secondary to an occlusive or partially occlusive coronary artery thrombus. Acute coronary syndromes are classified according to electrocardiogram (ECG) changes into STE ACS (STE MI) or NSTE ACS (NSTE MI and unstable angina) (Fig. 5–1). An STE MI, formerly

known as Q-wave or transmural MI, typically results in an injury that transects the thickness of the myocardial wall. Following an STE MI, pathologic Q waves are frequently seen on the ECG, indicating transmural myocardial infarction, while such an ECG manifestation is seen less commonly in patients with NSTE MI.[4] Non–ST-segment elevation MI, formerly known as non–Q-wave or non-transmural MI, is limited to the sub-endocardial myocardium. Patients in this case do not usually develop a pathologic Q wave on the ECG. Moreover, an NSTE MI is smaller and not as extensive as an STE MI. Non–ST-elevation MI differs from unstable angina in that ischemia is severe enough to produce myocardial necrosis resulting in the release of a detectable amount of biochemical markers (intracellular macromolecules released into the peripheral circulation from necrotic myocytes as a result of myocardial cell death or infarction), mainly **troponins T** or **I** or **creatine kinase (CK) myocardial band (MB)** from the necrotic myocytes in the bloodstream.[3] The clinical significance of serum markers will be discussed in greater detail in later sections of this chapter.

Plaque Rupture and Clot Formation

Following plaque rupture, a clot (a partially occlusive or completely occlusive thrombus), forms on top of the ruptured plaque. The thrombogenic contents of the plaque are exposed to blood elements. Exposure of collagen and tissue factor induce platelet adhesion and activation, which promote the release of platelet-derived vasoactive substances including adenosine diphosphate (ADP) and thromboxane A_2 (TXA_2).[5] These produce vasoconstriction and potentiate platelet activation. Furthermore, during platelet activation, a change in the conformation in the glycoprotein IIb/IIIa surface receptors of platelets occurs which cross-links platelets to each other through fibrinogen bridges. This is considered the final common pathway of platelet aggregation. Inclusion of platelets gives the clot a white appearance. Simultaneously, the extrinsic coagulation cascade pathway is activated as a result of exposure of blood components to the thrombogenic lipid core and endothelium, which are rich in tissue factor. This leads to the production of thrombin (factor IIa), which converts fibrinogen to fibrin through enzymatic activity.[5] Fibrin stabilizes the clot and traps red blood cells, which give the clot a red appearance. Therefore, the clot is composed of cross-linked platelets and fibrin strands.[8]

Ventricular Remodeling Following an Acute Myocardial Infarction

Ventricular remodeling is a process that occurs in several cardiovascular conditions including heart failure and following an MI. It is characterized by left ventricular dilation and reduced pumping function of the left ventricle leading to cardiac failure.[6] Because heart failure represents one of the principal causes of mortality and morbidity following an MI, preventing ventricular remodeling is an important therapeutic goal.[6]

Angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and aldosterone antagonists are all agents that slow down or reverse ventricular remodeling through neurohormonal blockage and/or through improvement in hemodynamics (decreasing preload or afterload).[6] These agents also improve survival and will be discussed in more detail in subsequent sections of this chapter.

Complications

This chapter will focus on management of the uncomplicated ACS patient. However, it is important for clinicians to recognize complications of MI, since MI is associated with increased mortality. The most serious complication of MI is cardiogenic shock, occurring in approximately 10% of hospitalized MI patients. Mortality in cardiogenic shock patients with MI is high, approaching 60%.[7] Other complications which may result from MI are heart failure, valvular dysfunction, ventricular and atrial tachyarrhythmias, bradycardia, heart block, pericarditis, stroke secondary to left ventricular thrombus embolization, venous thromboembolism, and left ventricular free wall rupture.[8] In fact, more than one-quarter of MI patients die, presumably from ventricular fibrillation, prior to reaching the hospital.[1]

Symptoms and Physical Examination Findings

The classic symptom of an ACS is midline anterior anginal chest discomfort, most often occurring when an individual is at rest, as a severe new onset, or as an increasing angina that is at least 20 minutes in duration. The chest discomfort may radiate to the shoulder, down the left arm, and to the back or to the jaw. Associated symptoms which may accompany the chest discomfort include nausea, vomiting, **diaphoresis**, or shortness of breath. While similar to stable angina, the duration may be longer and the intensity greater. On physical examination, no specific features are indicative of ACS.

12-Lead Electrocardiogram

❸ *There are key features of a 12-lead ECG that identify and risk-stratify a patient with an ACS. Within 10 minutes of presentation to an emergency department with symptoms of ischemic chest discomfort, a 12-lead ECG should be obtained and interpreted. If available, a prior 12-lead ECG should be reviewed to identify whether or not the findings on the current ECG are new or old, with new findings being more indicative of an ACS. Key findings on review of a 12-lead ECG that indicate myocardial ischemia or infarction are STE, ST-segment depression, and T-wave inversion* (Fig. 5–1). ST-segment and/or T-wave changes in certain groupings of leads help to identify the location of the coronary artery that is the cause of the ischemia or infarction. In addition, the appearance of a new left bundle-branch block accompanied by chest discomfort is highly specific for acute MI. About one-half of patients

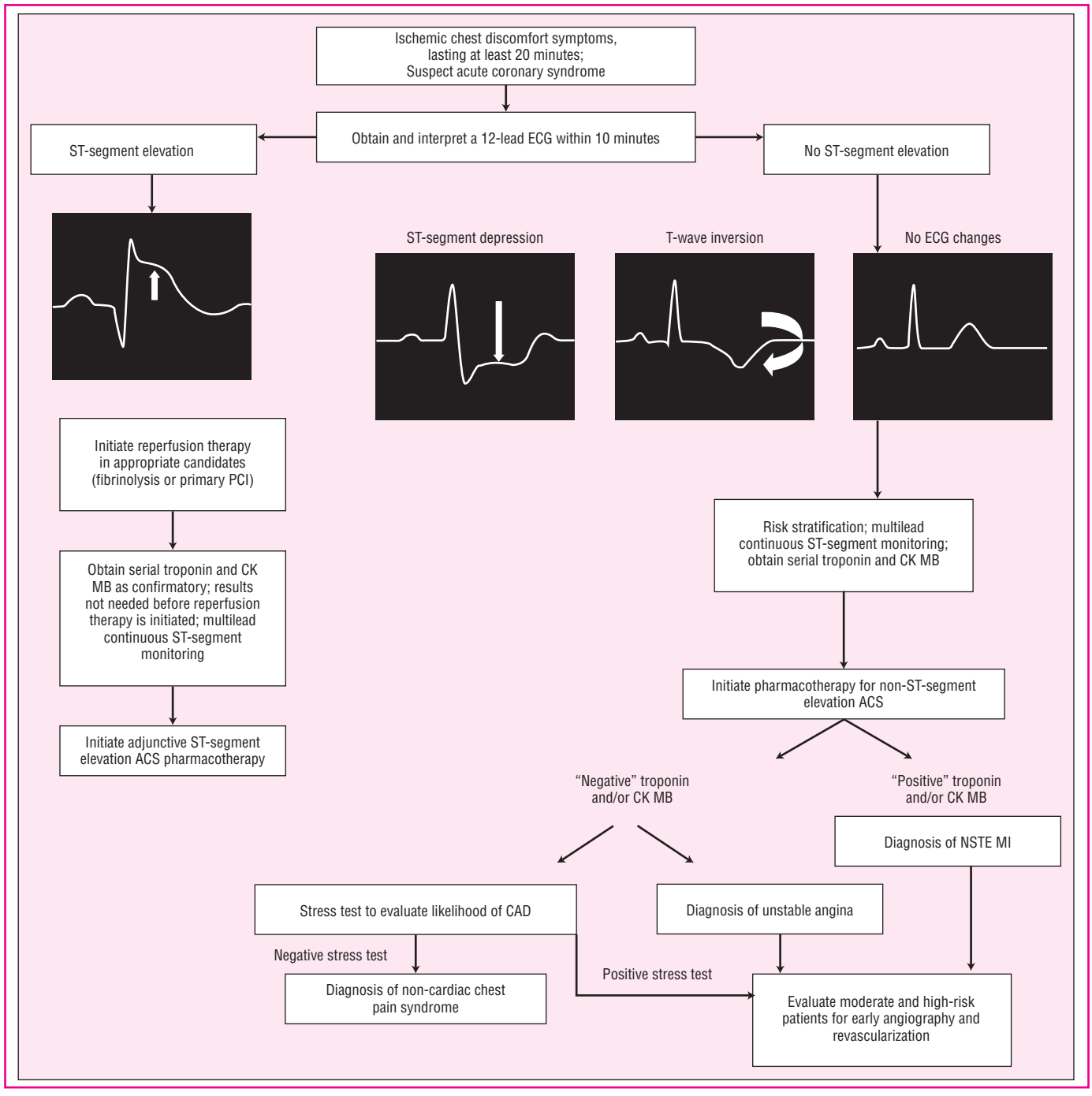


FIGURE 5–1. Evaluation of the acute coronary syndrome patient. (Reprinted from Spinler SA, de Denus S. Acute Coronary Syndromes. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 293, with permission.) ACS, acute coronary syndromes; CAD, coronary artery disease; CKMB, creatine kinase myocardial band; ECG, electrocardiogram; NSTE, non-ST elevation; PCI, percutaneous coronary intervention. Refer to Chapter 6, Figure 6–2 (page 109) for further details regarding ECG interpretation.

diagnosed with MI present with ST-segment elevation on their ECG, with the remainder having ST-segment depression, T-wave inversion, or in some instances, no ECG changes. Some parts of the heart are more "electrically silent" than others, and myocardial ischemia may not be detected on a surface ECG. Therefore, it is important to review findings from the ECG in conjunction with biochemical markers of myocardial necrosis, such as troponin I or T, and other risk factors for CHD to determine the patient's risk for experiencing a new MI or having other complications.



Clinical Presentation and Diagnosis

General
- The patient is typically in acute distress and may develop or present with cardiogenic shock.

Symptoms
- The classic symptom of ACS is midline anterior chest discomfort. Accompanying symptoms may include arm, back, or jaw pain, nausea, vomiting, or shortness of breath.
- Patients less likely to present with classic symptoms include elderly patients, diabetic patients, and women.

Signs
- No signs are classic for ACS.
- However, patients with ACS may present with signs of acute heart failure including jugular venous distention and an S_3 sound on auscultation.
- Patients may also present with arrhythmias and therefore may have tachycardia, bradycardia, or heart block.

Laboratory Tests
- Troponin I or T and CK-MB are measured.
- Blood chemistry tests are performed with particular attention given to potassium and magnesium, which may affect heart rhythm.
- The serum creatinine is measured to identify patients who may need dosing adjustments for some medications, as well as those who are at high risk of morbidity and mortality.
- Baseline complete blood count (CBC) and coagulation tests (activated partial thromboplastin time and International Normalized Ratio) should be obtained, as most patients will receive antithrombotic therapy, which increases the risk for bleeding.
- Fasting lipid panel.

Other Diagnostic Tests
- The 12-lead ECG is the first step in management. Patients are risk-stratified into two groups: ST-segment elevation ACS and suspected non–ST-segment elevation ACS.
- During hospitalization, a measurement of left ventricular function, such as an echocardiogram, is performed to identify patients with low ejection fractions (less than 40%) who are at high risk of death following hospital discharge.
- Selected low-risk patients may undergo early stress testing.

(Adapted from Spinler SA, de Denus S. Acute Coronary Syndromes. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 294, with permission.)

Biochemical Markers/Cardiac Enzymes

Biochemical markers of myocardial cell death are important for confirming the diagnosis of MI. ❸ *The diagnosis of myocardial infarction is confirmed based upon the results of the creatine kinase myocardial band and troponin tests. Evolving MI is defined by the ACC as "typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis."*[9] *Troponin and CK-MB rise in the blood following the onset of complete coronary artery occlusion subsequent to myocardial cell death.* Their time course is depicted in Fig. 5–2. Typically, blood is obtained from the patient three times, once in the emergency department and two additional times over the next 12 to 24 hours in order to measure troponin and CK-MB. A single measurement of a biochemical marker is not adequate to exclude a diagnosis of MI, as up to 15% of values which were initially below the level of detection (a "negative" test) rise to the level of detection (a "positive" test) in subsequent hours. An MI is identified if at least one troponin value is greater than the MI decision limit (set by the hospital laboratory) or two CK-MB results are greater than the MI decision limit (set by the hospital laboratory). While troponins and CK-MB appear in the blood within 6 hours of infarction, troponins stay elevated for up to 10 days while CK-MB returns to normal values within 48 hours. Therefore, if a patient is admitted with elevated troponins and CK-MB and several days later experiences recurrent chest discomfort, the troponin will be less sensitive to detect new myocardial damage because it will still be elevated. If early reinfarction is suspected, CK-MB is the preferred diagnostic test.[9]

Risk Stratification

Patient symptoms, past medical history, ECG, and troponin and/or CK-MB are utilized to stratify patients into low, medium, or high risk of death, MI, or likelihood of failing pharmacotherapy and needing urgent coronary angiography and **percutaneous coronary intervention** (PCI). ❸❹ *Initial treatment according to risk stratification is depicted in Fig. 5–1. Patients with ST-segment elevation are at the highest risk of death.* Initial treatment of ST-segment elevation ACS should proceed without evaluation of the troponin or CK-MB, as these patients have a greater than 97% chance of having an MI subsequently diagnosed with biochemical markers. The ACC/AHA defines a target time to initiate reperfusion treatment as within 30 minutes of hospital presentation for fibrinolytics (e.g., streptokinase, alteplase, reteplase, and tenecteplase) and within 90 minutes or less from presentation for primary PCI.[3] The sooner the infarct-related coronary artery is opened for these patients, the lower their mortality and the greater the amount of myocardium that is preserved.[10,11] While all patients should be evaluated for reperfusion therapy, not all patients may be eligible. Indications and contraindications for fibrinolytic therapy are described in the treatment section of this chapter. Less than 20% of hospitals in the United States. are equipped to perform primary PCI. If



Patient Encounter, Part 1

SD is a 55-year-old, 85 kg (187 lb) male who developed chest tightness while in a store in Sun Valley, Idaho, after 4 hours of skiing. SD developed substernal chest tightness at 2030 hours that radiated into his left arm following an altercation with another patron in the men's room. He became short of breath and diaphoretic. Local paramedics were summoned and he was given three 0.4 mg sublingual nitroglycerin tablets by mouth, 325 mg aspirin by mouth, and 5 mg metoprolol IV push without relief of chest discomfort. SD presented to St. Matthew's Hospital in Sun Valley at 2115 hours. St. Matthew's does not have a cardiac catheterization laboratory and transport time to St. Matthew's in Boise is 1.5 hours door to door via air transport.

PMH
Hypertension (HTN) × 10 years
Dyslipidemia × 6 months
Two-vessel coronary artery disease (60% right coronary artery [RCA] and 80% left anterior descending artery [LAD] occlusion) after intracoronary CYPHER™ stent placement to the mid-LAD artery lesion 10 months ago.

FH
Father with myocardial infarction at age 65; mother alive and well; one sibling with hypertension

SH
Smoked 1 pack per day × 30 years, quit 10 weeks ago

Allergies
No known drug allergies

Meds
Metoprolol 25 mg by mouth twice daily
ASA 325 mg by mouth once daily
Lovastatin 20 mg by mouth once daily at bedtime
Enalapril 5 mg by mouth once daily

ROS
7/10 chest pain/squeezing, diaphoretic

PE
Head, ears, eyes, nose and throat: normocephalic atraumatic
Cardiovascular: regular rate and rhythm S_1, S_2, $-S_3$, $+S_3$, $+S_4$, no murmurs or rubs

VS: Blood pressure 110/70; heart rate 98 beats per minute; temperature 37°C (98.6°F)
Lungs: rales bilaterally $^1/_4$ way up
Abd: non-tender, non-distended
Gastrointestinal: normal bowel sounds
Genitourinary: stool guaiac negative
Exts: no bruits, pulses 2+, femoral pulse present, good range of motion
Neurologic: alert and oriented × 3, cranial nerves intact

Labs
Sodium 138 mEq/L (138 mmol/L), potassium 4.2 mEq/L (4.2 mmol/L), chloride 105 mEq/L (105 mmol/L), bicarbonate 24 mEq/L (24 mmol/L), serum creatinine 1.0 mg/dL (88.4 µmol/L), glucose 95 mg/dL (5.27 mmol/L), white blood cell count $9.9 \times 10^3/mm^3$ (9.9×10^9/L), hemoglobin 15.7 g/dL (157 g/L or 9.7 mmol/L), hematocrit 47%, platelets $220 \times 10^3/mm^3$ (220×10^9/L), brain natriuretic peptide 3238 pg/mL (3238 ng/L), troponin I 16 ng/mL (16 mcg/L), oxygen saturation 99% on room air

ECG: normal sinus rhythm, PR 0.16 s, QRS 0.08 s, QT_c 0.38 s, occasional polymorphic premature ventricular contractions, 3 mm ST-segment elevation anterior leads

CXR: congestive heart failure, borderline upper normal heart size

Echocardiogram: hypocontractile left ventricle, akinesis of anterior apical wall, ejection fraction 20%

- What information is suggestive of acute MI?
- What complications of MI are present?

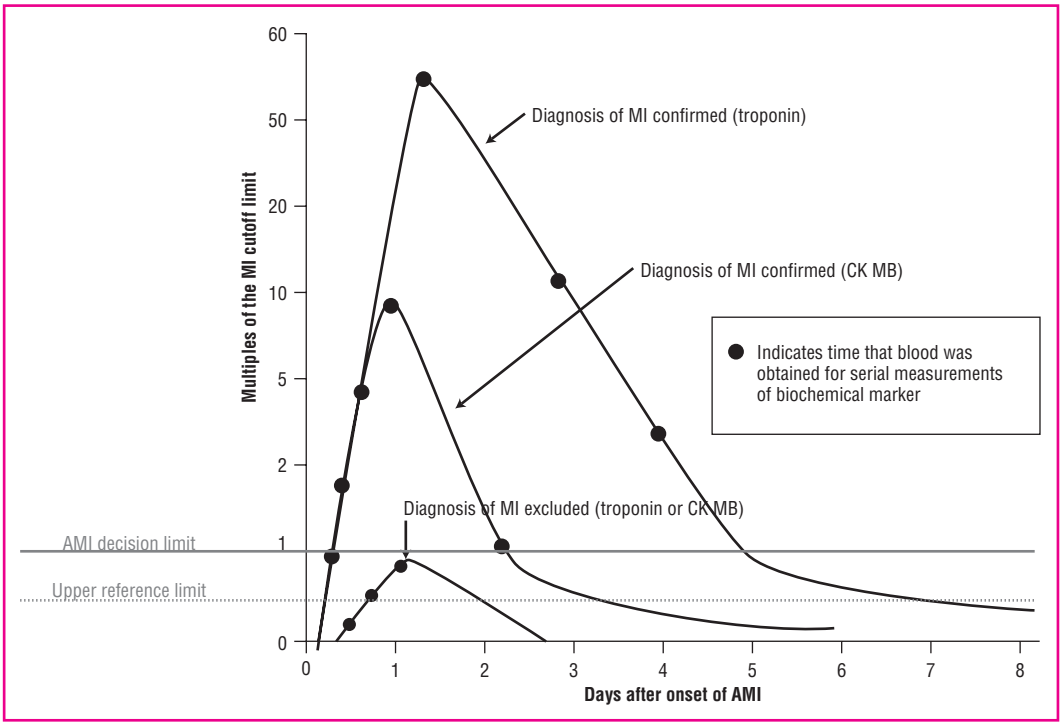


FIGURE 5–2. Biochemical markers in suspected acute coronary syndromes. (Reprinted from Spinler SA, de Denus S. Acute Coronary Syndromes. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 295, with permission.) AMI, acute myocardial infarction; CKMB, creatine kinase myocardial band; MI, myocardial infarction.

patients are not eligible for reperfusion therapy, additional pharmacotherapy for STE patients should be initiated in the emergency department and the patient transferred to a coronary intensive care unit. The typical length of stay for a patient with uncomplicated STE MI is 3 to 5 days.

Risk-stratification of the patient with NSTE ACS is more complex, as in-hospital outcomes for this group of patients varies with reported rates of death of 0% to 12%, reinfarction rates of 0% to 3%, and recurrent severe ischemia rates of 5% to 20%.[12] Not all patients presenting with suspected NSTE ACS will even have CAD. Some will eventually be diagnosed with non-ischemic chest discomfort. ❸ *In general, among NSTE patients, those with ST-segment depression (Fig. 5–1) and/or elevated troponin and/or CK-MB are at higher risk of death or recurrent infarction.*



Patient Encounter, Part 2: Treatment

- Identify your acute treatment goals for SD.
- Is reperfusion therapy with fibrinolysis indicated at this time?
- What adjunctive pharmacotherapy should be administered to SD in the emergency department?
- What additional pharmacotherapy should be initiated on the first day of SD's hospitalization?

TREATMENT

Desired Outcomes

Short-term desired outcomes in a patient with ACS are: (1) early restoration of blood flow to the infarct-related artery to prevent infarct expansion (in the case of MI) or prevent complete occlusion and MI (in unstable angina); (2) prevention of death and other complications; (3) prevention of coronary artery reocclusion; and (4) relief of ischemic chest discomfort.

Long-term desired outcomes are control of risk factors, prevention of additional cardiovascular events, and improvement in quality of life.

General Approach to Treatment

General treatment measures for all STE ACS and high- and intermediate-risk NSTE patients include admission to hospital, oxygen administration (if oxygen saturation is low, less than 90%), continuous multi-lead ST-segment monitoring for arrhythmias and ischemia, frequent measurement of vital signs, bed rest for 12 hours in hemodynamically stable patients, avoidance of Valsalva maneuver (prescribe stool softeners routinely), and pain relief (Fig. 5–3).

Because risk varies and resources are limited, it is important to triage and treat patients according to their risk category. Initial approaches to treatment of STE and NSTE ACS patients are outlined in Fig. 5–1. Patients with STE are at high risk of death, and efforts to re-establish coronary perfusion,

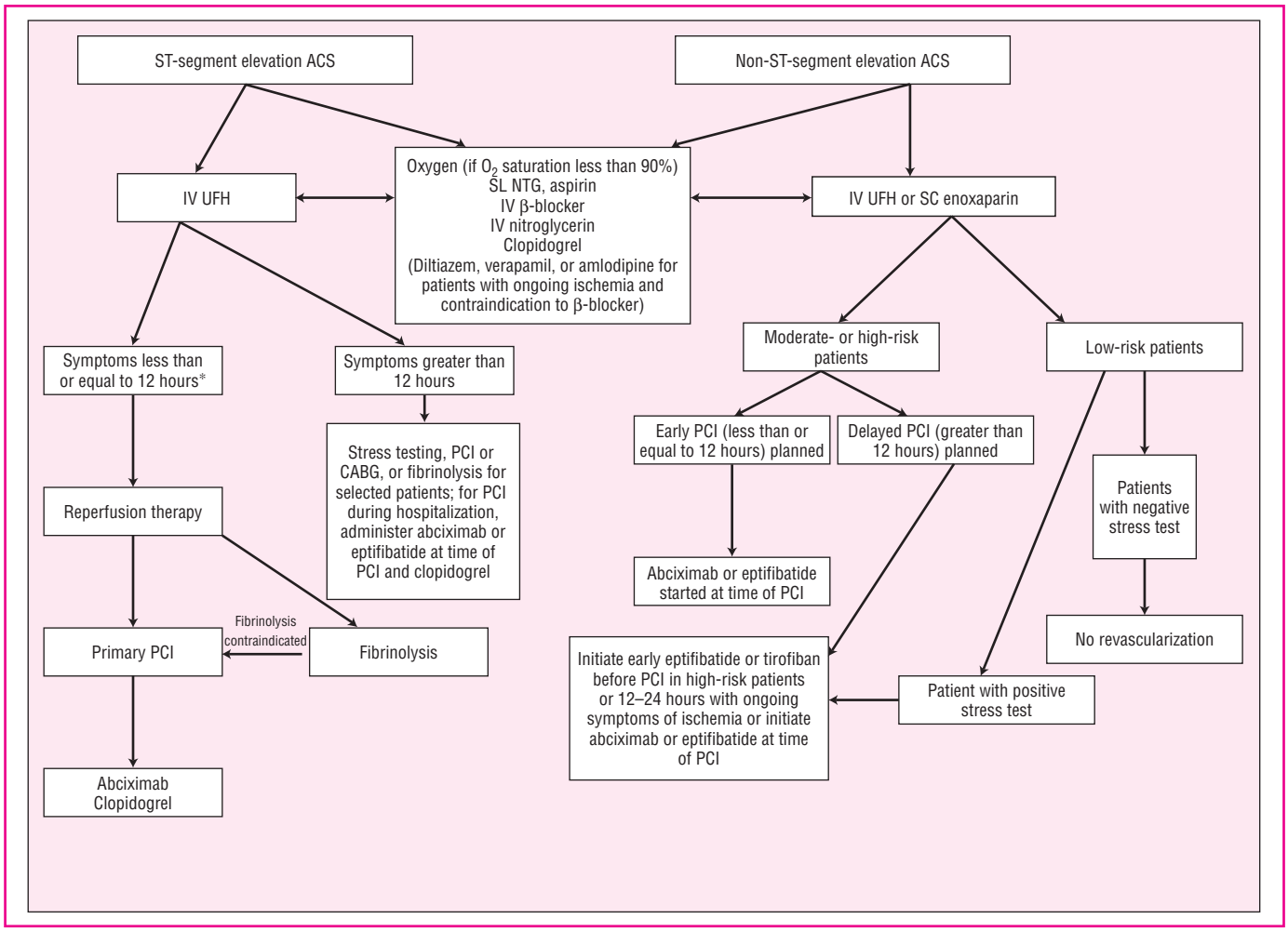


FIGURE 5–3. Initial pharmacotherapy for acute coronary syndromes. (Adapted from Spinler SA, de Denus S. Acute Coronary Syndromes. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 298, with permission.) *Or 12 to 24 hours with ongoing symptoms of ischemia. ACS, acute coronary syndromes; CABG, coronary artery bypass graft; IV, intravenous; NTG, nitroglycerin; PCI, percutaneous coronary intervention; SC, subcutaneous; SL, sublingual; UFH, unfractionated heparin.

as well as adjunctive pharmacotherapy, should be initiated immediately.

❸ *Features identifying low-, moderate-, and high-risk NSTE ACS patients are described using the thrombolysis in myocardial infarction (TIMI) risk score in Table 5–1.*[13]

Nonpharmacologic Therapy

Primary Percutaneous Coronary Intervention for ST-Segment Elevation Acute Coronary Syndromes

❹ *Early reperfusion therapy with either primary percutaneous coronary intervention or administration of a fibrinolytic agent within 3 hours of symptom onset is the recommended therapy for patients presenting with STE ACS.*[3] For primary PCI, the patient is taken from the emergency department to the cardiac catheterization laboratory and undergoes coronary angiography with either balloon angioplasty or placement of a bare metal or drug-eluting intracoronary stent. Results from a recent meta-analysis of trials comparing fibrinolysis to primary PCI indicate a lower mortality rate with primary PCI.[14] One reason for the superiority of primary PCI compared to fibrinolysis is that more than 90% of occluded infarct-related coronary arteries are opened with primary PCI compared to fewer than 60% of coronary arteries opened with currently available fibrinolytics.[15] In addition, intracranial hemorrhage and major bleeding risks from primary PCI are lower than the risks of severe bleeding events following fibrinolysis. An invasive strategy of primary PCI is generally preferred in patients presenting to institutions with skilled interventional cardiologists and a catheterization laboratory immediately available, in patients in cardiogenic shock, those with contraindications to fibrinolytics, and those presenting with symptom onset greater than 3 hours ago.[3] A quality indicator (quality indicators are measures of health care performance developed from practice guidelines intended to permit the quality of patient care to be assessed and ultimately improved)

TABLE 5–1. TIMI Risk Score for Non–ST-Segment Elevation Acute Coronary Syndromes[2,17]

Past Medical History	Clinical Presentation
• Age 65 years or older • Three or more risk factors for CAD: Hypercholesterolemia HTN DM Smoking Family history of premature CHD • Known CAD (50% or greater stenosis of a coronary artery) • Use of aspirin within the past 7 days	• ST-segment depression (0.5 mm or greater) • Two or more episodes of chest discomfort within the past 24 hours • Positive biochemical marker for infarction[a]

Using the TIMI Risk Score

One point is assigned for each of the seven medical history and clinical presentation findings. The point total is calculated and the patient is assigned a risk for experiencing the composite endpoint of death, myocardial infarction, or urgent need for revascularization as follows:

High-Risk	Medium-Risk	Low-Risk
TIMI risk score 5–7 points	TIMI risk score 3–4 points	TIMI risk score 0–2 points

Other Ways to Identify High-Risk Patients

Other findings that alone or in combination may identify a high-risk patient:

- ST-segment depression
- Positive biochemical marker for infarction
- Deep symmetric T-wave inversions (2 mm or greater)
- Acute heart failure
- DM
- Chronic kidney disease
- Refractory chest discomfort despite maximal pharmacotherapy for ACS
- Recent MI within the past 2 weeks

[a]A positive biochemical marker for infarction is a value of troponin I, troponin T, or creatine kinase MB of greater than the MI detection limit.
ACS, acute coronary syndromes; CAD, coronary artery disease; CHD, coronary heart disease; DM, diabetes mellitus; HTN, hypertension; MI, myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.
(Reprinted from Spinler SA, de Denus S. Acute Coronary Syndromes. In DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 296, with permission.)

in the care of MI patients with ST-segment elevation is the time from hospital presentation to the time that the occluded artery is opened with PCI. This "door-to-primary PCI" time should be equal to or less than 90 minutes.[3,16] Unfortunately, most hospitals do not have interventional cardiology services capable of performing primary PCI 24 hours a day. Therefore, only 7% of MI patients are currently treated with primary PCI.

Percutaneous coronary intervention during hospitalization for STE MI may also be appropriate in other patients following STE MI, such as those in whom fibrinolysis is not successful, those presenting later in cardiogenic shock, those with life-threatening ventricular arrhythmias, and those with persistent rest ischemia or signs of ischemia on stress testing following MI.[3,15]

Percutaneous Coronary Intervention in Non–ST-Segment Elevation Acute Coronary Syndromes

❺ *The most recent non–ST-segment elevation ACC/AHA clinical practice guidelines recommend coronary angiography with either PCI or* ***coronary artery bypass graft (CABG) surgery*** *revascularization as an early treatment (early invasive strategy) for high-risk and moderate-risk NSTE ACS patients.*[2] Several recent clinical trials support an "early invasive" strategy with PCI or CABG versus a "medical stabilization" management strategy, whereby coronary angiography with revascularization is reserved for patients with symptoms refractory to pharmacotherapy and patients with signs of ischemia on stress testing.[17] An "early invasive" approach results in fewer MIs, less need for additional revascularization procedures over the next year following hospitalization, and less cost than the conservative "medical stabilization" approach.[17] All patients undergoing PCI should receive aspirin therapy indefinitely. Clopidogrel is administered (concomitantly with aspirin) for at least 30 days and up to 12 months following PCI[18] (Table 5–2).

Additional Testing and Risk Stratification

At some point during hospitalization but prior to discharge, patients with MI should have their left ventricular function (LVF) evaluated for risk stratification.[2,3] The most common way LVF is measured is using an echocardiogram to calculate the patient's left ventricular ejection fraction (LVEF). Left ventricular function is the single best predictor of mortality following MI. Patients with LVEFs less than 40% are at highest risk of death. Patients with ventricular fibrillation or sustained ventricular tachycardia occurring more than 2 days following MI and those with LVEF less than 30% (measured at least 1 month after STE MI and 3 months after coronary artery revascularization with either PCI or CABG) benefit from placement of an implantable cardioverter defibrillator (ICD).[3]

Pre-discharge from the hospital stress testing (Fig. 5–3) may be indicated in: (1) moderate- or low-risk patients in order to determine who would benefit from coronary angiography to establish the diagnosis of CAD and (2) patients following MI to predict intermediate- and long-term risk of recurrent MI and death.[19] In most cases, patients with a positive stress test indicating coronary ischemia will then undergo coronary angiography and subsequent revascularization of significantly occluded coronary arteries. If a patient has a negative exercise stress test for ischemia, the patient is at lower risk for subsequent CHD events.

Early Pharmacologic Therapy for ST-Segment Elevation Acute Coronary Syndromes

Pharmacotherapy for early treatment of ACS is outlined in Fig. 5–3. ❻ *According to the ACC/AHA ST-segment elevation ACS practice guidelines, in addition to reperfusion therapy, early pharmacotherapy of STE should include intranasal oxygen*

TABLE 5–2. Pharmacotherapy for Acute Coronary Syndromes (ST-Segment Elevation and Non–ST-Segment Elevation)[2,3,20,21,22]

Drug	Clinical Condition and ACC/AHA Guideline Recommendation	Contraindications[a]	Dose
Aspirin	STE ACS, class I recommendation[b] for all patients. NSTE ACS, class I recommendation for all patients.	• Hypersensitivity • Active bleeding • Severe bleeding risk	• 160–325 mg on hospital day 1 • 75–162 mg daily starting hospital day 2 and continued indefinitely
Clopidogrel	STE ACS, class I recommendation in patients allergic to aspirin. NSTE ACS, class I recommendation for all hospitalized patients in whom a non-interventional approach is planned. In PCI in STE and NSTE ACS, class I recommendation. In STE ACS with fibrinolytics, large randomized trial data published after 2004 guidelines.	• Hypersensitivity • Active bleeding • Severe bleeding risk	• 300–600 mg loading dose on hospital day 1 followed by a maintenance dose of 75 mg orally once daily starting on hospital day 2; no data on loading dose in patients greater than 75 years old • Administer indefinitely in patients with an aspirin allergy (class I recommendation) • Administer for at least 9 months in medically managed patients with NSTE ACS (class I recommendation) • Administer for at least 30 days to 1 year in patients with STE or NSTE ACS (class I recommendation) undergoing PCI • Administer for a minimum of 6 months in patients receiving a paclitaxel-eluting stent during PCI • Administer for a minimum of 3 months in patients receiving a tacrolimus-eluting stent during PCI • If possible, withhold for at least 5 days in patients in whom CABG is planned to decrease bleeding risk (class I recommendation)
Unfractionated heparin (UFH)	STE ACS, class I recommendation in patients undergoing PCI, and for those patients treated with alteplase, reteplase, or tenecteplase; class IIa recommendation for patients not treated with fibrinolytic therapy. NSTE ACS, class I recommendation in combination with aspirin. PCI, class I recommendation.	• Active bleeding • History of heparin-induced thrombocytopenia • Severe bleeding risk • Recent stroke	• For STSE ACS administer 60 units/kg IV bolus (maximum 4000 units) followed by a constant IV infusion at 12 units/kg/hour (maximum 1000 units/hour) • For NSTE ACS administer 60–70 units/kg IV bolus (maximum 5000 units) followed by a constant IV infusion of 12–15 units/kg/hour (maximum 1000 units/hour) • Titrated to maintain aPTT between 1.5 and 2.5 times control for NSTE ACS and 1.5–2 times control (approximately 50–70 seconds) in STE ACS • The first aPTT should be measured at 4–6 hours for NSTE ACS and STE ACS in patients not treated with thrombolytics • The first aPTT should be measured at 3 hours in patients with STE ACS who are treated with thrombolytics
Low-molecular-weight heparin	STE ACS, class IIb recommendation for patients less than 75 years old treated with fibrinolytics, class III for patients greater than 75 years old treated with thrombolytics, and class IIa for patients not undergoing reperfusion therapy. NSTE ACS, class I recommendation in combination with aspirin, class IIa recommendation over UFH in patients without renal failure who are not anticipated to undergo CABG surgery within 24 hours.	• Active bleeding • History of heparin-induced thrombocytopenia • Severe bleeding risk • Recent stroke • CrCl less than 10 mL/minute (enoxaparin) • CrCl less than 30 mL/minute (dalteparin)	• Enoxaparin 1 mg/kg SC every 12 hours (CrCl greater than or equal to 30 mL/minute) • Enoxaparin 1 mg/kg SC every 24 hours (CrCl 10–29 mL/minute) • Dalteparin 120 IU/kg SC every 12 hours (maximum single bolus dose of 10,000 units) • Administer 30 mg IV bolus for STE ACS patients age less than 75 years • For STE ACS, first 2 subcutaneous doses should be 100 mg for patients weighing equal to or greater than 100 kg (220 lb)

Fibrinolytics	STE ACS, class I recommendation in patients presenting within 12 hours following the onset of symptoms, class IIa in patients presenting between 12–24 hours following the onset of symptoms with continuing signs of ischemia. NSTE ACS: class III recommendation.	• Absolute and relative contraindications per Table 5–3	Streptokinase: 1.5 million units IV over 60 minutes Alteplase: 15 mg IV bolus followed by 0.75 mg/kg IV over 30 minutes (max 50 mg) followed by 0.5 mg/kg (max 35 mg) over 60 minutes (max dose = 100 mg) Reteplase: 10 units IV × 2, 30 minutes apart Tenecteplase: less than 60 kg = 30 mg IV bolus 60–69.9 kg = 35 mg IV bolus 70–79.9 kg = 40 mg IV bolus 80–89.9 kg = 45 mg IV bolus greater than or equal to 90 kg = 50 mg IV bolus
Glycoprotein IIb/IIIa receptor blockers	NSTE ACS, class IIa recommendation for either tirofiban or eptifibatide for patients with either continuing ischemia, elevated troponin or other high-risk features, class I recommendation for patients undergoing PCI, class IIb recommendation for patients without high-risk features who are not undergoing PCI. STE ACS, class IIa for abciximab for primary PCI and class IIb for either tirofiban or eptifibatide for primary PCI, class III in combination with a fibrinolytic agent	• Active bleeding • Prior stroke • Thrombocytopenia	**Drug with/without PCI** / **Dose for PCI** / **Dose for NSTE ACS** / **Adjustment for renal insufficiency or obesity** Abciximab: 0.25 mg/kg IV bolus followed by 0.125 mcg/kg/minute (maximum 10 mcg/minute) for 12 hours / Not recommended / None Eptifibatide: 180 mcg/kg IV bolus × 2, 10 minutes apart with an infusion of 2 mcg/kg/minute started after the first bolus for 18–96 hours / 180 mcg/kg IV bolus followed by an infusion of 2 mcg/kg/minute for 18–96 hours / Reduce maintenance infusion to 1 mcg/kg/minute for patients with CrCl less than 50 mL/minute; not recommended for patients with serum creatinine greater than 4 mg/dL (354 µmol/L); patients weighing greater than or equal to 121 kg (266 lbs) should receive a maximum infusion rate of 22.6 mg per bolus and a maximum infusion rate of 15 mg/hour Tirofiban: Not recommended / 0.4 mcg/kg IV infusion for 30 minutes followed by an infusion of 0.1 mcg/kg/minute for 18–96 hours / Reduce bolus dose to 0.2 mcg/kg/minute and the maintenance infusion to 0.05 mcg/kg/minute for patients with CrCl less than 30 mL/minute

TABLE 5–2. Pharmacotherapy for Acute Coronary Syndromes (ST-Segment Elevation and Non-ST-Segment Elevation)[2,3,20,21,22] (*Continued*)

Drug	Clinical Condition and ACC/AHA Guideline Recommendation	Contraindications[a]	Dose
Nitroglycerin	STE and NSTE ACS, class I indication in patients with ongoing ischemic discomfort, control of hypertension or management of pulmonary congestion.	• Hypotension • Sildenafil or vardenafil within 24 hours or tadalafil within 48 hours	• 0.4 mg SL, repeated every 5 minutes × 3 doses • 5 to 10 mcg/minute by continuous infusion • Titrated up to 75–100 mcg/minute until relief of symptoms or limiting side-effects (headache or hypotension with a systolic blood pressure less than 90 mm Hg or more than 30% below starting mean arterial pressure levels if significant hypertension is present) • Topical patches or oral nitrates are acceptable alternatives for patients without ongoing or refractory symptoms
β-Blockers[c]	STE and NSTE ACS, class I recommendation in all patients without contraindications for oral β-blockers, class I (NSTE ACS) and IIa (STE ACS) for IV β-blockers, class IIb recommendation for patients with moderate left ventricular failure with signs of heart failure provided they can be closely monitored.	• PR ECG segment greater than 0.24 seconds • Second- or third-degree AV block • Heart rate less than 60 beats per minute • Systolic blood pressure less than 90 mm Hg • Shock • Left ventricular failure with congestive heart failure • Severe reactive airway disease	*Target resting heart rate 50–60 beats per minute* ***Metoprolol*** • 5 mg increments by slow (over 1–2 minutes) intravenous administration • Repeated every 5 minutes for a total initial dose of 15 mg • Followed in 1–2 hours by 25–50 mg by mouth every 6 hours • If a very conservative regimen is desired, initial doses can be reduced to 1–2 mg • Alternatively, initial intravenous therapy can be omitted ***Propranolol*** • 0.5–1 mg intravenous dose • Followed in 1–2 hours by 40–80 mg by mouth every 6–8 hours • Alternatively, initial intravenous therapy can be omitted ***Atenolol*** • 5 mg IV dose • Followed 5 minutes later by a second 5 mg IV dose then 50–100 mg orally every day initiated 1–2 hours after the intravenous dose • Alternatively, initial intravenous therapy can be omitted ***Esmolol*** • Starting maintenance dose of 0.1 mg/kg/minute IV • Titration in increments of 0.05 mg/kg/minute every 10–15 minutes as tolerated by blood pressure until the desired therapeutic response has been obtained, limiting symptoms develop, or a dose of 0.20 mg/kg/minute is reached • Optional loading dose of 0.5 mg/kg may be given by slow IV administration (2–5 minutes) for more rapid onset of action
Calcium channel blockers	STE ACS class IIa recommendation and NSTE ACS class I recommendation for patients with ongoing ischemia who are already taking adequate doses of nitrates and β-blockers or in patients with contraindications to or intolerance to β-blockers (diltiazem or verapamil for STE ACS and diltiazem, verapamil, or amlodipine for NSTE ACS). NSTE ACS, class IIb recommendation for diltiazem for patients with AMI.	• Pulmonary edema • Evidence of left ventricular dysfunction • Systolic blood pressure less than 100 mm Hg • PR ECG segment greater than 0.24 seconds for diltiazem or verapamil • Second- or third-degree AV block for diltiazem or verapamil • Heart rate less than 60 beats per minute for diltiazem or verapamil	• Diltiazem 120–360 mg controlled-release once daily • Verapamil 180–480 mg sustained-release per day • Nifedipine 30–90 mg sustained-release once daily • Amlodipine 5–10 mg once daily

ACE inhibitors	STE ACS, class I recommendation within the first 24 hours after hospital presentation for patients with anterior wall infarction, clinical signs of heart failure and those with EF less than 40% in the absence of contraindications, class IIa recommendation for all other patients in the absence of contraindications. NSTE ACS, class I recommendation for patients with heart failure, left ventricular dysfunction, and EF less than 40%, hypertension, or type 2 diabetes mellitus. Consider in all patients with CAD. Indicated indefinitely for all post-AMI patients.	• Systolic blood pressure less than 100 mm Hg • History of intolerance to an ACE inhibitor • Bilateral renal artery stenosis • Serum potassium greater than 5.5 mEq/L (5.5 mmol/L)	**Drug** — **Initial Dose (mg)** — **Target Dose (mg)** Captopril — 6.25–12.5 — 50 twice daily to 50 three times daily Enalapril — 2.5–5 — 10 twice daily Lisinopril — 2.5–5 — 10–20 daily Ramipril — 1.25–2 — 5 twice daily or 10 mg once daily Trandolapril — 1 — 4 mg once daily
Angiotensin receptor blocker	STE ACS, class I recommendation in patients with clinical signs of heart failure or EF less than 40% and intolerant of an ACE inhibitor, class IIa in patients with clinical signs of heart failure or EF less than 40% and no documentation of ACE inhibitor intolerance.	• Systolic blood pressure less than 100 mm Hg • Bilateral renal artery stenosis • Serum potassium greater than 5.5 mEq/L (5.5 mmol/L)	**Drug** — **Initial Dose (mg)** — **Target Dose (mg)** Candesartan — 4–8 mg — 32 mg once daily Valsartan — 40 mg — 160 mg twice daily
Aldosterone antagonists	STE ACS, class I recommendation for patients with MI and EF less than 40% and either diabetes mellitus or heart failure symptoms who are already receiving an ACE inhibitor.	• Hypotension • Hyperkalemia; serum potassium greater than 5.5 mEq/L (5.5 mmol/L) • Serum creatinine greater than 2.5 mg/dL (221 mmol/L)	**Drug** — **Initial Dose (mg)** — **Maximum Dose (mg)** Eplerenone — 25 mg — 50 mg once daily Spironolactone — 12.5 mg — 25–50 mg once daily
Morphine sulfate	STE and NSTE ACS, class I recommendation, for patients whose symptoms are not relieved after three serial sublingual nitroglycerin tablets or whose symptoms recur with adequate anti-ischemic therapy.	• Hypotension • Respiratory depression • Confusion • Obtundation	• 2–5 mg IV dose • May be repeated every 5–30 minutes as needed to relieve symptoms and maintain patient comfort

[a]Allergy or prior intolerance contraindication for all categories of drugs listed in this chart.
[b]Class I recommendations are conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.
Class II recommendations are those conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. For Class IIa recommendations, the weight of the evidence/opinion is in favor of usefulness/efficacy. Class IIb recommendations are those for which usefulness/efficacy is less well established by evidence/opinion.
[c]Choice of the specific agent is not as important as ensuring that appropriate candidates receive this therapy. If there are concerns about patient intolerance due to existing pulmonary disease, especially asthma, selection should favor a short-acting agent, such as propranolol or metoprolol or the ultra-short-acting agent esmolol. Mild wheezing or a history of chronic obstructive pulmonary disease should prompt a trial of a short-acting agent at a reduced dose (e.g., 2.5 mg IV metoprolol, 12.5 mg oral metoprolol, or 25 mcg/kg/minute esmolol as initial doses) rather than complete avoidance of β-blocker therapy.
ACC, American College of Cardiology; ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; AHA, American Heart Association; AMI, acute myocardial infarction; aPTT, activated partial thromboplastin time; AV, atrioventricular; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CrCl, creatinine clearance; ECG, electrocardiogram; EF, ejection fraction; MI, myocardial infarction; NSTE, non–ST-segment elevation; PCI, percutaneous coronary intervention; STE, ST-segment elevation.
(Reprinted from Spinler SA, de Denus S. Acute Coronary Syndromes. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 299–302, with permission.)

(if oxygen saturation is less than 90%), sublingual (SL) nitroglycerin (NTG) followed by intravenous (IV) NTG, aspirin, an IV β-blocker, unfractionated heparin (UFH), and fibrinolysis in eligible candidates. Recent results from two clinical trials in patients with STE ACS indicate that clopidogrel should be administered along with aspirin to patients receiving fibrinolytics to reduce mortality and reinfarction as well as to improve the patency of the infarcted artery.[20,21] Morphine is administered to patients with refractory angina as an analgesic and a venodilator that lowers preload. These agents should be administered early, while the patient is still in the emergency department. Dosing and contraindications for SL and IV NTG, aspirin, IV β-blockers, UFH, clopidogrel, and fibrinolytics are listed in Table 5–2.[2,3,22]

Fibrinolytic Therapy

Administration of a fibrinolytic agent is indicated in patients with STE ACS who present to the hospital within 24 hours of the onset of chest discomfort and have at least a 1 mm STE in two or more contiguous ECG leads.[3] The mortality benefit of fibrinolysis is highest with early administration and diminishes after 12 hours. The use of fibrinolytics between 12 and 24 hours after symptom onset should be limited to patients with ongoing ischemia. Fibrinolytic therapy is preferred over primary PCI in patients presenting within 3 hours of symptom onset where there is a delay in "door-to-primary PCI" less than 90 minutes. Other indications and contraindications for fibrinolysis are listed in Table 5–3.[3] It is not necessary to obtain the results of biochemical markers before initiating fibrinolytic therapy. Because administration of fibrinolytics result in clot lysis, patients who are at high-risk of major bleeding (including intracranial hemorrhage) have either a relative or absolute contraindication to fibrinolytic therapy. Patients presenting with an absolute contraindication will likely not receive fibrinolytic therapy, as primary PCI is preferred. Patients with a relative contraindication may receive fibrinolytic therapy if the perceived risk of death from the MI is higher than the risk of major hemorrhage.

Comparative pharmacology of commonly prescribed fibrinolytics is described in Table 5–4.[26] According to the ACC/AHA STE ACS practice guidelines, a more fibrin-specific agent such as alteplase, reteplase, or tenecteplase, is preferred over a non–fibrin-specific agent, such as streptokinase.[3] Fibrin-specific fibrinolytics open a greater percentage of infarcted arteries. In a large clinical trial, administration of alteplase reduced mortality by 1% (absolute reduction) and costs about $30,000 per year of life saved compared to streptokinase.[23] Two other trials compared alteplase to reteplase and alteplase to tenecteplase and found similar mortality between agents.[24,25] Therefore, either alteplase, reteplase, or tenecteplase are acceptable as first-line agents. Intracranial hemorrhage and major bleeding are the most serious side effects of fibrinolytic agents (Table 5–4). The risk of intracranial hemorrhage is higher with fibrin-specific agents than with streptokinase. However, the risk of systemic bleeding other than intracranial hemorrhage is higher with streptokinase than with other, more fibrin-specific agents.[23]

Twenty to 40 percent of patients presenting with STE ACS receive fibrinolysis compared with 7% receiving primary PCI.[26,27] Therefore, many patients do not receive early reperfusion therapy. The primary reason for lack of reperfusion therapy is that most patients present more than 12 hours after the time of symptom onset.[27] The percentage of eligible patients who receive reperfusion therapy is a quality indicator of care in

TABLE 5–3. Indications and Contraindications to Fibrinolytic Therapy per ACC/AHA Guidelines for Management of Patients with ST-Segment Elevation Myocardial Infarction[3]

Indications

1. Ischemic chest discomfort at least 20 minutes in duration but 12 hours or less since symptom onset
   and
   ST-segment elevation of at least 1 mm in height in two or more contiguous leads, or new or presumed new left bundle-branch block
2. Ongoing ischemic chest discomfort at least 20 minutes in duration 12–24 hours since symptom onset
   and
   ST-segment elevation of at least 1 mm in height in two or more contiguous leads

Absolute Contraindications

- Active internal bleeding (not including menses)
- Previous intracranial hemorrhage at any time; ischemic stroke within 3 months
- Known intracranial neoplasm
- Known structural vascular lesion (e.g., arteriovenous malformation)
- Suspected aortic dissection
- Significant closed head or facial trauma within 3 months

Relative Contraindications

- Severe, uncontrolled hypertension on presentation (blood pressure greater than 180/110 mm Hg)
- History of prior ischemic stroke greater than 3 months ago, dementia, or known intracranial pathology not covered above under absolute contraindications
- Current use of anticoagulants
- Known bleeding diathesis
- Traumatic or prolonged (greater than 10 minutes) CPR or major surgery (less than 3 weeks ago)
- Non-compressible vascular puncture (such as a recent liver biopsy or carotid artery puncture)
- Recent (within 2–4 weeks) internal bleeding
- For streptokinase administration, previous streptokinase use (greater than 5 days) or prior allergic reactions
- Pregnancy
- Active peptic ulcer
- History of severe, chronic, poorly controlled hypertension

ACC, American College of Cardiology; AHA, American Heart Association; CPR, cardiopulmonary resuscitation.
(Reprinted from Spinler SA, de Denus S. Acute Coronary Syndromes. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 303, with permission.)

TABLE 5–4. Comparison Between Fibrinolytic Agents

Agent	Fibrin Specificity	TIMI-3 Blood Flow Complete Perfusion at 90 Minutes	Systemic Bleeding Risk/ICH Risk	Administration	Average Wholesale Price[3]	Other Approved Uses
Streptokinase	+	35%	+++/+	Infusion over 60 minutes	$613	Pulmonary embolism, deep vein thrombosis, arterial thromboembolism, clearance of an occluded arteriovenous catheter
Alteplase (rt-PA)	+++	50–60%	++/++	Bolus followed by infusions over 90 minutes; weight-based dosing	$2,750	Pulmonary embolism, stroke, clearance of an occluded arteriovenous catheter
Reteplase (rPA)	++	50–60%	++/++	Two bolus doses, 30 minutes apart	$2,974	
Tenecteplase (TNK-tPA)	++++	50–60%	+/++	Single bolus dose; weight-based dosing	$2,833	

ICH, intracranial hemorrhage; TIMI, Thrombolysis in Myocardial Blood Flow (TIMI-3 blood flow indicates complete perfusion of the infracted artery). (Reprinted from Spinler SA, de Denus S. Acute Coronary Syndromes. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 303, with permission.)

patients with MI.[23] The "door-to-needle time", the time from presentation to start of fibrinolytic therapy, is another quality indicator.[23] While the ACC/AHA guidelines recommend a "door-to-needle time" of less than 30 minutes, the average time in the United States is approximately 37 minutes.[27] Therefore, strategies to shorten administration times should be implemented.

Aspirin

Aspirin has become the preferred antiplatelet agent in the treatment of all ACS.[2,3] Aspirin administration to all patients who don't have contraindications to aspirin therapy within the first 24 hours of hospital admission is a quality care indicator.[23] The antiplatelet effects of aspirin are mediated by inhibiting the synthesis of TXA_2 through an irreversible inhibition of platelet cyclooxygenase-1. In patients undergoing PCI, aspirin prevents acute thrombotic occlusion during the procedure. In patients receiving fibrinolytics, aspirin reduces mortality, and its effects are additive to fibrinolysis alone.[28]

Although an initial dose of 160 to 325 mg is required to achieve rapid platelet inhibition, long-term therapy with doses of 75 to 150 mg daily are as effective as higher doses. In addition, doses of less than 325 mg daily are associated with a lower rate of bleeding.[29,30] The major bleeding rate associated with chronic aspirin administration in doses less than 100 mg per day is 1.6%, whereas the rate with doses more than 100 mg per day is 2.3%.[30] Therefore, a daily maintenance dose of 75 to 160 mg is recommended.[2]

Other gastrointestinal disturbances, including dyspepsia and nausea, are infrequent when low-dose aspirin is used. Aspirin therapy should be continued indefinitely.

Thienopyridines

Administration of clopidogrel is recommended for all patients with STE ACS (Table 5–2).[3] Clopidogrel blocks adenosine diphosphate receptors on platelets, preventing the expression of glycoprotein IIb/IIIa receptors and thus platelet activation and aggregation.

Clopidogrel reduces death, MI, or stroke in patients with NSTE ACS when combined with aspirin.[31] It also reduces death, MI, or stroke in secondary prevention of vascular events in patients with a recent MI, stroke, or symptomatic peripheral vascular disease.[32] Most recently, early therapy with clopidogrel 75 mg once daily in patients with STE ACS reduced mortality and reinfarction in patients treated with fibrinolytics without increasing the risk of major bleeding.[21] Therefore, the combination of clopidogrel and aspirin is indicated for all patients with ACS. For PCI, clopidogrel is administered as a 300 to 600 mg loading dose followed by a 75 mg per day maintenance dose, in combination with aspirin, to prevent subacute stent thrombosis and long-term events, such as the composite endpoint of death, myocardial infarction, or need to undergo repeat PCI.[2,18] The most frequent side effect of clopidogrel is rash or gastrointestinal events (nausea, vomiting, or diarrhea). Rarely, thrombotic thrombocytopenic purpura has been reported with clopidogrel. The most serious side effect of clopidogrel is bleeding, which will be discussed in more detail in the section on pharmacotherapy for NSTE ACS.

Glycoprotein IIb/IIIa Receptor Inhibitors

Abciximab is a first-line glycoprotein IIb/IIIa receptor inhibitor for patients undergoing primary PCI[3,15,18] who have not received fibrinolytics. It should not be administered for

medical management of the STE ACS patient who will not be undergoing PCI. Abciximab, in combination with aspirin, a thienopyridine, and UFH (administered as an infusion for the duration of the procedure), is preferred over eptifibatide and tirofiban in this setting because abciximab is the most common glycoprotein IIb/IIIa receptor inhibitor studied in primary PCI trials, and a meta-analysis of trials demonstrated a reduction in short- and long-term mortality.[3,18,33]

Dosing and contraindications for abciximab are described in Table 5–2. Glycoprotein IIb/IIIa receptor inhibitors block the final common pathway of platelet aggregation; namely, cross-linking of platelets by fibrinogen bridges between the glycoprotein IIb and IIIa receptors on the platelet surface. Administration of a glycoprotein IIb/IIIa receptor inhibitor increases the risk of bleeding, especially if it is given in the setting of recent (less than 4 hours) administration of fibrinolytic therapy.[31,33] An immune-mediated thrombocytopenia occurs in approximately 5% of patients receiving abciximab.[34]

Anticoagulants

Unfractionated heparin, administered as a continuous infusion, is a first-line anticoagulant for treatment of patients with STE ACS, both for medical therapy and for patients undergoing PCI.[3,15,18] Unfractionated heparin binds to antithrombin and then to clotting factors Xa and IIa (thrombin). Anticoagulant therapy should be initiated in the emergency department and continued for 48 hours or longer in patients who will be bridged over to receive chronic warfarin anticoagulation following acute MI.[3] In the United States, UFH is typically continued until the patient has undergone PCI during hospitalization for STE ACS. Unfractionated heparin dosing is described in Table 5–2. The dose of the UFH infusion is adjusted frequently to a target activated partial thromboplastin time (aPTT) (Table 5–2). When co-administered with a fibrinolytic, aPTTs above the target range are associated with an increased rate of bleeding, while aPTTs below the target range are associated with increased mortality and reinfarction.[35] Unfractionated heparin is discontinued immediately after the PCI procedure.

A meta-analysis of small randomized studies from the 1970s and 1980s suggests that UFH reduces mortality by approximately 17%.[3] Other beneficial effects of anticoagulation are prevention of cardioembolic stroke, as well as venous thromboembolism in MI patients.[3] Besides bleeding, the most frequent adverse effect of UFH is an immune-mediated clotting disorder, **heparin-induced thrombocytopenia**, which occurs in up to 5% of patients treated with UFH. Heparin-induced thrombocytopenia is less common in patients receiving low-molecular-weight heparins (LMWHs), such as enoxaparin or dalteparin.

Low-molecular-weight heparins have not been studied in the setting of primary PCI. Low-molecular-weight heparins, like UFH, bind to antithrombin and inhibit both factor Xa and IIa. However, because their composition contains mostly short saccharide chain lengths, they preferentially inhibit factor Xa over factor IIa, which requires larger chain lengths for binding and inhibition. Limited data, primarily with enoxaparin, suggests that LMWHs may be an alternative to UFH in STE ACS.[36] A larger trial evaluating enoxaparin versus UFH in combination with fibrinolytics for STE ACS is ongoing.

Nitrates

One sublingual nitroglycerin tablet should be administered every 5 minutes for up to three doses in order to relieve myocardial ischemia. If patients have been previously prescribed sublingual NTG and ischemic chest discomfort persists for more than 5 minutes after the first dose, the patient should be instructed to contact emergency medical services before self-administering subsequent doses in order to activate emergency care sooner. Intravenous nitroglycerin should then be initiated in all patients with an ACS who do not have a contraindication and who have persistent ischemia, heart failure, or uncontrolled blood pressure. Intravenous nitroglycerin should be continued for approximately 24 hours after ischemia is relieved (Table 5–2). Nitrates promote the release of nitric oxide from the endothelium, which results in venous and arterial vasodilation. Venodilation lowers preload and myocardial oxygen demand. Arterial vasodilation may lower blood pressure, thus reducing myocardial oxygen demand. Arterial vasodilation also relieves coronary artery vasospasm, dilating coronary arteries to improve myocardial blood flow and oxygenation. Although used to treat ACS, nitrates have been suggested to play a limited role in the treatment of an ACS patient, as two large, randomized clinical trials failed to show a mortality benefit for IV nitrate therapy followed by oral nitrate therapy in acute MI.[37,38] The most significant adverse effects of nitrates are tachycardia, flushing, headache, and hypotension. Nitrate administration is contraindicated in patients who have received oral phosphodiesterase 5 inhibitors, such as sildenafil and vardenafil, within the past 24 hours, and tadalafil within the past 48 hours.[3]

Beta-Blockers

Intravenous or oral doses of a β-blocker should be administered early in the care of a patient with STE ACS, and then oral agents should be continued indefinitely. Early administration of a β-blocker to patients lacking a contraindication within the first 24 hours of hospitalization is a quality care indicator.[2,3] In ACS the benefit of β-blockers mainly results from the competitive blockade of β_1-adrenergic receptors located on the myocardium. β_1-Blockade produces a reduction in heart rate, myocardial contractility, and blood pressure, decreasing myocardial oxygen demand. As a result of these effects, β-blockers reduce the risk for recurrent ischemia, increase in infarct size and risk of reinfarction, and occurrence of ventricular arrhythmias in the hours and days following MI.[39]

Landmark clinical trials have established the role of early β-blocker therapy in reducing MI mortality, reinfarction, and arrhythmias. Most of these trials were performed in the 1970s and 1980s before routine use of early reperfusion therapy.[40,41] However, data regarding the acute benefit of β-blockers in MI

in the reperfusion era is derived mainly from a recently reported large clinical trial, which suggests that there may be an early risk of cardiogenic shock when initiating intravenous β-blockers followed by oral β-blockers early in the course of STE MI, especially in patients presenting with pulmonary congestion.[42] Therefore, a low dose of an oral β-blocker should be initiated, followed by careful assessment for signs of hypotension and heart failure prior to any dose titration in patients with STE MI. Early administration of β-blockers (to patients without contraindications) within the first 24 hours of hospital admission is a standard of quality patient care.[3] However, the AHA is currently undertaking a re-evaluation of this practice guideline recommendation given the results of the aforementioned trial reporting adverse effects associated with β-blocker use in certain MI populations.

The most serious side effects of β-blocker administration early in ACS are hypotension, bradycardia, and heart block. While initial, acute administration of β-blockers is not appropriate for patients who present with decompensated heart failure, initiation of β-blockers may be attempted before hospital discharge in the majority of patients following treatment of acute heart failure. β-Blockers are continued indefinitely.

Calcium Channel Blockers

Calcium channel blockers in the setting of STE ACS are used for relief of ischemic symptoms in patients who have contraindications to β-blockers. Patients prescribed calcium channel blockers for treatment of hypertension who were not receiving and do not have any contraindications to β-blockers should have the calcium channel blocker discontinued and a β-blocker initiated. Although all calcium channel blockers produce coronary vasodilatation and decrease blood pressure, other effects are more heterogeneous between these agents. Dihydropyridine calcium channel blockers (e.g., amlodipine, felodipine, and nifedipine) primarily produce their anti-ischemic effects through peripheral vasodilatation with no clinical effects on AV node conduction and heart rate. The nondihydropyridine calcium channel blockers (e.g., diltiazem and verapamil), on the other hand, have additional anti-ischemic effects by reducing contractility, AV nodal conduction, and slowing heart rate.

Current data suggest little benefit on clinical outcomes beyond symptom relief for calcium channel blockers in the setting of ACS.[43] Moreover, the use of first-generation short-acting dihydropyridines, such as nifedipine, should be avoided because they appear to worsen outcomes through their negative inotropic effects, induction of reflex sympathetic activation, tachycardia, and increased myocardial ischemia.[43] Therefore, calcium channel blockers should be avoided in the acute management of MI unless there is a clear symptomatic need or a contraindication to β-blockers.

Adverse effects and contraindications of calcium channel blockers are described in Table 5–2. Verapamil, diltiazem, and first-generation dihydropyridines should also be avoided in patients with acute decompensated heart failure or left ventricular dysfunction because they can worsen heart failure and potentially increase mortality secondary to their negative inotropic effects. In patients with heart failure requiring treatment with a calcium channel blocker, amlodipine, a second-generation dihydropyridine that does not cause reflex tachycardia, is the preferred agent.[44]

Early Pharmacotherapy for Non–ST-Segment Elevation Acute Coronary Syndromes

In general, early pharmacotherapy of NSTE ACS (Fig. 5–3) is similar to that of STE ACS with three exceptions: (1) fibrinolytic therapy is not administered; (2) glycoprotein IIb/IIIa receptor blockers are administered to high-risk patients for medical therapy as well as to PCI patients; and (3) at this time, there are no standard quality indicators for patients with NSTE ACS who are not diagnosed with MI.

❼ *According to the ACC/AHA non–ST-segment elevation ACS practice guidelines, in the absence of contraindications, early pharmacotherapy of NSTE ACS should include intranasal oxygen (if oxygen saturation is low), SL NTG followed by IV NTG, aspirin, an IV β-blocker, and UFH or LMWH. Most patients should receive additional therapy with clopidogrel. High-risk patients should also receive a glycoprotein IIb/IIIa receptor blocker.* Morphine is also administered to patients with refractory angina as described previously. These agents should be administered early, while the patient is still in the emergency department. Dosing and contraindications for SL and IV NTG (for selected patients), aspirin, IV β-blockers, UFH, and LMWHs are listed in Table 5–2.[2,22]

Fibrinolytic Therapy

Fibrinolytic therapy is not indicated in any patient with NSTE ACS, as increased mortality has been reported with fibrinolytics compared to controls in clinical trials in which fibrinolytics have been administered to patients with NSTE ACS (patients with normal or ST-segment depression ECGs).[10]

Aspirin

Aspirin reduces the risk of death or developing MI by about 50% (compared to no antiplatelet therapy) in patients with NSTE ACS.[29] Therefore, aspirin remains the cornerstone of early treatment for all ACS. Dosing of aspirin for NSTE ACS is the same as that for STE ACS (Table 5–2). Aspirin is continued indefinitely.

Thienopyridines

For patients with NSTE ACS, clopidogrel started on the first day of hospitalization as a 300 to 600 mg loading dose and followed the next day by 75 mg orally per day is recommended for most patients.[2] Although the use of aspirin in ACS is the mainstay of antiplatelet therapy, morbidity and mortality following an ACS remain high. Clopidogrel, administered as a 300 mg loading dose followed by 75 mg once daily for 9 to

12 months, reduces the combined risk of death from cardiovascular causes, non-fatal MI, or stroke by 20%.[45] Administration of clopidogrel for at least 30 days in patients undergoing intracoronary stenting is the standard of care. Recently, the combination of clopidogrel with aspirin has been extended to 3 months for sirolimus-eluting stents and at least 6 months for patients with paclitaxel-eluting stents.[18] Because of the potential for increased risk of bleeding, clopidogrel should be discontinued for at least 5 days before elective CABG surgery.[2]

Glycoprotein IIb/IIIa Receptor Inhibitors

Administration of tirofiban or eptifibatide is recommended for high-risk NSTE ACS patients as medical therapy without planned revascularization and for patients with continued or recurrent ischemia despite treatment with aspirin and an anticoagulant. In these patients, the benefit of glycoprotein IIb/IIIa inhibitors appears to be limited to those undergoing PCI.[18,46] Patients undergoing PCI in these trials received several hours to days of pre-treatment with the glycoprotein IIb/IIIa receptor blocker before proceeding to PCI. Abciximab should not be used in this setting, because its use in such a setting has not been shown to be beneficial.

In patients with NSTE ACS scheduled for early PCI, administration of either abciximab or eptifibatide (double bolus) is recommended. The use of tirofiban in these patients is not recommended, because it has been shown to be inferior to abciximab.[2] Medical therapy with glycoprotein IIb/IIIa receptor inhibitors in patients not undergoing PCI is reserved for higher-risk patients, such as those with positive troponin or ST-segment depression, and patients who have continued or recurrent ischemia despite other antithrombotic therapy.[2]

Doses and contraindications to glycoprotein IIb/IIIa receptor blockers are described in Table 5–2. Major bleeding and rates of transfusion are increased with administration of a glycoprotein IIb/IIIa receptor inhibitor in combination with aspirin and an anticoagulant,[30] but there is no increased risk of intracranial hemorrhage in the absence of concomitant fibrinolytic treatment. The risk of thrombocytopenia with tirofiban and eptifibatide appears lower than that with abciximab. Bleeding risks appear similar between agents.

Anticoagulants

Either UFH or LMWH should be administered to patients with NSTE ACS. Therapy should be continued for up to 48 hours or until the end of the angiography or PCI procedure. In patients initiating warfarin therapy, UFH or LMWHs should be continued until the International Normalized Ratio (INR) with warfarin is in the therapeutic range for 2 consecutive days. The addition of UFH to aspirin reduces the rate of death or MI in patients with NSTE ACS.[47] Enoxaparin was mentioned as "preferred" over UFH in the 2002 ACC/AHA clinical practice guidelines, as two large clinical trials found a reduction in the combined endpoint of death, MI, or need for PCI in patients primarily treated with a medical management strategy.[2] However, in patients with NSTE ACS undergoing early PCI, similar rates of death or MI and a slightly higher bleeding rate with enoxaparin was found in a large trial comparing enoxaparin and UFH. This trial, however, was confounded by a large number of patients who received both UFH and enoxaparin. Therefore, either enoxaparin or UFH may be administered, but switching between UFH and enoxaparin should be avoided as it appears to increase bleeding rates.[48] In some clinical trials, the risk of heparin-induced thrombocytopenia has been shown to be lower with LMWHs compared to UFH. Dosing information and contraindications are described in Table 5–2.

Nitrates

Sublingual NTG followed by intravenous NTG should be administered to patients with NSTE ACS and ongoing ischemia (Table 5–2). The mechanism of action, dosing, contraindications, and adverse effects are the same as those described in the section on early pharmacologic therapy for STE ACS. Intravenous NTG is typically continued for approximately 24 hours following ischemia relief.

Beta-Blockers

Intravenous β-blockers followed by oral β-blockers should be administered to all patients with NSTE ACS in the absence of contraindications. Benefits of β-blockers in this patient group are assumed to be similar to those seen in patients with STE ACS. β-Blockers are continued indefinitely.

Calcium Channel Blockers

As described in the previous section, calcium channel blockers should not be administered to most patients with ACS. Their role is a second-line treatment for patients with certain contraindications to β-blockers and those with continued ischemia despite β-blocker and nitrate therapy. Administration of either amlodipine, diltiazem, or verapamil is preferred.[2] Agent selection is based on heart rate and left ventricular dysfunction (diltiazem and verapamil are contraindicated in patients with bradycardia, heart block, or systolic heart failure). Dosing and contraindications are described in Table 5–2.



Patient Encounter, Part 3: Secondary Prevention of MI

- Identify the long-term treatment goals for SD.
- What additional pharmacotherapy should be initiated prior to hospital discharge?
- Create a care plan for SD for hospital discharge which includes pharmacotherapy, desired treatment outcomes, and monitoring for efficacy and adverse effects.

Secondary Prevention Following Myocardial Infarction

The long-term goals following MI are to: (1) control modifiable CHD risk-factors, (2) prevent the development of systolic heart failure, (3) prevent recurrent MI and stroke, and (4) prevent death, including sudden cardiac death. Pharmacotherapy, which has been proven to decrease mortality, heart failure, reinfarction, or stroke, should be initiated prior to hospital discharge for secondary prevention. ❽ *Guidelines from the ACC/AHA suggest that in the absence of contraindications, following MI from either STE ACS or NSTE ACS, patients should receive indefinite treatment with aspirin, a β-blocker, and an ACE inhibitor.*[2,3] *For NSTE ACS, most patients should receive clopidogrel, in addition to aspirin, for up to 9 months.*[2] *Most patients will receive a statin to reduce low-density lipoprotein cholesterol to less than 100 mg/dL. Selected patients will also be treated with long-term warfarin anticoagulation. Newer therapies include eplerenone, an aldosterone antagonist. For all ACS patients, treatment and control of modifiable risk factors such as hypertension, dyslipidemia, and diabetes mellitus is essential.* Benefits and adverse effects of long-term treatment with these medications are discussed in more detail below.

❾ *Because the costs for chronic preventative pharmacotherapy are the same for primary and secondary prevention, while the risk of events is higher with secondary prevention, secondary prevention is more cost effective than primary prevention of CHD.* Pharmacotherapy demonstrating cost effectiveness to prevent death in the ACS and post-MI patient includes fibrinolytics ($2,000 to $33,000 cost per year of life saved), aspirin, glycoprotein IIb/IIIa receptor blockers ($13,700 to $16,500 per year of life added), β-blockers (less than $5,000 to $15,000 cost per year of life saved), ACE inhibitors ($3,000 to $5,000 cost per year of life saved), eplerenone ($15,300 to $32,400 per year of life gained), statins ($4,500 to $9,500 per year of life saved) and gemfibrozil ($17,000 per year of life saved).[49–58] Because cost-effectiveness ratios of less than $50,000 per added life-year are considered economically attractive from a societal perspective,[49] pharmacotherapy described above for ACS and secondary prevention are standards of care because of their efficacy and cost attractiveness to payors.

Aspirin

Aspirin decreases the risk of death, recurrent infarction, and stroke following myocardial infarction. Aspirin prescription at hospital discharge is a quality care indicator in MI patients.[3] All patients should receive aspirin indefinitely; those patients with a contraindication to aspirin should receive clopidogrel.[2,3]

The risk of major bleeding from chronic aspirin therapy is approximately 2% and is dose-related. Aspirin doses higher than 75 to 81 mg are no less effective than doses of 160 to 325 mg, but do have lower rates of bleeding. Therefore, chronic doses of aspirin should not exceed 81 mg.

Clopidogrel

For patients with either STE or NSTE ACS, clopidogrel decreases the risk of death, MI, or stroke.[21,45] The ACC/AHA guidelines suggest a minimum therapy duration of 9 months in patients following NSTE ACS.[2] In patients receiving clopidogrel for STE MI who do not undergo PCI, clopidogrel should be administered for at least 14 to 28 days.[21] Patients who have undergone a PCI with stent implantation may receive clopidogrel for up to 12 months.[18] Because of the risk of bleeding with concomitant therapy of clopidogrel and aspirin at doses greater than 100 mg, low-dose aspirin should be administered with clopidogrel.[59] Although not specifically studied, longer duration of therapy with clopidogrel plus aspirin may be considered for patients with many recurrent vascular events such as stroke, MI, or recurrent ACS.

Anticoagulation

Warfarin should be considered in selected patients following an ACS, including patients with a left ventricular thrombus, patients demonstrating extensive ventricular wall motion abnormalities on cardiac echocardiogram, a history of thromboembolic disease, or chronic atrial fibrillation.[3] A meta-analysis of 10 clinical trials of secondary prevention with aspirin, warfarin, and the combination of the two suggested that warfarin plus low-dose aspirin reduced the rate of MI and stroke, but did not reduce mortality. The risk of major bleeding was increased more than two-fold.[60] Many consider these benefits to be small in comparison with the large management issues related to warfarin therapy, such as INR monitoring and drug interactions. Furthermore, because a large proportion of ACS patients in North America undergo coronary revascularization with subsequent stent implantation, patients require a combination of aspirin and clopidogrel to prevent stent thrombosis, a platelet-dependent phenomenon that warfarin does not effectively prevent.[61] Therefore, because of the complexity of managing current anticoagulants, the use of warfarin is unlikely to gain wide acceptance. Despite the superiority of warfarin plus aspirin over aspirin alone, it is not currently the preferred antithrombotic agent recommended by any professional association practice guidelines in the absence of the conditions for select patients outlined previously.

Beta-Blockers, Nitrates, and Calcium Channel Blockers

Current treatment guidelines recommend that following an ACS, patients should receive a β-blocker indefinitely[2,3] whether they have residual symptoms of angina or not.[62] β-Blocker prescription at hospital discharge in the absence of contraindications is a quality care indicator.[3] Overwhelming data support the use of β-blockers in patients with a previous MI. Currently, there are no data to support the superiority of one β-blocker over another, although the only β-blocker with intrinsic sympathomimetic activity that has been shown to be beneficial following MI is acebutolol.[63]

Although β-blockers should be avoided in patients with decompensated heart failure from left ventricular systolic dysfunction complicating an MI, clinical trial data suggest that it is safe to initiate β-blockers prior to hospital discharge in these patients once heart failure symptoms have resolved.[64] These patients may actually benefit more than those without left ventricular dysfunction.[65] In patients who cannot tolerate or have a contraindication to a β-blocker, a calcium channel blocker can be used to prevent anginal symptoms, but should not be used routinely in the absence of such symptoms.[2,3,62]

Finally, all patients should be prescribed short-acting, sublingual NTG or lingual NTG spray to relieve any anginal symptoms when necessary and instructed on its use.[2,3] Chronic long-acting nitrate therapy has not been shown to reduce CHD events following MI. Therefore, intravenous NTG is not routinely followed by chronic, long-acting oral nitrate therapy in ACS patients who have undergone revascularization, unless the patient has chronic stable angina or significant coronary stenoses that were not revascularized.[62]

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Angiotensin-converting enzyme inhibitors should be initiated in all patients following MI to reduce mortality, decrease reinfarction, and prevent the development of heart failure.[2,3] Dosing and contraindications are described in Table 5–2. The benefit of ACE inhibitors in patients with MI most likely comes from their ability to prevent cardiac remodeling. The largest reduction in mortality is observed in patients with left ventricular dysfunction (low LVEF) or heart failure symptoms. Early initiation (within 24 hours) of an *oral* ACE inhibitor appears to be crucial during an acute MI, as 40% of the 30-day survival benefit is observed during the first day, 45% from days 2 to 7, and approximately 15% from days 8 to 30.[66] However, current data do not support the early administration of *intravenous* ACE inhibitors in patients experiencing an MI, as mortality may be increased.[67] Administration of ACE inhibitors should be continued indefinitely. Hypotension should be avoided, as coronary artery filling may be compromised. Additional trials suggest that most patients with CAD, not just ACS or heart failure patients, benefit from ACE inhibitors. Therefore, ACE inhibitors should be considered in all patients following an ACS in the absence of a contraindication.

Many patients cannot tolerate chronic ACE inhibitor therapy secondary to adverse effects outlined below. Alternatively, the angiotensin receptor blockers (ARBs), candesartan and valsartan, have been documented in trials to improve clinical outcomes in patients with heart failure.[68,69] Therefore, either an ACE inhibitor or candesartan or valsartan are acceptable choices for chronic therapy for patients who have a low ejection fraction (EF) and heart failure following MI. Since more than five different ACE inhibitors have proven benefits in MI while only two ARBs have been studied, the benefits of ACE inhibitors are generally considered a class effect while the benefits of ARBs are still under study. Angiotensin-converting enzyme inhibitor prescription (or alternatively an ARB) at hospital discharge following MI, in the absence of contraindications, to patients with depressed LVF (EF less than 40%) is currently a quality care indicator, and there are plans to make administration of an ACE inhibitor in all patients without contraindications a quality care indicator.[3]

Besides hypotension, the most frequent adverse reaction to an ACE inhibitor is cough, which may occur in up to 30% of patients. Patients with an ACE inhibitor cough and either clinical signs of heart failure or LVEF less than 40% may be prescribed an ARB.[3] Other, less common but more serious adverse effects to ACE inhibitors and ARBs include acute renal failure, hyperkalemia, and angioedema.

Aldosterone Antagonists

To reduce mortality, administration of an aldosterone antagonist, either eplerenone or spironolactone, should be considered within the first 2 weeks following MI in all patients who are already receiving an ACE inhibitor (or ARB) and have an EF of equal to or less than 40% and either heart failure symptoms or diagnosis of diabetes mellitus.[3] Aldosterone plays an important role in heart failure and in MI because it promotes vascular and myocardial fibrosis, endothelial dysfunction, hypertension, left ventricular hypertrophy, sodium retention, potassium and magnesium loss, and arrhythmias. Aldosterone antagonists have been shown in experimental and human studies to attenuate these adverse effects.[70] Spironolactone decreases all-cause mortality in patients with stable, severe heart failure.[71]

Eplerenone, like spironolactone, is an aldosterone antagonist that blocks the mineralocorticoid receptor. In contrast to spironolactone, eplerenone has no effect on the progesterone or androgen receptor, thereby minimizing the risk of gynecomastia, sexual dysfunction, and menstrual irregularities.[70] In a recent clinical trial,[72] eplerenone significantly reduced mortality, as well as hospitalization for heart failure in post-MI patients with an EF less than 40% and symptoms of heart failure at any time during hospitalization. The risk of hyperkalemia, however, was increased. Therefore, patients with a serum creatinine (SCr) greater than 2.5 mg/dL (221 μmol/L) or creatinine clearance less than 50 mL/minute or serum potassium concentration of greater than 5.0 mmol/L (5.0 mEq/L) should not receive eplerenone (in addition to either an ACE inhibitor or ARB). Currently, there are no data to support that the more selective, more expensive eplerenone is superior to, or should be preferred to, the less expensive generic spironolactone unless a patient has experienced gynecomastia, breast pain, or impotence while receiving spironolactone. Finally, it should be noted that hyperkalemia is just as likely to appear with both of these agents.

Lipid-Lowering Agents

There are now overwhelming data supporting the benefits of statins in patients with CAD in prevention of total mortality, cardiovascular mortality, and stroke. According to the National

TABLE 5–5. Therapeutic Drug Monitoring for Adverse Effects of Pharmacotherapy for Acute Coronary Syndromes

Drug	Adverse Effects	Monitoring
Aspirin	Dyspepsia, bleeding, gastritis	Clinical signs of bleeding,[a] gastrointestinal upset; baseline CBC and platelet count; CBC platelet count every 6 months
Clopidogrel	Bleeding, TTP (rare)	Clinical signs of bleeding[a]; baseline CBC and platelet count; CBC and platelet count every 6 months following hospital discharge
Unfractionated heparin	Bleeding, heparin-induced thrombocytopenia	Clinical signs of bleeding[a]; baseline CBC and platelet count; aPTT every 6 hours until target then every 24 hours; daily CBC; platelet count every 2 days (minimum, preferably every day)
Low-molecular-weight heparins	Bleeding, heparin-induced thrombocytopenia	Clinical signs of bleeding[a]; baseline CBC and platelet count; daily CBC, platelet count every 2 days (minimum, preferably every day); SCr daily
Fibrinolytics	Bleeding, especially intracranial hemorrhage	Clinical signs of bleeding[a]; baseline CBC and platelet count; mental status every 2 hours for signs of intracranial hemorrhage; daily CBC
Glycoprotein IIb/IIIa receptor blockers	Bleeding, acute profound thrombocytopenia	Clinical signs of bleeding[a]; baseline CBC and platelet count; daily CBC; platelet count at 4 hours after initiation then daily
Intravenous nitrates	Hypotension, flushing, headache, tachycardia	BP and HR every 2 hours
β-Blockers	Hypotension, bradycardia, heart block, bronchospasm, heart failure, fatigue, depression, sexual dysfunction, nightmares, masking hypoglycemia symptoms in diabetics	BP, RR, HR, 12-lead ECG and clinical signs of heart failure every 5 minutes during bolus intravenous dosing; BP, RR, HR, and clinical signs of heart failure every shift during oral administration during hospitalization, then BP and HR every 6 months following hospital discharge
Diltiazem and verapamil	Hypotension, bradycardia, heart block, heart failure, gingival hyperplasia	BP and HR every shift during oral administration during hospitalization then every 6 months following hospital discharge; dental exam and teeth cleaning every 6 months
Amlodipine	Hypotension, dependent peripheral edema, gingival hyperplasia	BP every shift during oral administration during hospitalization, then every 6 months following hospital discharge; dental exam and teeth cleaning every 6 months
Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers	Hypotension, cough (with ACE inhibitors), hyperkalemia, prerenal azotemia, angioedema (ACE inhibitors more so than ARBs)	BP every 2 hours × 3 for first dose, then every shift during oral administration during hospitalization, then once every 6 months following hospital discharge; baseline SCr and potassium; daily SCr and potassium while hospitalized then every 6 months (or 1–2 weeks after each outpatient dose titration); closer monitoring required in selected patients using spironolactone or eplerenone or if renal insufficiency; counsel patient on throat, tongue, and facial swelling
Aldosterone antagonists	Hypotension, hyperkalemia, increased serum creatinine	BP and HR every shift during oral administration during hospitalization, then once every 6 months; baseline SCr and serum potassium concentration; SCr and potassium at 48 hours, at 7 days, then monthly for 3 months, then every 3 months thereafter following hospital discharge
Warfarin	Bleeding, skin necrosis	Clinical signs of bleeding[a]; baseline CBC and platelet count; CBC and platelet count every 6 months following hospital discharge; baseline aPTT and INR; daily INR until two consecutive INRs are within the target range then once weekly × 2 weeks, then every month
Morphine	Hypotension, respiratory depression	BP and RR 5 minutes after each bolus dose

[a]Clinical signs of bleeding include bloody stools, melena, hematuria, hematemesis, bruising, and oozing from arterial or venous puncture sites.
ACE, angiotensin-converting enzyme; aPTT, activated partial thromboplastin time; ARB, angiotensin receptor blocker; BP, blood pressure; CBC, complete blood count; ECG, electrocardiogram; HR, heart rate; INR, International Normalized Ratio; RR, respiratory rate; SCr, serum creatinine, TTP, thrombotic thrombocytopenic purpura.
(Reprinted from Spinler SA, de Denus S. Acute Coronary Syndromes. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 314, with permission.)

Cholesterol Education Program (NCEP) Adult Treatment Panel recommendations, all patients with CAD should receive dietary counseling and pharmacologic therapy in order to reach a low-density lipoprotein (LDL) cholesterol of less than 100 mg/dL (2.59 mmol/L), with statins being the preferred agents to lower LDL cholesterol.[73] Results from landmark clinical trials have unequivocally demonstrated the value of statins in secondary prevention following MI in patients with moderate to high cholesterol.[73,74] Although the primary effect of statins is to decrease LDL cholesterol, statins are believed to produce many non–lipid-lowering or "pleiotropic" effects such as anti-inflammatory and antithrombotic properties. Newer recommendations from the NCEP give an optional LDL cholesterol goal of less than 70 mg/dL (1.81 mmol/L).[75,76] In patients with an ACS, statin therapy initiation should not be delayed and statins should be prescribed at or prior to discharge in most patients.[77]

A fibrate derivative or niacin should be considered in select patients with a low high-density lipoprotein (HDL) cholesterol less than 40 mg/dL (1.04 mmol/L) and/or a high triglyceride level greater than 200 mg/dL (2.26 mmol/L). In a large randomized trial in men with established CAD and low levels of HDL cholesterol, the use of gemfibrozil (600 mg twice daily) significantly decreased the risk of non-fatal myocardial infarction or death from coronary causes.[78]

Other Modifiable Risk Factors

Smoking cessation, managing hypertension, weight loss, and tight glucose control for patients with diabetes mellitus, in addition to treatment of dyslipidemia, are important treatments for secondary prevention of CHD events.[3] Smoking cessation counseling at the time of discharge following MI is a quality care indicator.[3] The use of nicotine patches or gum, or of bupropion alone or in combination with nicotine patches, should be considered in appropriate patients.[3] Hypertension should be strictly controlled according to published guidelines.[79] Patients who are overweight should be educated on the importance of regular exercise, healthy eating habits, and reaching and maintaining an ideal weight.[80] Finally, because diabetics have up to a four-fold increased risk of mortality compared to non-diabetics, the importance of tight glucose control, as well as other CHD risk factor modifications, cannot be overstated.[81]

OUTCOME EVALUATION

- To determine the efficacy of nonpharmacologic and pharmacotherapy for both STE and NSTE ACS, monitor patients for: (1) relief of ischemic discomfort; (2) return of ECG changes to baseline; and (3) absence or resolution of heart failure signs.
- Monitoring parameters for recognition and prevention of adverse effects from ACS pharmacotherapy are described in Table 5–5. In general, the most common adverse reactions from ACS therapies are hypotension and bleeding. To treat for bleeding and hypotension, discontinue the offending agent(s) until symptoms resolve. Severe bleeding resulting in hypotension secondary to hypovolemia may require blood transfusion.



Patient Care and Monitoring

For patients in acute distress and ACS is suspected:

- Follow recommendations in Fig. 5–1, Table 5–2, and Fig. 5–3. Also incorporate into your plan the recommendations detailed below under "For patients diagnosed with ACS."

For patients diagnosed with ACS:

1. Review patient's medical record to determine indications for each medication.
2. Review patient's medical record to determine contraindications for each medication. For aspirin, β-blockers, ACE inhibitors, and ARBs, document contraindications in patient's medical record.
3. Review doses of medications for appropriateness. Aspirin dose should be less than 160 mg/day. Titration toward target doses of ACE inhibitors and β-blockers should be in progress.
4. Interview the patient to assess complementary or alternative medication use. Counsel appropriately based on indications and drug interactions.
5. Evaluate the patient's medical record and medication history, and conduct a patient interview to assess for the presence of drug allergies, adverse drug reactions, and drug interactions.
6. Educate the patient on lifestyle modifications, including smoking cessation, diet, weight loss, and exercise. For patients with diabetes mellitus, tight glucose control should be emphasized.
7. Provide patient education with regard to CAD, MI, indications for medications, and potential adverse effects and drug interactions.
   - What is CAD?
   - How can the progression of CAD and MI be prevented?
   - How does each medication benefit the patient?
   - Why is adherence important?
   - What potential adverse effects may occur?
   - What potential drug interactions may occur?
   - Warning signs to report to the physician or emergency medical services include chest squeezing, burning, or pain; jaw pain; pain radiation down the arm; bleeding; and loss of consciousness.
   - Dial 911 if there is no chest discomfort relief after one sublingual NTG tablet.
   - Important to train caregiver or relative to administer cardiopulmonary resuscitation (CPR).
8. Document smoking cessation counseling and patient receipt of discharge instructions in the patient's medical record.

ABBREVIATIONS

ACC:	American College of Cardiology
ACE:	angiotensin-converting enzyme
ACS:	acute coronary syndromes

ADP: adenosine diphosphate
AHA: American Heart Association
AMI: acute myocardial infarction
aPTT: activated partial thromboplastin time
ARB: angiotensin receptor blocker
AV: atrioventricular
bpm: beats per minute
CABG: coronary artery bypass graft (surgery)
CAD: coronary artery disease
CBC: complete blood count
CHD: coronary heart disease
CK: creatine kinase
CK-MB: creatine kinase myocardial band
CPR: cardiopulmonary resuscitation
CrCl: creatinine clearance
CVD: cardiovascular disease
DM: diabetes mellitus
ECG: electrocardiogram
EF: ejection fraction
HDL: high-density lipoprotein
HR: heart rate
HTN: hypertension
ICD: implantable cardioverter defibrillator
ICH: intracranial hemorrhage
INR: International Normalized Ratio
IV: intravenous
LAD: left anterior descending (artery)
LDL: low-density lipoprotein
LMWH: low-molecular-weight heparin
LVEF: left ventricular ejection fraction
LVF: left ventricular function
MB: myocardial band
MI: myocardial infarction
NCEP: National Cholesterol Education Program
NSTE: non–ST-segment elevation
NTG: nitroglycerin
PCI: percutaneous coronary intervention
RCA: right coronary artery
rPA: reteplase
RR: respiratory rate
rt-PA: alteplase
SC: subcutaneous
SCr: serum creatinine
SL: sublingual
STE: ST-segment elevation
TIMI: Thrombolysis in myocardial infarction
TNK-tPA: tenecteplase
TTP: thrombotic thrombocytopenic purpura
TXA_2: thromboxane A_2
UA: unstable angina
UFH: unfractionated heparin

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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6 ARRHYTHMIAS

James E. Tisdale



LEARNING OBJECTIVES

UPON COMPLETION OF THE CHAPTER, THE READER WILL BE ABLE TO:

1. Describe the phases of the cardiac action potential, compare and contrast the cellular ionic changes corresponding to each phase, and explain the relationship between the cardiac action potential and the electrocardiogram (ECG).
2. Describe the modified Vaughan-Williams classification of antiarrhythmic drugs, and compare and contrast the effects of available antiarrhythmic drugs on ventricular conduction velocity, refractory period, automaticity, and inhibition of specific myocardial ion channels.
3. Compare and contrast the risk factors for and the features, mechanisms, etiologies, symptoms, and goals of therapy of: (1) sinus bradycardia; (2) atrioventricular (AV) nodal blockade; (3) atrial fibrillation (AF); (4) paroxysmal supraventricular tachycardia (PSVT); (5) ventricular premature depolarizations (VPDs); (6) ventricular tachycardia (VT, including torsades de pointes); and (7) ventricular fibrillation (VF).
4. Compare and contrast appropriate nonpharmacologic and pharmacologic treatment options for sinus bradycardia and AV nodal blockade.
5. Compare and contrast the mechanisms of action of drugs used for ventricular rate control, conversion to sinus rhythm and maintenance of sinus rhythm in patients with AF, and explain the importance of anticoagulation for patients with AF.
6. Compare and contrast the mechanisms of action of drugs used for acute termination of PSVT.
7. Compare and contrast the role of drug therapy versus nonpharmacologic therapy for long-term prevention of recurrence of PSVT.
8. Describe the role of drug therapy for management of asymptomatic and symptomatic VPDs.
9. Compare and contrast the mechanisms of action of drugs used for the treatment of acute episodes of VT (including torsades de pointes), and describe options and indications for nonpharmacologic treatment of VT and VF.
10. Design individualized drug therapy treatment plans for patients with: (1) sinus bradycardia; (2) AV nodal blockade; (3) AF; (4) PSVT; (5) VPDs; (6) VT (including torsades de pointes); and (7) VF.

KEY CONCEPTS

❶ Cardiac arrhythmias may be caused by abnormal impulse formation (automaticity), abnormal impulse conduction (reentry), or both.

❷ Numerous drugs (β-blockers, diltiazem, verapamil, digoxin, and amiodarone) can cause bradyarrhythmias (sinus bradycardia and AV nodal blockade).

❸ The goals of treatment of AF are: (1) ventricular rate control with drugs that inhibit AV nodal conduction; (2) restoration

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of sinus rhythm with direct current cardioversion or antiarrhythmic drugs (commonly referred to as "cardioversion" or "conversion to sinus rhythm"); (3) maintenance of sinus rhythm/reduction in the frequency of episodes using antiarrhythmic drugs; and (4) prevention of stroke.

❹ Antiarrhythmic drug therapy for maintenance of sinus rhythm/reduction in frequency of episodes of AF should be initiated only in patients in whom symptoms persist despite maximal doses of drugs for ventricular rate control.

❺ The majority of patients with AF should receive warfarin therapy (titrated to an International Normalized Ratio of 2 to 3) for stroke prevention, particularly if they have other risk factors for stroke.

❻ Adenosine is the drug of choice for termination of paroxysmal supraventricular tachycardia.

❼ Asymptomatic ventricular premature depolarizations should not be treated with antiarrhythmic drug therapy.

❽ Implantable cardioverter-defibrillators are more effective than antiarrhythmic drugs for reduction in the risk of sudden cardiac death due to VT or VF.

❾ The purpose of drug therapy for VF is facilitation of electrical defibrillation; in the absence of electrical defibrillation, drug therapy alone will not terminate VF.

❿ Drugs with the potential to cause QT interval prolongation and torsades de pointes should be avoided or used with extreme caution in patients with other risk factors for torsades de pointes.

NORMAL AND ABNORMAL CARDIAC CONDUCTION AND ELECTROPHYSIOLOGY

The heart functions via both mechanical and electrical activity. The mechanical activity of the heart refers to atrial and ventricular contraction, the mechanism by which blood is delivered to tissues. When deoxygenated blood returns to the heart via the venous circulation, the blood enters the right atrium. Right atrial contraction and changes in right ventricular pressure result in delivery of blood to the right ventricle through the tricuspid valve. Right ventricular contraction pumps blood through the pulmonic valve through the pulmonary arteries to the lungs, where the blood becomes oxygenated. The blood then flows through the pulmonary veins into the left atrium. Left atrial contraction and changes in left ventricular (LV) pressure result in delivery of blood through the mitral valve into the left ventricle. Contraction of the left ventricle results in pumping of blood through the aortic valve and to the tissues of the body.

The mechanical activity of the heart (contraction of the atria and ventricles) occurs as a result of the electrical activity of the heart. The heart possesses an intrinsic electrical conduction system (Fig. 6–1).[1] Normal myocardial contraction cannot occur without proper and normal function of the heart's electrical conduction system. Electrical depolarization of the atria results in atrial contraction, and ventricular depolarization is followed by ventricular contraction. Malfunction of the heart's electrical conduction system may result in dysfunctional atrial and/or ventricular contraction.

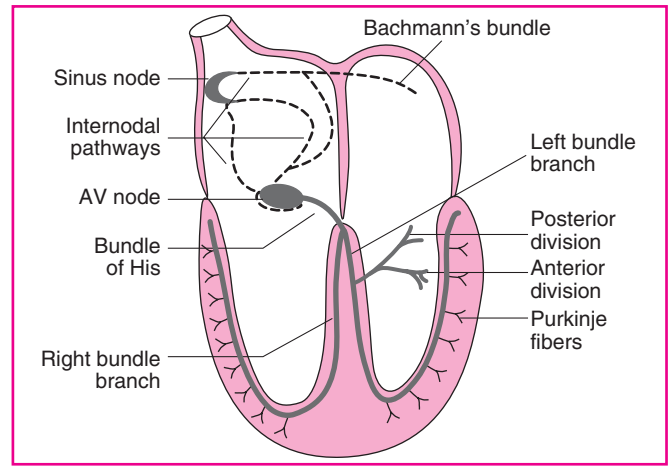


FIGURE 6–1. The cardiac conduction system. AV, atrioventricular. (Reprinted with permission from Cummins RO, (ed.) ACLS Provider Manual. Dallas: American Heart Association; 2003:253.)

The Cardiac Conduction System

Under normal circumstances, the sinoatrial (SA) node (also known as the sinus node), located in the upper portion of the right atrium, serves as the **pacemaker** of the heart and generates the electrical impulses that subsequently result in atrial and **ventricular depolarization** (Fig. 6–1).[1] The SA node serves as the heart's pacemaker because it has the greatest degree of **automaticity,** which is defined as the ability of a cardiac fiber or tissue to initiate depolarizations spontaneously. In adults at rest, the normal intrinsic depolarization rate of the SA node is 60 to 100 per minute. Other cardiac fibers also possess the property of automaticity, but normally the intrinsic depolarization rates are slower than that of the SA node. For example, the normal intrinsic depolarization rate of the atrioventricular (AV) node is 40 to 60 per minute, while that of the ventricular tissue is 30 to 40 per minute. Therefore, because of greater automaticity, the SA node normally serves as the pacemaker of the heart. However, if the SA node fails to generate depolarizations at a rate faster than that of the AV node, the AV node may take over as the pacemaker. Similarly, if the SA node and AV node fail to generate depolarizations at a rate greater than 30 to 40 per minute, ventricular tissue may take over as the pacemaker.

Following initiation of the electrical impulse from the SA node, the impulse travels through the internodal pathways of the specialized atrial conduction system and Bachmann's bundle (Fig. 6–1).[1] The atrial conducting fibers do not traverse the entire breadth of the left and right atria, as impulse conduction occurs across the internodal pathways, and when the impulse reaches the end of Bachmann's bundle, atrial depolarization spreads as a wave similar to that which occurs upon throwing a

pebble into water. As the impulse is conducted across the atria, each depolarized cell excites and depolarizes the surrounding connected cells, until both atria have been completely depolarized. Atrial contraction follows normal atrial depolarization.

Following atrial depolarization, impulses are conducted through the AV node, located in the lower right atrium (Fig. 6–1).[1] The impulse then enters the bundle of His, and is conducted through the ventricular conduction system, consisting of the left and right bundle branches. The left ventricle requires a larger conduction system than the right ventricle due to its larger mass; therefore, the left bundle branch bifurcates into the left anterior and posterior divisions (also commonly known as "fascicles"). The bundle branches further divide into the **Purkinje fibers,** through which impulse conduction results in ventricular depolarization, after which ventricular contraction occurs.

The Ventricular Action Potential

The ventricular **action potential** is depicted in Fig. 6–2.[2] Myocyte resting membrane potential is usually –70 to –90 mV, due to the action of the sodium-potassium adenosine triphosphatase (ATPase) pump, which maintains relatively high extracellular sodium concentrations and relatively low extracellular potassium concentrations. During each action potential cycle, the potential of the membrane increases to a threshold potential, usually –60 to –80 mV. When the membrane potential reaches this threshold, the fast sodium channels open, allowing sodium ions to rapidly enter the cell. This rapid influx of positive ions creates a vertical upstroke of the action potential, such that the potential reaches 20 to 30 mV. This is phase 0, which represents ventricular depolarization. At this point, the fast sodium channels become inactivated, and ventricular repolarization begins. The remaining phases of the action potential, 1 through 4, represent ventricular repolarization. Phase 1 repolarization occurs primarily as a result of an efflux of potassium ions (Fig. 6–2).[2] During phase 2 repolarization, potassium ions continue to exit the cell, but the membrane potential is balanced by an influx of calcium and sodium ions, transported through slow calcium and slow sodium channels, resulting in a plateau. During phase 3, the efflux of potassium ions greatly exceeds calcium and sodium influx, resulting in the major component of ventricular repolarization. During phase 4, sodium ions are actively pumped out of the myocyte via the sodium-potassium ATPase pump, resulting in restoration of membrane potential to its resting value. An understanding of the ionic fluxes that are responsible for each phase of the action potential facilitates understanding of the effects of specific drugs on the action potential. For example, drugs that primarily inhibit ion flux through sodium channels influence phase 0 (ventricular depolarization), while drugs that primarily inhibit ion flux through potassium channels influence the repolarization phases, particularly phase 3.

The Electrocardiogram

The **electrocardiogram** (ECG) is a non-invasive means of measuring the electrical activity of the heart. The relationship

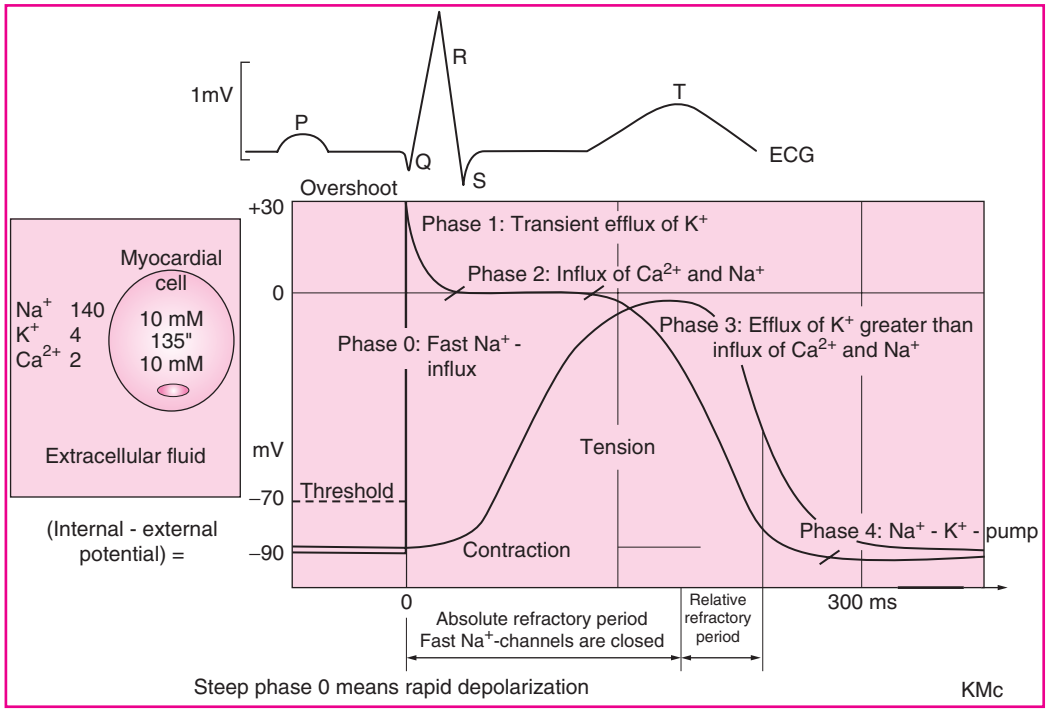


FIGURE 6–2. The ventricular action potential depicting the flow of specific ions responsible for each phase. The specific phases of the action potential that correspond to the absolute and relative refractory periods are portrayed, and the relationship between phases of the action potential and the ECG are shown. Ca, calcium; ECG, electrocardiogram; K, potassium; Na, sodium. (Reprinted with permission from Pauler P-E. *Textbook in Medical Physiology and Pathophysiology, Essentials and Clinical Problems*. Copenhagen: Copenhagen Medical Publishers; 2000.[2]) Accessed at http://www.mfi.ku.dk/ppauler/chapter11/chapter%2011.htm.

between the ventricular action potential and the ECG is depicted in Fig. 6–2.[2] The P wave on the ECG represents atrial depolarization (atrial depolarization is not depicted in the action potential shown in Fig. 6–2, which shows only the ventricular action potential, but not the atrial action potential). Phase 0 of the action potential corresponds to the QRS complex; therefore, the QRS complex on the ECG is a non-invasive representation of ventricular depolarization. The T wave on the ECG corresponds to phase 3 repolarization of the ventricles. The interval from the beginning of the Q wave to the end of the T wave, known as the QT interval, is used as a non-invasive marker of ventricular repolarization time. Atrial repolarization is not displayed on the ECG, because it occurs during ventricular depolarization and is obscured by the QRS complex.

Several intervals and durations are routinely measured on the ECG. The PR interval represents the time of conduction of impulses from the atria to the ventricles through the AV node; the normal PR interval in adults is 0.12 to 0.2 seconds. The QRS duration represents the time required for ventricular depolarization, which is normally 0.08 to 0.12 seconds in adults. The QT interval represents the time required for ventricular repolarization. The QT interval varies with heart rate—the faster the heart rate, the shorter the QT interval, and vice versa. Therefore, the QT interval is corrected for heart rate using Bazett's equation[3], which is:

$$QT_C = \frac{QT}{\sqrt{RR}}$$

where QTc is the QT interval corrected for rate, and RR is the interval from the onset of one QRS complex to the onset of the next QRS complex, measured in seconds. The normal QTc interval in adults is 0.36 to 0.44 seconds.

Refractory Periods

After an electrical impulse is initiated and conducted, there is a period of time during which cells and fibers cannot be depolarized again. This period of time is referred to as the absolute **refractory period** (Fig. 6–2),[2] and corresponds to phases 1, 2, and approximately half of phase 3 repolarization on the action potential. The absolute refractory period also corresponds to the period from the Q wave to approximately the first half of the T wave on the ECG (Fig. 6–2). During this period, if there is a premature stimulus for an electrical impulse, this impulse cannot be conducted, because the tissue is absolutely refractory.

However, there is a period of time following the absolute refractory period during which a premature electrical stimulus can be conducted, and is often conducted abnormally. This period of time is called the relative refractory period (Fig. 6–2).[2] The relative refractory period corresponds roughly to the latter half of phase 3 repolarization on the action potential and to the latter half of the T wave on the ECG. If a new (premature) electrical stimulus is initiated during the relative refractory period, it can be conducted abnormally, potentially in an arrhythmia.

Mechanisms of Cardiac Arrhythmias

❶ *In general, cardiac arrhythmias are caused by (1) abnormal impulse formation; (2) abnormal impulse conduction; or (3) both.*

Abnormal Impulse Initiation

Abnormal initiation of electrical impulses occurs as a result of abnormal automaticity. If the automaticity of the SA node increases, this results in an increased rate of generation of impulses and a rapid heart rate (sinus tachycardia). If other cardiac fibers become abnormally automatic, such that the rate of initiation of spontaneous impulses exceeds that of the SA node, other types of tachyarrhythmias may occur. Many cardiac fibers possess the capability for automaticity, including the atrial tissue, the AV node, the Purkinje fibers, and the ventricular tissue. In addition, fibers with the capability of initiating and conducting electrical impulses are present in the pulmonary veins. Abnormal atrial automaticity may result in premature atrial contractions or may precipitate atrial tachycardia or atrial fibrillation (AF); abnormal AV nodal automaticity may result in "junctional tachycardia" (the AV node is also sometimes referred to as the AV junction). Abnormal automaticity in the ventricles may result in ventricular premature depolarizations (VPDs) or may precipitate ventricular tachycardia (VT) or ventricular fibrillation (VF). In addition, abnormal automaticity originating from the pulmonary veins is a precipitant of AF.

Automaticity of cardiac fibers is controlled in part by activity of the sympathetic and parasympathetic nervous systems. Enhanced activity of the sympathetic nervous system may result in increased automaticity of the SA node or other automatic cardiac fibers. Enhanced activity of the parasympathetic nervous system tends to suppress automaticity; conversely, inhibition of activity of the parasympathetic nervous system increases automaticity. Other factors may lead to abnormal increases in automaticity of extra-SA nodal tissues, including hypoxia, atrial or ventricular stretch [as might occur following long-standing hypertension or after the development of heart failure (HF)], and electrolyte abnormalities such as hypokalemia or hypomagnesemia.

Abnormal Impulse Conduction

The mechanism of abnormal impulse conduction is traditionally referred to as "reentry." ❶ *Reentry is often initiated as a result of an abnormal premature electrical impulse (abnormal automaticity); therefore, in these situations, the mechanism of the arrhythmia is both abnormal impulse formation (automaticity) and abnormal impulse conduction (reentry).* In order for reentry to occur, three conditions must be present. There must be (1) at least two pathways down which an electrical impulse may

travel (which is the case in the majority of cardiac fibers); (2) a "unidirectional block" in one of the conduction pathways (this "unidirectional block" is sometimes a result of prolonged refractoriness in this pathway); and (3) slowing of the velocity of impulse conduction down the other conduction pathway.

The process of reentry is depicted in Fig. 6–3.[4] Under normal circumstances, when a premature impulse is initiated, it cannot be conducted in either direction down either pathway because the tissue is in its absolute refractory period from the previous beat. A premature impulse may be conducted down both pathways if it is only slightly premature and arrives after the tissue is no longer refractory. However, when refractoriness is prolonged down one of the pathways, a precisely timed premature beat may be conducted down one pathway, but cannot be conducted in either direction in the pathway with prolonged refractoriness because the tissue is still in its absolute refractory period (Fig. 6–3, panel 1a).[4] When the third condition for reentry is present, that is, when the velocity of impulse conduction in the other pathway is slowed, the impulse traveling forward down the other pathway still cannot be conducted. However, because the impulse in the other pathway is traveling so slowly, by the time it circles around and travels upward down the other pathway, that pathway is no longer in its absolute refractory period, and now the impulse may travel upward in that pathway. In other words, the electrical impulse "reenters" a previously stimulated pathway in the wrong direction. This results in circular movement of electrical impulses; as the impulse travels in this circular fashion, it excites each cell around it, and if the impulse is traveling at a rate faster than the intrinsic rate of the SA node, a tachycardia occurs in the tissue in question. Reentry may occur in numerous tissues, including the atria, the AV node, and the ventricles.

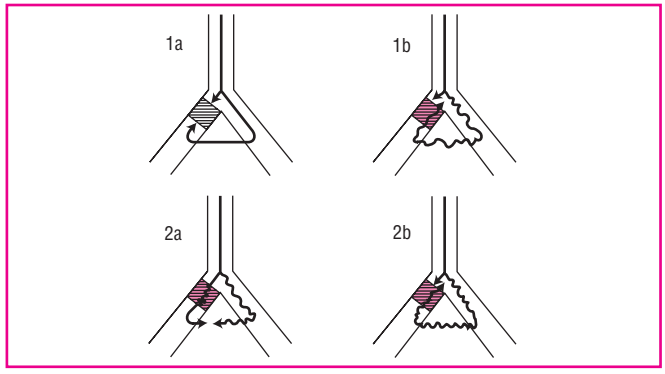


FIGURE 6–3. The process of initiation of reentry. (1a) Two pathways for impulse conduction, with bidirectional block in one pathway (shaded area), resulting in a non-viable reentrant loop. (1b) Two pathways for impulse conduction; slowing of conduction down one pathway, with no change in refractory period down the other pathway, resulting in unidirectional block. The retrograde impulse may reenter the area of unidirectional block, potentially resulting in a tachyarrhythmia. (2a) Two pathways for impulse conduction; lack of unidirectional block, therefore the potential reentrant pathway is non-viable. (2b) Two pathways for impulse conduction; refractory period is prolonged down one pathway, with no change in conduction down the other pathway, resulting in unidirectional block. The retrograde impulse may reenter the area of unidirectional block, potentially resulting in a tachyarrhythmia. (Reprinted with permission from Bauman JL, Dekker Schoen M. Arrhythmias. In: DiPiro JT, Talbert RL, Yee GC, et al. (eds.) *Pharmacotherapy. A Physiologic Approach*, 6th ed. New York: McGraw-Hill; 2005:324.[4])

Prolonged refractoriness and/or slowed impulse conduction velocity may be present in cardiac tissues for a variety of reasons. Myocardial ischemia may alter ventricular refractory periods or impulse conduction velocity, facilitating ventricular reentry. In patients with past myocardial infarction, the infarcted myocardium is dead and cannot conduct impulses. However, there is typically a border zone of tissue which is damaged, and in which refractory periods and conduction velocity are often deranged, facilitating ventricular reentry. In patients with left atrial or LV hypertrophy as a result of long-standing hypertension, refractory periods and conduction velocity are often perturbed. In patients with HF due to LV dysfunction, ventricular refractoriness and conduction velocity are often altered due to LV hypertrophy, collagen deposition, and other anatomic and structural changes.

Vaughan-Williams Classification of Anti-arrhythmic Drugs

The Vaughan-Williams classification of antiarrhythmic drugs, first described in 1970[5] and subsequently further expanded,[6,7] is presented in Table 6–1. This classification is based on the effects of specific drugs on ventricular conduction velocity, repolarization/refractoriness and automaticity. Class I drugs, which are the sodium channel blocking agents, primarily inhibit ventricular automaticity and slow conduction velocity. However, due to differences in the potency of the drugs to slow conduction velocity, the class I drugs are subdivided into class IA, IB, and IC. The class IC drugs have the greatest potency for slowing ventricular conduction, the class IA drugs have intermediate potency, and the class IB drugs have the lowest potency, with minimal effects on conduction velocity. Class II drugs are the adrenergic β-receptor inhibitors (β-blockers), class III drugs are those that inhibit ventricular repolarization or prolong refractoriness, and class IV drugs are the calcium channel blockers (CCBs), diltiazem and verapamil.

The Vaughan-Williams classification of antiarrhythmic drugs has been criticized for a number of reasons. The classification is based on the effects of drugs on normal, rather than diseased, myocardium. In addition, many of the drugs may be placed into more than one class. For example, the class IA drugs prolong repolarization/refractoriness, either via the parent drug[8,9] or an active metabolite,[10] and therefore also may be placed in class III. Sotalol is also a β-blocker, and therefore fits into class II. Amiodarone inhibits sodium and potassium channels, is a non-competitive inhibitor of β-receptors, and inhibits calcium

TABLE 6–1. Vaughan-Williams Classification of Anti-arrhythmic Agents*

Class	Drug	Conduction Velocity	Repolarization/ Refractoriness	Automaticity
IA	Quinidine Procainamide Disopyramide	↓	↑	↓
IB	Lidocaine Mexiletine Tocainide	0/↓	↓/0	↓
IC	Flecainide Moricizine Propafenone	↓↓	0	↓
II	β-blockers:[a] Acebutolol Atenolol Betaxolol Bisoprolol Carteolol Carvedilol[b] Esmolol Labetalol[b] Metoprolol Nadolol Penbutolol Pindolol Propranolol Timolol	0	0	0
III	Amiodarone[c] Dofetilide Ibutilide Sotalol	0	↑	0
IV	Calcium channel blockers:[a] Diltiazem Verapamil	0	0	0

↑, increase/prolong; ↓, decrease; 0, no effect; 0/↓, does not change or may decrease: ↓/0, decreases or does not change.
*Adenosine and digoxin are agents used for the management of arrhythmias that do not fit into the Vaughan Williams classification.
[a]Slows conduction, prolongs refractory period, and reduces automaticity in SA node and AV node tissue, but not in the ventricles.
[b]Combined α and β-blocker.
[c]Amiodarone slows conduction velocity and inhibits automaticity.

channels, and therefore may be placed into any of the four classes. For this reason, drugs within each class cannot be considered "interchangeable." Nonetheless, despite attempts to develop mechanism-based classifications that better distinguish the actions of antiarrhythmic drugs,[11] the Vaughan-Williams classification continues to be widely used because of its simplicity and the fact that it is relatively easy to remember and understand.

CARDIAC ARRHYTHMIAS

In general, cardiac arrhythmias are classified into two broad categories: supraventricular (those occurring above the ventricles) and ventricular (those occurring in the ventricles). The names of specific arrhythmias are generally composed of two words; the first word indicates the location of the electrophysiologic abnormality resulting in the arrhythmia (sinus, AV node, atrial, or ventricular), and the second word describes the arrhythmia in terms of whether it is abnormally slow (bradycardia) or fast (tachycardia), or the type of arrhythmia (block, fibrillation, or flutter).

SUPRAVENTRICULAR ARRHYTHMIAS

Sinus Bradycardia

Sinus bradycardia is an arrhythmia that originates in the SA node, defined by a sinus rate less than 60 beats per minute (bpm).[12]

Epidemiology and Etiology

Many individuals, particularly those who partake in regular vigorous exercise, have heart rates less than 60 bpm. For those individuals, sinus bradycardia is normal and healthy, and does not require evaluation or treatment. However, some individuals develop symptomatic sinus node dysfunction. In the absence of correctable underlying causes, idiopathic sinus node dysfunction is referred to as "sick sinus syndrome,[12]" and occurs with greater frequency with advancing age. The prevalence of sick sinus syndrome is approximately 1 in 600 individuals over the age of 65 years.[12]

Sick sinus syndrome leading to sinus bradycardia may be caused by degenerative changes in the sinus node that occur with advancing age. ❷ *However, there are other possible etiologies of sinus bradycardia, including drugs (Table 6–2).*[13]

TABLE 6–2. Etiologies of Sinus Bradycardia[12,13]

Idiopathic ("sick sinus syndrome")
Myocardial ischemia
Carotid-sinus hypersensitivity
Neurocardiac syncope
Electrolyte abnormalities: hypokalemia or hyperkalemia
Hypothyroidism
Hypothermia
Amyloidosis
Sarcoidosis
Systemic lupus erythematosus
Scleroderma
Sleep apnea
Drugs:

Amiodarone	Flecainide
β-Blockers	Fluoxetine
Cisplatin	Isradipine
Citalopram	Nitroglycerin
Clonidine	Propafenone
Cocaine	Sotalol
Digoxin	Thalidomide
Diltiazem	Verapamil
Donepezil	



Clinical Presentation and Diagnosis: Sinus Bradycardia

Symptoms

- Many patients are asymptomatic, particularly those with normal resting heart rates less than 60 bpm as a result of physical fitness due to regular vigorous exercise.
- Susceptible patients may develop symptoms, depending on the degree of heart rate lowering.
- Symptoms of bradyarrhythmias include dizziness, fatigue, lightheadedness, syncope, chest pain (in patients with underlying myocardial ischemia), and shortness of breath and other symptoms of heart failure (in patients with underlying left ventricular dysfunction).

Diagnosis

- Cannot be made on the basis of symptoms alone, as the symptoms of all bradyarrhythmias are similar.
- History of present illness, presenting symptoms, and 12-lead ECG that reveals sinus bradycardia.
- Assess possible correctable etiologies, including myocardial ischemia, serum potassium concentration (for hyperkalemia), and thyroid function tests (for hypothyroidism).
- Determine whether the patient is taking any drugs known to cause sinus bradycardia. If the patient is currently taking digoxin, determine the serum digoxin concentration and ascertain whether it is supratherapeutic (greater than 2 ng/mL [2.56 nmol/L]).

Pathophysiology

Sick sinus syndrome leading to sinus bradycardia occurs as a result of fibrotic tissue in the SA node, which replaces normal SA node tissue.[12]

Treatment

Desired Outcomes

The desired outcomes for treatment are to restore normal heart rate and alleviate patient symptoms.

Pharmacologic Therapy

Treatment of sinus bradycardia is only necessary in patients who become symptomatic. ❷ *If the patient is taking any medication(s) that may cause sinus bradycardia, the drug(s) should be discontinued whenever possible.* If the patient remains in sinus bradycardia after discontinuation of the drug(s) and after five half-lives of the drug(s) have elapsed, then the drugs(s) can usually be excluded as the etiology of the arrhythmia. In certain circumstances, however, discontinuation of the medication(s) may be undesirable, even if it may be the cause of symptomatic sinus bradycardia. For example, if the patient has a history of myocardial infarction or HF, discontinuation of a β-blocker is undesirable, because β-blockers have been shown to reduce mortality and prolong life in patients with those diseases, and the benefits of therapy with β-blockers outweigh the risks associated with sinus bradycardia. In these patients, a permanent pacemaker may be implanted in order to allow the patient to maintain therapy with β-blockers.

Acute treatment of the symptomatic patient consists primarily of administration of the anticholinergic drug atropine, which may be given in doses of 0.5 mg intravenously (IV) every 3 to 5 minutes. The maximum recommended total dose of atropine is 3 mg;[14] however, this total dose should not be administered to patients with sinus bradycardia, but rather should be reserved for patients with cardiac arrest due to asystole, as complete vagal inhibition at this dose can increase myocardial oxygen demand and precipitate ischemia or tachyarrhythmias in patients with underlying coronary artery disease (CAD). Therefore, for management of sinus bradycardia, the maximum atropine dose should be approximately 2 mg. In patients with hemodynamically unstable or severely symptomatic sinus bradycardia that is unresponsive to atropine and in whom temporary or **transvenous pacing** is not available or is ineffective, epinephrine (2 to 10 mcg/minute, titrate to response) and/or dopamine (2 to 10 mcg/kg/minute) may be administered.[14] Both drugs stimulate adrenergic α- and β-receptors.

In patients with sinus bradycardia due to underlying correctable disorders (such as electrolyte abnormalities or hypothyroidism), management consists of correcting those disorders.

Nonpharmacologic Therapy

Long-term management of patients with sick sinus syndrome requires implantation of a permanent pacemaker.[12]

Outcome Evaluation

- Monitor the patient for heart rate and alleviation of symptoms.
- Monitor for adverse effects of medications, such as atropine (dry mouth, mydriasis, urinary retention, and tachycardia).

AV Nodal Blockade

AV nodal blockade occurs when conduction of electrical impulses through the AV node is impaired to varying degrees. AV nodal blockade is classified into three categories. First-degree AV block is defined simply as prolongation of the PR interval to greater than 0.2 seconds. During first-degree AV block, all impulses initiated by the SA node that have resulted in atrial depolarization are conducted through the AV node; the abnormality is simply that the impulses are conducted more slowly than normal through the AV node, resulting in prolongation of the PR interval.[15] Second-degree AV block is further distinguished into two types: Mobitz type I (also known as Wenckebach) and Mobitz type II. In both types of second-degree AV block, some of the impulses initiated by the SA node are not conducted through the AV node. This often occurs in a regular pattern; for example, every third or fourth impulse

generated by the SA node may not be conducted. During third-degree AV block, which is also referred to as "complete heart block," none of the impulses generated by the SA node are conducted through the AV node. This results in "AV dissociation," during which the atria continue to depolarize normally as a result of normal impulses initiated by the SA node; however, the ventricles initiate their own depolarizations, because no SA node–generated impulses are conducted to the ventricles. Therefore, on the ECG, there is no relationship between the P waves and the QRS complexes.

Epidemiology and Etiology

The incidence of AV nodal blockade is unknown. AV nodal blockade may be caused by degenerative changes in the AV node. ❷ *In addition, there are many other possible etiologies of AV nodal blockade, including drugs (Table 6–3).*[13]

Pathophysiology

First-degree AV nodal blockade occurs due to inhibition of conduction within the upper portion of the node.[15] Mobitz type I second-degree AV nodal blockade occurs as a result of inhibition of conduction further down within the node.[12,15] Mobitz type II second-degree AV nodal blockade is caused by inhibition of conduction within or below the level of the bundle of His.[12,15] Third-degree AV nodal blockade may be a result of inhibition of conduction either within the AV node or within the bundle of His or the His-Purkinje system.[12,15] AV block may occur as a result of age-related AV node degeneration.



Clinical Presentation and Diagnosis: AV Nodal Blockade

Symptoms

- First-degree AV nodal blockade is rarely symptomatic, because it rarely results in bradycardia.
- Second-degree AV nodal blockade may cause bradycardia, as not all impulses generated by the SA node are conducted through the AV node to the ventricles.
- In third-degree AV nodal blockade, or complete heart block, the heart rate is usually 30 to 40 bpm, resulting in symptoms.
- Symptoms of bradyarrhythmias such as second- or third-degree AV block consist of dizziness, fatigue, lightheadedness, syncope, chest pain (in patients with underlying myocardial ischemia), and shortness of breath and other symptoms of heart failure (in patients with underlying left ventricular dysfunction).

Diagnosis

- Made on the basis of patient presentation, including history of present illness and presenting symptoms, as well as a 12-lead ECG that reveals AV nodal blockade.
- Assess potentially correctable etiologies, including myocardial ischemia, serum potassium concentration (for hyperkalemia), and thyroid function tests (for hypothyroidism)
- Determine whether the patient is taking any drugs known to cause AV block.
- If the patient is currently taking digoxin, determine the serum digoxin concentration and ascertain whether it is supratherapeutic (greater than 2 ng/mL [2.56 nmol/L]).

TABLE 6–3. Etiologies of Atrioventricular Nodal Blockade[12,13,15]

Idiopathic degeneration of the atrioventricular node	
Myocardial ischemia or infarction	
Neurocardiac syncope	
Carotid-sinus hypersensitivity	
Electrolyte abnormalities: hypokalemia or hyperkalemia	
Hypothyroidism	
Hypothermia	
Infectious diseases: Chagas' disease or endocarditis	
Amyloidosis	
Sarcoidosis	
Systemic lupus erythematosus	
Scleroderma	
Sleep apnea	
Drugs:	
Adenosine	Hydroxychloroquine
β-Blockers	Phenylpropanolamine
Amiodarone	Propafenone
Carbamazepine	Propofol
Chloroquine	Sotalol
Digoxin	Thioridazine
Diltiazem	Tricyclic antidepressants
Gatifloxacin	Verapamil

Treatment

Desired Outcomes

The desired outcomes for treatment are to restore normal sinus rhythm and alleviate patient symptoms.

Pharmacologic Therapy

Treatment of first-degree AV nodal blockade is rarely necessary, because symptoms rarely occur. However, the ECGs of patients with first-degree AV nodal blockade should be monitored to assess the possibility of progression of first-degree AV nodal blockade to second- or third-degree block. Second- or third-degree AV nodal blockade requires treatment, because bradycardia usually results in symptoms. If the patient is taking any medication(s) that may cause AV nodal blockade, the drug(s) should be discontinued whenever possible. If the patient's rhythm still exhibits AV nodal blockade after discontinuing the medication(s) and after five half-lives of the drug(s) have elapsed, then the drug(s) can usually be excluded as the etiology of the arrhythmia. However, in certain circumstances, discontinuation of a medication that is

inducing AV nodal blockade may be undesirable. For example, if the patient has a history of myocardial infarction or HF, discontinuation of a β-blocker is undesirable because β-blockers have been shown to reduce mortality and prolong life in patients with those diseases, and the benefits of therapy with β-blockers outweighs the risks associated with AV nodal blockade. In these patients, a permanent pacemaker may be implanted in order to allow the patient to maintain therapy with β-blockers.

Acute treatment of patients with second- or third-degree AV nodal blockade consists primarily of administration of atropine, which may be administered in the same doses as recommended for management of sinus bradycardia. In patients with hemodynamically unstable or severely symptomatic AV nodal blockade that is unresponsive to atropine and in whom temporary or transvenous pacing is not available or is ineffective, epinephrine (2 to 10 mcg/minute, titrate to response) and/or dopamine (2 to 10 mcg/kg/minute) may be administered.[14]

In patients with second- or third-degree AV block due to underlying correctable disorders (such as electrolyte abnormalities or hypothyroidism), management consists of correcting those disorders.

Nonpharmacologic Therapy

Long-term management of patients with AV nodal blockade due to idiopathic degeneration of the AV node requires implantation of a permanent pacemaker.[12]

Outcome Evaluation

- Monitor the patient for termination of AV nodal blockade and restoration of normal sinus rhythm, heart rate, and alleviation of symptoms.
- If atropine is administered, monitor the patient for adverse effects including dry mouth, mydriasis, urinary retention, and tachycardia.

Atrial Fibrillation

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice. It is important for clinicians to understand AF, because it is associated with substantial morbidity and mortality and because many strategies for drug therapy are available. Drugs used to treat AF often have a narrow therapeutic index and a broad adverse effect profile.

Epidemiology and Etiology

Approximately 2.3 million Americans have AF. The prevalence of AF increases with advancing age; roughly 9% of patients between the ages of 80 and 89 years have AF.[16] Similarly, the incidence of AF increases with age, and it occurs more commonly in men than women.[16]

Etiologies of AF are presented in Table 6–4. The common feature of the majority of etiologies of AF is the development of left atrial hypertrophy. Hypertension may be the most important risk factor for development of AF. However, AF occurs commonly in patients with CAD. In addition, HF is increasingly recognized as a cause of AF; approximately 25% to 30% of patients with New York Heart Association (NYHA) class III heart failure have AF,[17] and the arrhythmia is present in as many as 50% of patients with NYHA class IV heart failure.[18]

TABLE 6–4. Etiologies of Atrial Fibrillation

Hypertension	
Coronary artery disease	
Heart failure	
Diabetes	
Hyperthyroidism	
Rheumatic heart disease	
Diseases of the heart valves:	
Mitral stenosis or regurgitation	
Mitral valve prolapse	
Chronic obstructive pulmonary disease	
Pulmonary embolism	
Idiopathic ("lone" atrial fibrillation)	
Thoracic surgery:	
Coronary artery bypass graft surgery	
Pulmonary resection	
Thoracoabdominal esophagectomy	
Drugs:[13]	
Adenosine	Milrinone
Albuterol	Theophylline
Alcohol	
Ipratropium bromide	

Drug-induced AF is relatively uncommon, and the list of drugs that may induce AF is relatively small.[13] However, acute ingestion of large amounts of alcohol may cause AF; this phenomenon has been referred to as the "holiday heart" syndrome.[19]

Pathophysiology

❶ *Atrial fibrillation may be caused by both abnormal impulse formation and abnormal impulse conduction.* Traditionally, AF was believed to be initiated by premature impulses initiated in the atria. However, it is now understood that in many patients AF is triggered by electrical impulses generated within the pulmonary veins.[20] These impulses initiate the process of reentry within the atria, and AF is believed to be sustained by multiple reentrant wavelets operating simultaneously within the atria.[21] Some believe that, at least in some patients, the increased automaticity in the pulmonary veins may be the sole mechanism of AF and that the multiple reentrant wavelet hypothesis may be incorrect.[21] However, the concept of multiple simultaneous reentrant wavelets remains the predominant hypothesis regarding the mechanism of AF.

Atrial fibrillation leads to electrical remodeling of the atria. Episodes of AF that are of longer duration and episodes that occur with increasing frequency result in progressive shortening of atrial refractory periods, further potentiating the reentrant circuits in the atria.[22] Therefore, it is often said that "atrial



Clinical Presentation and Diagnosis: Atrial Fibrillation

Symptoms

- Approximately 20% to 30% of patients with AF remain asymptomatic.
- Symptoms typical of tachyarrhythmias include palpitations, dizziness, lightheadedness, shortness of breath, chest pain (if underlying CAD is present), near-syncope, and syncope. Patients commonly complain of palpitations; often the complaint is "I can feel my heart beating fast" or "It feels like my heart is going to beat out of my chest."
- Other symptoms are dependent on the degree to which cardiac output is diminished, which is in turn dependent on the heart rate and the degree to which **stroke volume** is reduced by the rapidly beating heart.
- In some patients, the first symptom of AF is stroke.

Diagnosis

- Because the symptoms of all tachyarrhythmias are dependent on heart rate and are therefore essentially the same, the diagnosis depends on the presence of AF on the ECG.
- Atrial fibrillation is characterized on ECG by an absence of P waves, an undulating baseline that represents roughly 350 to 600 attempted atrial depolarizations per minute, and an irregularly irregular rhythm, meaning that the intervals between the R waves are irregular and that there is no pattern to the irregularity.

fibrillation begets atrial fibrillation," that is, AF causes atrial electrophysiologic alterations that promote further AF.[21,22]

The AV node is incapable of conducting 350 to 600 impulses per minute; however, it may conduct 100 to 200 impulses per minute, resulting in ventricular rates ranging from 100 to 200 bpm.

Atrial fibrillation is classified as **paroxysmal,** persistent, or permanent (Fig. 6–4).[23] Patients with paroxysmal AF have episodes that start suddenly and spontaneously, last minutes to hours, or rarely as long as 7 days, and terminate suddenly and spontaneously. Some patients with paroxysmal AF have episodes that do not terminate spontaneously but require intervention, and this is known as persistent AF. Approximately one-third of patients with AF progress to the point of permanent AF; these patients are subsequently never in normal sinus rhythm, but rather are always in AF.

Atrial fibrillation is associated with substantial morbidity and mortality. Atrial fibrillation is associated with a risk of ischemic stroke of approximately 5% per year.[23] The risk of stroke is increased two- to seven-fold in patients with AF compared to patients without this arrhythmia.[23] Atrial fibrillation is the cause of roughly one of every six strokes.[21] During AF, atrial contraction is absent. Therefore, due to the fact that atrial contraction is responsible for approximately 30% of left ventricular filling, this blood that is not ejected from the left atrium to the left ventricle pools in the atrium, particularly in the left atrial appendage. Blood pooling facilitates the formation of a thrombus, which subsequently may travel through the mitral valve into the left ventricle and may be ejected during ventricular contraction. The thrombus then may travel through a carotid artery into the brain, resulting in an ischemic stroke.



Patient Encounter, Part 1

DA is a 58-year-old male who presents to the emergency department (ED) complaining that his "heart is beating fast," which started when he was taking out the garbage. He also complains of feeling lightheaded and short of breath. His pulse is irregularly irregular, with a rate of 135 bpm.

- What information is suggestive of atrial fibrillation?
- What additional information do you need in order to develop a treatment plan?



Patient Encounter, Part 2: Medical History, Physical Exam and Diagnostic Tests

PMH

Hypertension × 15 years
Coronary artery disease × 10 years
Myocardial infarction 1998
Heart failure × 3 years

Meds

Aspirin 81 mg once daily
Metoprolol 50 mg twice daily
Enalapril 5 mg twice daily
Furosemide 40 mg daily

PE

Height 5'10" (178 cm), wt. 80 kg (176 lb), BP 110/70 mm Hg, pulse 135 bpm, RR 20/minute; remainder of physical exam non-contributory

Labs

All within normal limits

Chest x-ray: Mild pulmonary edema

Echo: Moderately reduced left ventricular function, left ventricular ejection fraction 35%

ECG: Atrial fibrillation

- What is your assessment of DA's condition?
- What are your treatment goals?
- What pharmacologic or nonpharmacologic alternatives are available for each treatment goal?

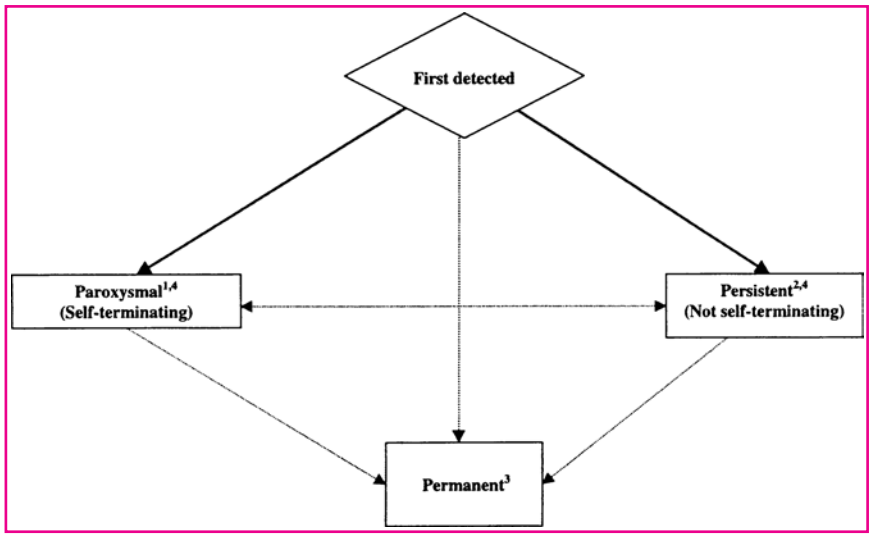


FIGURE 6–4. Classification of atrial fibrillation. [1]Episodes that generally last less than or equal to 7 days (most less than 24 hours). [2]Episodes that usually last greater than 7 days. [3]Cardioversion failed or not attempted. [4]Either paroxysmal or persistent atrial fibrillation may be recurrent. (Reprinted with permission from Fuster V, Rydén LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology, American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients with Atrial Fibrillation). J Am Coll Cardiol 2001; 38:1266i–lxx.[23])

Atrial fibrillation leads to the development of HF, as a result of tachycardia-induced cardiomyopathy.[25] Atrial fibrillation increases the risk of mortality approximately two-fold compared to that in patients without AF;[23] the causes of death are likely stroke or HF.

Treatment

Desired Outcomes

❸ *The goals of therapy of AF are: (1) ventricular rate control; (2) termination of AF and restoration of sinus rhythm (commonly referred to as "cardioversion" or "conversion to sinus rhythm"); (3) maintenance of sinus rhythm, or reduction in the frequency of episodes of paroxysmal AF; and (4) prevention of stroke.*

Hemodynamically Unstable AF

For patients who present with an episode of AF that is hemodynamically unstable, emergent conversion to sinus rhythm is necessary using **direct current cardioversion** (DCC). Hemodynamic instability may be defined as the presence of any one of the following:[14] (1) patient has altered mental status, (2) hypotension (systolic blood pressure less than 90 mm Hg) or other signs of shock, (3) ventricular rate greater than 150 bpm, and/or (4) patient is experiencing squeezing, crushing chest pain suggestive of myocardial ischemia.

Direct current cardioversion is the process of administering a synchronized electrical shock to the chest. The purpose of DCC is to simultaneously depolarize all of the myocardial cells, resulting in interruption and termination of the multiple reentrant circuits and restoration of normal sinus rhythm. The initial energy level of the shock is 100 joules (J); if the DCC attempt is unsuccessful, successive cardioversion attempts may be made at 200, 300, and 360 J.[14] Delivery of the shock is synchronized to the ECG by the cardioverter machine, such that the electrical charge is not delivered during the latter portion of the T wave (i.e., the relative refractory period), to avoid delivering an electrical impulse that may be conducted abnormally, which may result in a life-threatening ventricular arrhythmia.

The remainder of this section will be devoted to management of hemodynamically stable AF.

Pharmacologic Therapy

Ventricular Rate Control is achieved by inhibiting the proportion of electrical impulses conducted from the atria to the ventricles through the AV node. Therefore, drugs that are effective for ventricular rate control are those that inhibit AV nodal impulse conduction: β-blockers, diltiazem, verapamil, and digoxin (Tables 6–5 and 6–6). Amiodarone also inhibits AV nodal conduction, but is not a preferred drug for ventricular rate control in AF due to its unfavorable adverse-effect profile (Table 6–6).

In patients who present with their first detected episode of AF, or for those who present with an episode of persistent AF, ventricular rate control is usually initially achieved using intravenous drugs. A decision algorithm for selecting a specific drug for acute ventricular rate control is presented in Fig. 6–5. In general, IV diltiazem is a preferred drug for ventricular rate control in patients with normal LV function, as ventricular rate control can often be achieved within several minutes. In patients with HF due to LV dysfunction, digoxin may be preferred because diltiazem is associated with negative inotropic effects and may exacerbate HF.[26] However, in patients with HF who are substantially symptomatic and in whom it is undesirable to wait 4 to 6 hours for the effects of digoxin to occur, IV diltiazem may be used for up to 24 hours without inducing HF exacerbation in most patients.

A decision strategy for long-term rate control in patients with paroxysmal or permanent AF is presented in Fig. 6–6. In general, while digoxin is effective for ventricular rate control in

TABLE 6–5. Drugs for Ventricular Rate Control in Atrial Fibrillation

Drug	Mechanism of Action	Loading Dose	Daily Dose	Drug Interactions
β-Blockers[a]	Inhibit AV nodal conduction by slowing AV nodal conduction and prolonging AV nodal refractoriness	Esmolol: 500 mcg/kg IV over 1 minute Propranolol: 0.15 mg/kg IV Metoprolol: 2.5–5 mg IV × 2–3 doses	Esmolol: 50–200 mcg/kg/minute continuous infusion Propranolol: 80–240 mg/day Metoprolol: 50–200 mg/day	
Diltiazem	Inhibits AV nodal conduction by slowing AV nodal conduction and prolonging AV nodal refractoriness	1. 0.25 mg/kg IV load over 2 minutes 2. If necessary, 0.35 mg/kg IV over 2 minutes after first dose	Continuous infusion of 5–15 mg/hour Oral: 120–360 mg/day	Inhibits elimination of cyclosporine
Verapamil	Inhibits AV nodal conduction by slowing AV nodal conduction and prolonging AV nodal refractoriness	1. 5–10 mg IV over 2–3 minutes 2. If necessary, an additional dose of 5–10 mg may be administered 30 minutes later	120–360 mg/day	Inhibits digoxin elimination
Digoxin	Inhibits AV nodal conduction by: 1. Vagal stimulation 2. Directly slowing AV nodal conduction and prolonging AV nodal refractoriness	0.25 mg every 2 hours up to 1.5 mg	0.125–0.25 mg PO once daily	Amiodarone, verapamil, quinidine inhibit digoxin elimination

AV, atrioventricular; IV, intravenous; PO, orally.
[a]While oral β-blockers are important agents for mortality reduction in patients with heart failure, intravenous β-blockers should be avoided, due to the potential for heart failure exacerbation.

patients at rest, digoxin is less effective than CCBs or β-blockers for ventricular rate control in patients undergoing physical activity, including activities of daily living. This is likely because activation of the sympathetic nervous system during exercise and activity overwhelms the stimulating effect of digoxin on the parasympathetic nervous system. Therefore, in patients with normal LV function, CCBs or β-blockers are preferred for long-term ventricular rate control. Diltiazem may be preferable to verapamil in older patients due to a lower incidence of constipation. However, in patients with HF, oral diltiazem and verapamil are contraindicated as a result of their negative inotropic activity and propensity to exacerbate HF. Therefore, the options in this population are β-blockers or digoxin. The majority of patients with HF receive therapy with oral β-blockers for the goal of achieving mortality reduction. In patients with HF that develop rapid AF while receiving therapy with β-blockers, digoxin should be administered for purposes of ventricular rate control. Fortunately, studies have found the combination of digoxin and β-blockers to be effective for ventricular rate control, likely as a result of suppression of the inhibitory effects of the sympathetic nervous system on the efficacy of digoxin.

Conversion to Sinus Rhythm Termination of AF in hemodynamically stable patients may be performed using antiarrhythmic drug therapy or elective DCC. Drugs that may be used for conversion to sinus rhythm are presented in Table 6–7; these agents slow atrial conduction velocity and/or prolong refractoriness, facilitating interruption of reentrant circuits and restoration of sinus rhythm. DCC is generally more effective than drug therapy for conversion of AF to sinus rhythm. However, patients who undergo elective DCC must be sedated and/or anesthetized to avoid the discomfort associated with delivery of 100 to 360 J of electricity to the chest. Therefore, it is important that patients scheduled to undergo elective DCC do not eat within approximately 8 to 12 hours of the procedure to avoid aspiration of stomach contents during the period of sedation/anesthesia. This often factors into the decision as to whether to employ elective DCC or drug therapy for conversion of AF to sinus rhythm. If a patient presents with AF requiring conversion to sinus rhythm, and the patient has eaten a meal that day, then pharmacologic methods must be used for cardioversion on that day, or DCC must be postponed to the following day to allow for a period of fasting prior to the procedure.

A decision strategy for conversion of AF to sinus rhythm is presented in Fig. 6–7. The cardioversion decision strategy depends greatly on the duration of AF. If the AF episode began within 48 hours, conversion to sinus rhythm is safe and may be attempted with elective DCC or specific drug therapy (Fig. 6–7). However, if the duration of the AF episode is longer than 48 hours or if there is uncertainty regarding the duration of the episode, two strategies for conversion may be considered. Because data indicate that a thrombus may form in the left

TABLE 6–6. Adverse Effects of Drugs Used to Treat Arrhythmias

Drug	Adverse Effects
Adenosine	Chest pain, flushing, shortness of breath, sinus bradycardia/AV block
Amiodarone	IV: Hypotension, sinus bradycardia Oral: Blue-grey skin discoloration, photosensitivity, corneal microdeposits, pulmonary fibrosis, hepatotoxicity, sinus bradycardia, hypo- or hyperthyroidism, AV block
Atropine	Tachycardia, urinary retention, blurred vision, dry mouth, mydriasis
Digoxin	Nausea, vomiting, anorexia, green-yellow halos around objects, ventricular arrhythmias
Diltiazem	Hypotension, sinus bradycardia, heart failure exacerbation, AV block
Dofetilide	Torsades de pointes
Esmolol	Hypotension, sinus bradycardia, AV block, heart failure exacerbation
Flecainide	Dizziness, blurred vision, heart failure exacerbation
Ibutilide	Torsades de pointes
Lidocaine	Dizziness, confusion, seizures (if dose too high)
Metoprolol	Hypotension, sinus bradycardia, AV block, fatigue, heart failure exacerbation[a]
Procainamide	Hypotension, torsades de pointes
Propafenone	Dizziness, blurred vision
Propranolol	Hypotension, bradycardia, AV block, heart failure exacerbation[a]
Sotalol	Sinus bradycardia, AV block, fatigue, torsades de pointes
Verapamil	Hypotension, heart failure exacerbation, bradycardia, AV block, constipation (oral)

AV, atrioventricular; IV, intravenous.
[a]Associated with intravenous administration, inappropriately high oral doses at initiation of therapy, or overly aggressive and rapid dose titration.

atrium during AF episodes of 48 hours or longer, conversion should be deferred unless it is known that an atrial thrombus is not present. In the past, common practice in patients with AF of greater than 48 hours' duration was to anticoagulate patients with warfarin, maintaining a therapeutic International Normalized Ratio (INR) for 3 weeks, after which cardioversion may be performed. Patients were subsequently anticoagulated for 4 weeks following the restoration of sinus rhythm. Today, rather than send patients with ongoing AF home for 3 weeks of anticoagulation, it is becoming standard practice at many institutions to perform a transesophageal echocardiogram (TEE) to determine whether an atrial thrombus is present; if such a thrombus is not present, DCC or pharmacologic cardioversion may be performed within 24 hours. If this strategy is selected, patients should undergo anticoagulation with intravenous unfractionated heparin, with the dose targeted to a partial thromboplastin time (PTT) of 60 seconds (range 50 to 70 seconds), or warfarin therapy (target INR 2.5; range 2 to 3) for several days prior to the TEE and cardioversion procedure. If no thrombus is present during TEE and cardioversion is successful, patients should undergo anticoagulation with warfarin (target INR 2.5; range 2 to 3) for at least 4 weeks. If a thrombus is observed during TEE, then cardioversion should be postponed and anticoagulation should be continued indefinitely. Another TEE should be performed prior to a subsequent cardioversion attempt.[27]

Conversion of AF to sinus rhythm is usually performed in patients with the first detected episode of AF or in patients with an episode of persistent AF. In patients with permanent AF, conversion to sinus rhythm is usually not attempted because cardioversion is unlikely to be successful, and in those

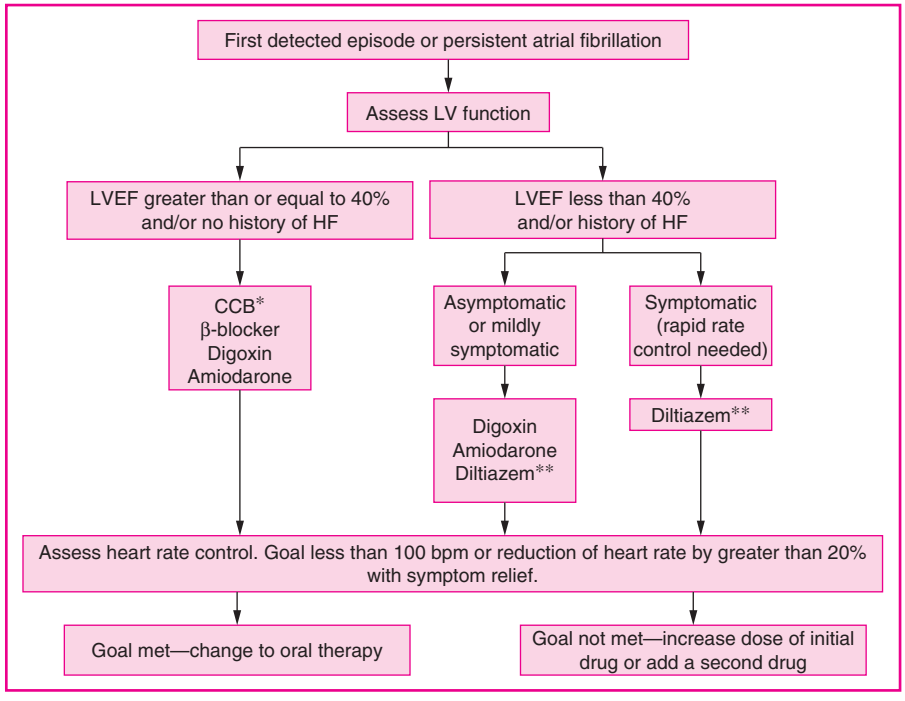


FIGURE 6–5. Decision algorithm for ventricular rate control using intravenous drug therapy for patients presenting with the first detected episode or an episode of persistent atrial fibrillation that is hemodynamically stable.
*Diltiazem is generally preferred over verapamil because of a lower risk of severe hypotension.
**Intravenous diltiazem can be used cautiously for up to 24 hours in patients with non-decompensated heart failure.
bpm, beats per minute; CCB, calcium channel blocker (diltiazem or verapamil); HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction.
(Algorithm adapted with permission from Tisdale JE, Moser LR. Tachyarrhythmias. In: Mueller BA, Bertch KE, Dunsworth TS, et al. (eds.) *Pharmacotherapy Self-Assessment Program*, 4th ed. Kansas City: American College of Clinical Pharmacy; 2001: 217–267.)[50]

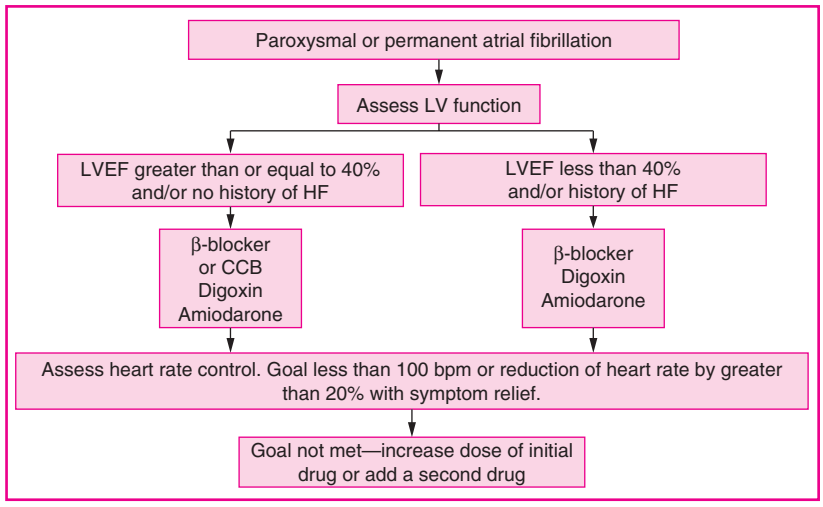


FIGURE 6–6. Decision algorithm for long-term ventricular rate control with oral drug therapy for patients with paroxysmal or permanent atrial fibrillation. bpm, beats per minute; CCB, calcium channel blocker (diltiazem or verapamil); HF, heart failure; LV, left ventricular function; LVEF, left ventricular ejection fraction. (Algorithm adapted with permission from Tisdale JE, Moser LR. Tachyarrhythmias. In: Mueller BA, Bertch KE, Dunsworth TS, et al. (eds.) *Pharmacotherapy Self-Assessment Program*, 4th ed. Kansas City: American College of Clinical Pharmacy; 2001: 217–267.)[50]

patients in whom sinus rhythm is restored successfully, AF usually recurs shortly thereafter.

Maintenance of Sinus Rhythm/Reduction in the Frequency of Episodes of Paroxysmal AF In many patients, permanent maintenance of sinus rhythm following cardioversion is an unrealistic goal. Many, if not most, patients experience recurrence of AF after cardioversion. Therefore, a more realistic goal for many patients is not permanent maintenance of sinus rhythm, but rather reduction in the frequency of episodes of paroxysmal AF.

In recent years, numerous studies have been performed to determine whether drug therapy for maintenance of sinus rhythm is preferred to drug therapy for ventricular rate control.[28–31] In these studies, patients have been assigned randomly to receive therapy either with drugs for rate control or with drugs for rhythm control (Table 6–8). These studies have found

TABLE 6–7. Drugs for Conversion of Atrial Fibrillation to Normal Sinus Rhythm

Treatment	Loading Dose	Continuous Infusion Rate	Drug Interactions
Amiodarone	5–7 mg/kg IV over 30–60 minutes	700–1200 mg over 24 hours	Inhibits elimination of digoxin and warfarin
Dofetilide	See below[a]; patients must be hospitalized for 3 days during initiation of therapy	—	Cimetidine, hydrochlorothiazide, ketoconazole, medroxyprogesterone, promethazine, trimethoprim, verapamil (all inhibit dofetilide elimination)
Ibutilide	1 mg IV over 10 minutes, followed by a second 1 mg IV dose if necessary	—	—
Propafenone	600 mg single oral dose	—	—
Flecainide	200–300 mg single oral dose	—	—
Procainamide	12–17 mg/kg, no faster than 20 mg/minute	1–4 mg/minute	Cimetidine, ranitidine, and trimethoprim inhibit procainamide elimination

IV, intravenously.

[a]Dofetilide dosing:

Calculated Creatinine Clearance	Dofetilide Dose
Greater than 60 mL/minute	500 mcg twice daily
40–60 mL/minute	250 mcg twice daily
20–40 mL/minute	125 mcg twice daily
Less than 20mL/minute	Contraindicated

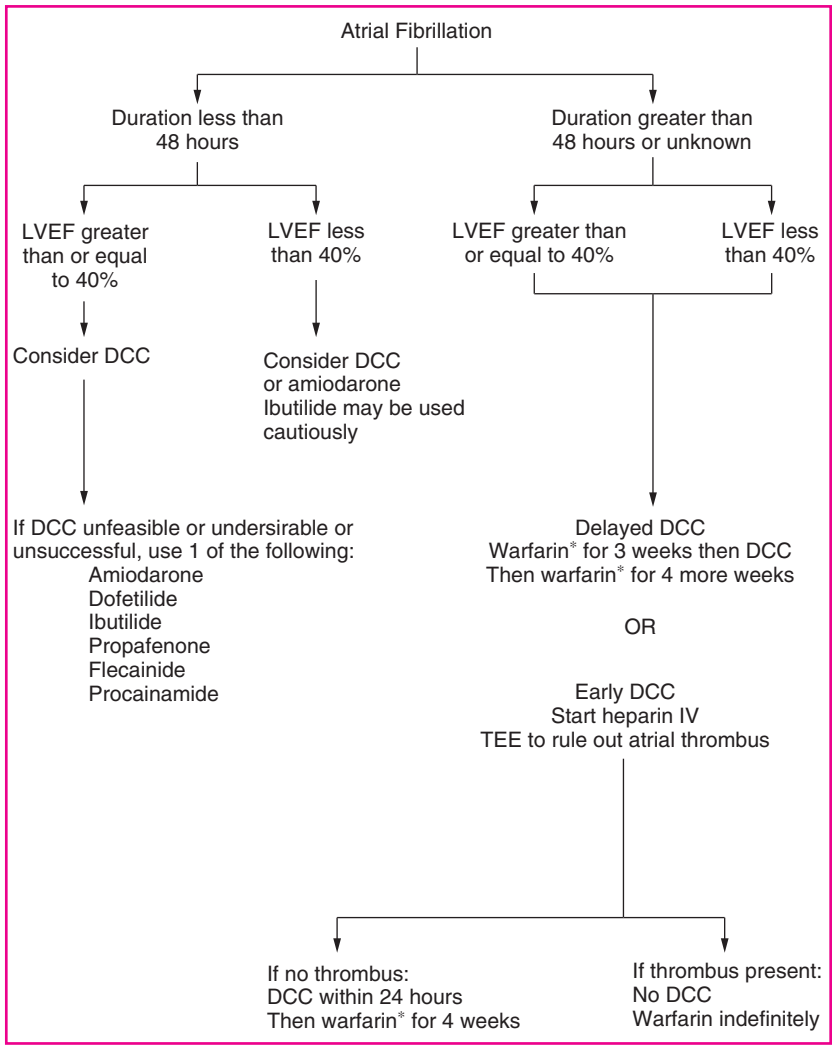


FIGURE 6–7. Decision algorithm for conversion of atrial fibrillation to normal sinus rhythm. DCC, direct current cardioversion; IV, intravenously; LVEF, left ventricular ejection fraction; TEE, transesophageal echocardiogram.
*Target International Normalized Ratio = 2.5 (range 2 to 3).
(Algorithm adapted with permission from Tisdale JE, Moser LR. Tachyarrhythmias. In: Mueller BA, Bertch KE, Dunsworth TS, et al. (eds.) *Pharmacotherapy Self-Assessment Program*, 4th ed. Kansas City: American College of Clinical Pharmacy; 2001: 217–267.)[50]

no significant differences in mortality in patients who received rhythm control therapy versus those who received rate control therapy.[28–31] However, patients assigned to the rhythm control strategy were more likely to be hospitalized[28,30,31] and were more likely to experience adverse effects associated with drug therapy.[28,29] ❹ *Therefore, drug therapy for the purpose of maintaining sinus rhythm or reducing the frequency of episodes of AF should be initiated only in those patients with episodes of paroxysmal AF who continue to experience symptoms despite maximum tolerated doses of drugs for ventricular rate control.* A decision strategy for maintenance therapy of sinus rhythm is presented in Fig. 6–8. Drug therapy for maintenance of sinus rhythm and/or reduction in the frequency of episodes of paroxysmal AF should not be initiated in patients with underlying correctable causes of AF, such as hyperthyroidism; rather, the underlying cause of the arrhythmia should be corrected.

TABLE 6–8. Drugs for Maintenance of Sinus Rhythm/ Reduction in the Frequency of Episodes of Atrial Fibrillation

Drug	Dose
Amiodarone	100–400 mg PO once daily
Dofetilide	As described in Table 6–7
Sotalol	80–160 mg PO twice daily
Propafenone	150–300 mg PO three times daily
Flecainide	100–150 mg PO twice daily
Procainamide	50 mg/kg/day, divided 4–6 × daily

PO, orally.

Stroke Prevention All patients with paroxysmal, persistent, or permanent AF should receive therapy for stroke prevention, unless compelling contraindications exist. A decision strategy for stroke prevention in AF is presented in Fig. 6–9.[27] ❺ *In general, most patients require therapy with warfarin; in some patients with no additional risk factors for stroke, aspirin may be acceptable.* For some patients, serious consideration of the benefits of warfarin versus the risks of bleeding associated with warfarin therapy is warranted. The potential bleeding risks associated with warfarin may outweigh the benefits in

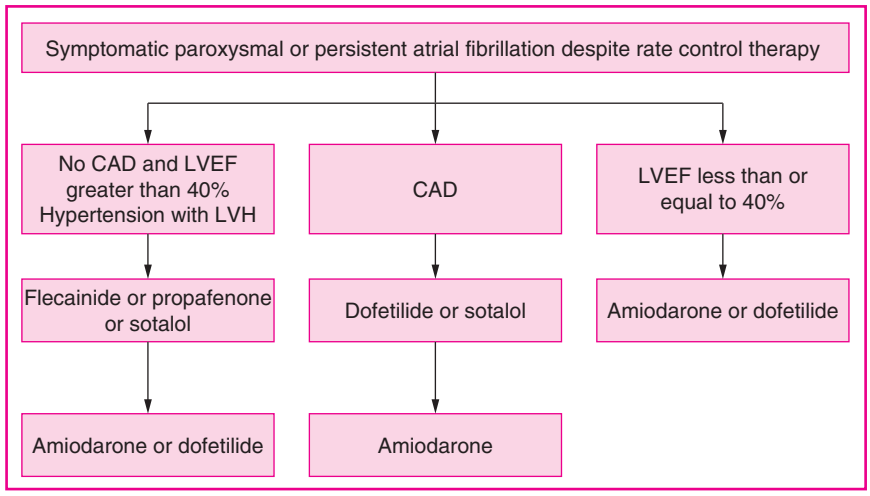


FIGURE 6–8. Decision algorithm for maintenance of sinus rhythm/reduction in the frequency of episodes of atrial fibrillation. CAD, coronary artery disease; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy. (Algorithm adapted with permission from Tisdale JE, Moser LR. Tachyarrhythmias. In: Mueller BA, Bertch KE, Dunsworth TS, et al. (eds.) *Pharmacotherapy Self-Assessment Program*, 4th ed. Kansas City: American College of Clinical Pharmacy; 2001: 217–267.)[50]

patients with a pretreatment INR of greater than 2.0, alcoholism, anticipated poor compliance, a history of falls, or current bleeding diathesis. In these situations, patients are at risk of severe bleeding associated with warfarin, including intracerebral bleeding, which may be associated with consequences as serious as those associated with a thrombotic stroke.

Outcome Evaluation

- Monitor the patient to determine whether the goal of ventricular rate control is met: heart rate less than 100 bpm or decrease in heart rate of 20% from the pretreatment value.
- Monitor ECG to assess continued presence of AF and to determine whether conversion to sinus rhythm has occurred.
- Monitor INR approximately monthly to make sure it is therapeutic (target 2.5; range 2 to 3).
- Monitor patients for adverse effects of specific drug therapy (Table 6–6). Monitor patients receiving warfarin for signs and symptoms of bruising or bleeding.



Patient Encounter, Part 3: Creating a Care Plan

Based on the information presented, create a care plan for DA's acute AF episode, and for long-term management of his AF.

Your plan should include: (1) a statement of the drug-related needs and/or problems, (2) the goals of therapy, (3) a patient-specific detailed therapeutic plan, and (4) a plan for follow-up to determine whether the goals have been achieved and adverse effects avoided.

Paroxysmal Supraventricular Tachycardia

Paroxysmal supraventricular tachycardia (PSVT) is a term that refers to a number of arrhythmias that occur above the ventricles and that require atrial or AV nodal tissue for initiation and maintenance.[32] The most common of these arrhythmias is

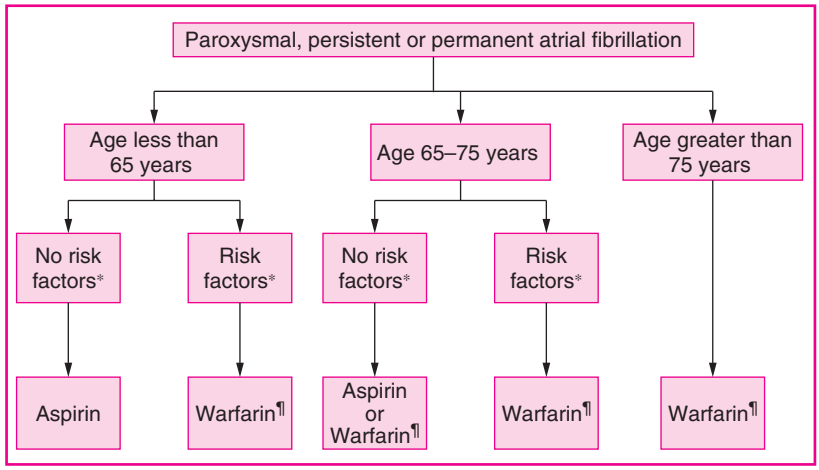


FIGURE 6–9. Decision algorithm for stroke prevention in atrial fibrillation.[27]
*Risk factors for stroke: prior transient ischemic attack or stroke; hypertension; heart failure; rheumatic heart valve disease; prosthetic heart valve.
¶Target International Normalized Ratio = 2.5 (range 2 to 3).
(Algorithm adapted with permission from Tisdale JE, Moser LR. Tachyarrhythmias. In: Mueller BA, Bertch KE, Dunsworth TS, et al. (eds.) *Pharmacotherapy Self-Assessment Program*, 4th ed. Kansas City: American College of Clinical Pharmacy; 2001: 217–267.)[50]

known as atrioventricular reciprocating tachycardia, in which the arrhythmia is caused by a reentrant circuit that involves the AV node or tissue adjacent to the AV node. Other types of PSVT include the relatively uncommon Wolff-Parkinson-White syndrome, which is caused by reentry through an accessory extra-AV nodal pathway. For the purposes of this section, the term PSVT will refer to AV nodal reentrant tachycardia.

Epidemiology and Etiology

While PSVT can be associated with myocardial ischemia or infarction, it often occurs in relatively young individuals with no history of cardiac disease. The overall incidence of PSVT is unknown.

Pathophysiology

❶ *Paroxysmal supraventricular tachycardia is caused by reentry that includes the AV node as a part of the reentrant circuit. Typically, electrical impulses travel forward (antegrade) down the AV node and then travel back up the AV node (retrograde) in a repetitive circuit. In some patients, the retrograde conduction pathway of the reentrant circuit may exist in extra-AV nodal tissue adjacent to the AV node. One of these pathways usually conducts impulses rapidly, while the other usually conducts impulses slowly.* Most commonly, during PSVT the impulse conducts antegrade through the slow pathway and retrograde through the faster pathway; in approximately 10% of patients, the reentrant circuit is reversed.[32]



Clinical Presentation and Diagnosis: PSVT

- May occur at any age, but most commonly during the fourth and fifth decades of life.[32]
- Occurs more commonly in females than in males; approximately two-thirds of patients that experience PSVT are women.[32]

Symptoms

- Symptoms typical of tachyarrhythmias include palpitations, dizziness, lightheadedness, shortness of breath, chest pain (if underlying CAD is present), near-syncope, and syncope. Patients commonly complain of palpitations; often the complaint is "I can feel my heart beating fast" or "It feels like my heart is going to beat out of my chest."
- Other symptoms are dependent on the degree to which cardiac output is diminished, which is in turn dependent on the heart rate and the degree to which stroke volume is reduced by the rapidly beating heart.

Diagnosis

- Because the symptoms of all tachyarrhythmias are dependent on heart rate and are therefore essentially the same, diagnosis depends on the presence of PSVT on the ECG, characterized by narrow QRS complexes (usually less than 0.12 seconds). P waves may or may not be visible, depending on the heart rate.
- PSVT is a regular rhythm and occurs at rates ranging from 100 to 250 bpm.

Treatment

Desired Outcomes

The desired outcomes for treatment are to terminate the arrhythmia, restore sinus rhythm, and prevent recurrence. Drug therapy is employed to terminate the arrhythmia and restore sinus rhythm; nonpharmacologic measures are employed to prevent recurrence.

Termination of PSVT

Hemodynamically unstable PSVT should be treated with immediate synchronized DCC, using an initial energy level of 50 J; if the DCC attempt is unsuccessful, successive cardioversion attempts may be made at 100, 200, 300, and 360 J.[14]

The primary method of termination of hemodynamically stable PSVT is inhibition of impulse conduction and prolongation of the refractory period within the AV node. Since PSVT is propagated via a reentrant circuit involving the AV node, inhibition of conduction within the AV node interrupts and terminates the reentrant circuit.

Prior to initiation of drug therapy for termination of hemodynamically stable PSVT, some simple nonpharmacologic methods known as **vagal maneuvers** may be attempted.[33] Vagal maneuvers stimulate the activity of the parasympathetic nervous system, which inhibits AV nodal conduction, facilitating termination of the arrhythmia. Perhaps the simplest vagal maneuver is cough, which stimulates the vagus nerve. Instructing the patient to cough two or three times may successfully terminate the PSVT. Another vagal maneuver that may be attempted is carotid sinus massage; one of the carotid sinuses, located in the neck in the vicinity of the carotid arteries, may be gently massaged, stimulating vagal activity.[33] Carotid sinus massage should not be performed in patients with a history of stroke or transient ischemic attack, or in those in whom carotid bruits may be heard on auscultation. The **Valsalva maneuver,** during which patients bear down against a closed glottis, may also be attempted.[33]

If vagal maneuvers are unsuccessful, intravenous drug therapy should be initiated.[32] Drugs that may be used for termination of hemodynamically stable PSVT are presented in Table 6–9. A decision strategy for pharmacologic termination of hemodynamically stable PSVT is presented in Fig. 6–10.[33] ❻ *Adenosine is the drug of choice for pharmacologic termination of PSVT and is successful in 90% to 95% of patients.* The drug is associated with adverse effects (Table 6–6) including flushing, sinus bradycardia or AV nodal blockade, and bronchospasm in susceptible patients. In addition, adenosine may cause chest pain that mimics the discomfort of myocardial ischemia, but which is not actually associated with ischemia. The half-life of adenosine is approximately 10 seconds, due to deamination in the blood; therefore, in the vast majority of patients, adverse effects are of short duration.

TABLE 6–9. Drugs for Termination of Paroxysmal Supraventricular Tachycardia

Drug	Mechanism	Dose	Drug Interactions
Adenosine	Direct AV nodal inhibition	6 mg IV rapid bolus If no response in 1–2 minutes, 12 mg IV rapid bolus If no response in 1–2 minutes, 12 mg IV rapid bolus	Theophylline inhibits response to adenosine Dipyridamole accentuates response to adenosine
Verapamil	Direct AV nodal inhibition	1. 5–10 mg IV over 2–3 minutes 2. If necessary, an additional dose of 5-10 mg may be administered 30 minutes later	Inhibits digoxin elimination
Diltiazem	Direct AV nodal inhibition	1. 0.25 mg/kg IV load over 2 minutes 2. If necessary, 0.35 mg/kg IV over 2 minutes after first dose	Inhibits elimination of cyclosporine
Digoxin	1. Vagal stimulation 2. Direct AV nodal inhibition	0.25 mg IV every 2 hours, up to 1.5 mg	Amiodarone and verapamil (inhibit digoxin elimination)
β-Blockers	Direct AV nodal inhibition	Esmolol: 500 mcg/kg IV, over 1 minute then 50–200 mcg/kg/minute continuous infusion Propranolol: 0.15 mg/kg IV Metoprolol: 2.5–5 mg IV × 2–3 doses	
Amiodarone	Direct AV nodal inhibition	5–7 mg/kg IV over 30–60 minutes then 700–1200 mg IV infusion over 24 hours	Inhibits elimination of digoxin and warfarin

AV, atrioventricular; IV, intravenous

If adenosine therapy is unsuccessful for termination of PSVT, subsequent choices of therapy depend on whether the patient has HF and/or a depressed left ventricular ejection fraction (LVEF).

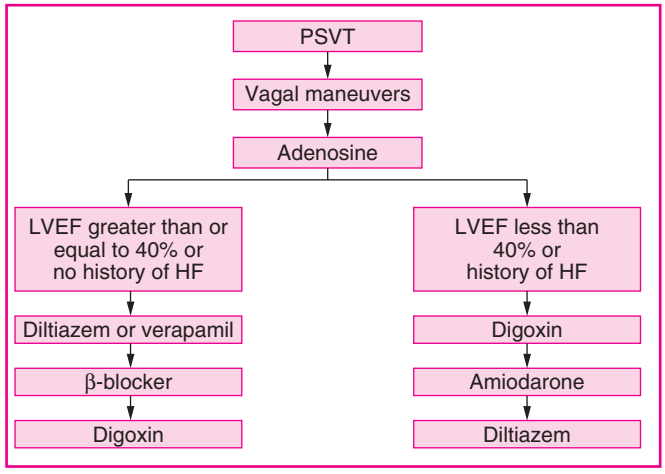


FIGURE 6–10. Decision algorithm for termination of paroxysmal supraventricular tachycardia. HF, heart failure; LVEF, left ventricular ejection fraction; PSVT, paroxysmal supraventricular tachycardia. (Algorithm adapted with permission from Tisdale JE, Moser LR. Tachyarrhythmias. In: Mueller BA, Bertch KE, Dunsworth TS, et al. (eds.) *Pharmacotherapy Self-Assessment Program*, 4th ed. Kansas City: American College of Clinical Pharmacy; 2001: 217–267.)[50]

Nonpharmacologic Therapy: Prevention of Recurrence

In the past, prevention of recurrence of PSVT was attempted using long-term oral therapy with drugs such as verapamil or digoxin. Unfortunately, oral therapy with these drugs was associated with relatively limited success. Currently, the treatment of choice for long-term prevention of recurrence of PSVT is **radiofrequency catheter ablation**. During this procedure, a catheter is introduced transvenously and directed to the right atrium under fluoroscopic guidance. The catheter is directed to the AV node, and radiofrequency energy is delivered to ablate, or destroy, one of the pathways of the reentrant circuit. This procedure usually achieves a complete cure of PSVT and is associated with a relatively low risk of complications, and therefore obviates the need for long-term antiarrhythmic drug therapy in this population.

Outcome Evaluation

- Monitor patients for termination of PSVT and restoration of normal sinus rhythm.
- Monitor patients for adverse effects of adenosine or any other anti-arrhythmic agents administered (Table 6–6).

VENTRICULAR ARRHYTHMIAS

Ventricular Premature Depolarizations

Ventricular premature depolarizations (VPDs) are ectopic electrical impulses originating in ventricular tissue, resulting

in wide, misshapen, abnormal QRS complexes. Ventricular premature depolarizations are also commonly known by other terms, including premature ventricular contractions (PVCs), ventricular premature beats (VPBs), and ventricular premature contractions (VPCs).

Epidemiology, Etiology, and Pathophysiology

Ventricular premature depolarizations occur with variable frequency, depending on underlying comorbid conditions. The prevalence of complex or frequent VPDs is approximately 33% and 12% in men with and without CAD, respectively;[34] in women, the prevalence of complex or frequent VPDs is 26% and 12% in those with and without CAD, respectively.[35] Ventricular premature depolarizations occur more commonly in patients with ischemic heart disease, a history of myocardial infarction, and HF due to LV dysfunction. They may also occur as a result of hypoxia, anemia, and following cardiac surgery.

❶ *Ventricular premature depolarizations occur as a result of abnormal ventricular automaticity, as a result of enhanced activity of the sympathetic nervous system and altered electrophysiologic characteristics of the heart during myocardial ischemia and following myocardial infarction.*

In patients with underlying CAD or a history of myocardial infarction, the presence of complex or frequent VPDs is associated with an increased risk of mortality due to sudden cardiac death.[36]

Treatment

Desired Outcomes

The desired outcomes for treatment are to alleviate patient symptoms.



Clinical Presentation and Diagnosis: Ventricular Premature Depolarizations

- VPDs are usually categorized as simple or complex: simple VPDs are those that occur as infrequent, isolated single abnormal beats; complex VPDs are those that occur more frequently and/or in specific patterns.
- Two consecutive VPDs are referred to as a couplet.[35] The term bigeminy refers to VPDs occurring with every other beat; trigeminy means VPDs occurring with every third beat; quadrigeminy means VPDs occurring every fourth beat.[35] VPDs occurring at a rate of more than 10 per hour or 6 or more per minute are defined as frequent.[35]

Symptoms

- The majority of patients who experience simple or complex VPDs are asymptomatic. Occasionally, patients with complex or frequent VPDs may experience symptoms of palpitations, lightheadedness, fatigue, near-syncope or syncope.

Pharmacologic Therapy

❼ *Asymptomatic VPDs should not be treated with antiarrhythmic drug therapy.* Based on the knowledge that complex or frequent VPDs increase the risk of sudden cardiac death in patients with a history of myocardial infarction, the Cardiac Arrhythmia Suppression Trials (CAST I and II)[37,38] tested the hypothesis that suppression of asymptomatic VPDs with the drugs flecainide, encainide, or moricizine in patients with a relatively recent history of myocardial infarction would lead to a reduction in the incidence of sudden cardiac death. However, the results of the trial showed that not only did these antiarrhythmic agents not reduce the risk of sudden cardiac death, patients who received therapy with encainide or flecainide experienced a significant *increase* in the risk of death compared to those that received placebo.[37] During the continuation of the study with moricizine, a trend was found toward an increase in the incidence of death in the patients who received this antiarrhythmic drug as well.[38] A subsequent meta-analysis of studies of other Vaughan-Williams class I drugs, including quinidine, procainamide, and disopyramide, found that the patients with complex VPDs who received these drugs following myocardial infarction were also at increased risk of death.[39] Therefore, all available evidence shows that patients with complex VPDs following myocardial infarction do not benefit from therapy with antiarrhythmic agents and that many of these drugs increase the risk of death. ❼ *Therefore, asymptomatic VPDs should not be treated.*

Patients with symptomatic VPDs should be treated with β-blockers, as the majority of patients with symptomatic VPDs have underlying CAD. β-Blockers have been shown to reduce mortality in this population and have been shown to be effective for VPD suppression.[40]

Outcome Evaluation

- Monitor patients for relief of symptoms.
- Monitor for adverse effects of β-blockers—heart rate, blood pressure, fatigue, masking of symptoms of hypoglycemia and/or glucose intolerance (in patients with diabetes), wheezing or shortness of breath (in patients with asthma or chronic obstructive pulmonary disease), etc.

Ventricular Tachycardia

Ventricular tachycardia is a series of three or more consecutive VPDs at a rate of greater than 100 bpm. Ventricular tachycardia is defined as non-sustained if it lasts less than 30 seconds and terminates spontaneously; sustained VT lasts greater than 30 seconds and does not terminate spontaneously, but rather requires therapeutic intervention for termination.

Epidemiology, Etiology, and Pathophysiology

Etiologies of VT are presented in Table 6–10. The incidence of VT is variable, depending on underlying comorbidities. Up to 20% of patients who experience acute myocardial infarction

TABLE 6–10. Etiologies of Ventricular Tachycardia and Ventricular Fibrillation

Coronary artery disease
Myocardial infarction
Heart failure
Electrolyte abnormalities: hypokalemia and hypomagnesemia
Drugs:
Adenosine
Amiodarone
Chlorpromazine
Digoxin
Disopyramide
Flecainide
Ibutilide
Moricizine
Procainamide
Propafenone
Sotalol
Terbutaline
Theophylline
Thioridazine
Trazodone
Tricyclic antidepressants

experience ventricular arrhythmias.[41] Approximately 2% to 4% of patients with myocardial infarction develop VT during the period of hospitalization.[41] Non-sustained VT occurs in 34% to 79% of patients with HF.[42] Other etiologies of VT include electrolyte abnormalities such as hypokalemia, hypoxia, and some drugs (Table 6–10).

❶ *Ventricular tachycardia is usually initiated by a precisely timed VPD, occurring during the relative refractory period, which provokes reentry within ventricular tissue.*

Sustained VT requires immediate intervention, because if untreated, the rhythm may cause sudden cardiac death via hemodynamic instability and the absence of a pulse (pulseless VT) or via degeneration of VT into VF.

Treatment

Desired Outcomes

The desired outcomes for treatment are to terminate the arrhythmia and restore sinus rhythm, and to prevent sudden cardiac death.

Pharmacologic Therapy

Termination of VT Hemodynamically unstable VT should be terminated immediately using synchronized DCC beginning with 100 J and increasing subsequent shocks to 200, 300, and 360 J.[14] In the event that VT is present but the patient has no pulse (and therefore no blood pressure), asynchronous defibrillation should be performed, starting with 200 J and increasing to 300 and 360 J.[14]

Drugs used for the termination of hemodynamically stable VT are presented in Table 6–11. Intravenous drug administration is required. A decision algorithm for management of hemodynamically stable VT is presented in Fig. 6–11. Amiodarone is considered the preferred first-line antiarrhythmic agent for management of VT, regardless of the patient's underlying LV function.[14] In patients with normal LV function who do not respond to amiodarone, IV procainamide may be administered;[14] data suggest superior efficacy of procainamide compared with that of lidocaine.[43] However, in patients with HF due to LV dysfunction, procainamide should be avoided, due to



Clinical Presentation and Diagnosis: Ventricular Tachycardia

Symptoms

- As with other tachyarrhythmias, symptoms associated with VT are dependent primarily on heart rate and include palpitations, dizziness, lightheadedness, shortness of breath, chest pain (if underlying CAD is present), near-syncope, and syncope.
- Patients with non-sustained VT may be asymptomatic, if the duration of the arrhythmia is sufficiently short. However, if the rate is sufficiently rapid, patients with non-sustained VT may experience symptoms.
- Patients with sustained VT are usually symptomatic, provided that the rate is fast enough to provoke symptoms. Patients with rapid sustained VT may be hemodynamically unstable.
- In some patients, sustained VT results in the absence of a pulse, resulting in the syndrome of sudden cardiac death.

Diagnosis

- Diagnosis of VT requires ECG confirmation of the arrhythmia.
- Ventricular tachycardia is characterized by wide, misshapen QRS complexes, with the rate varying from 100 to 250 bpm.
- In the majority of patients with VT, the shape and appearance of the QRS complexes are consistent and similar, and is referred to as monomorphic VT. However, some patients experience polymorphic VT, in which the shape and appearance of the QRS complexes vary.

TABLE 6–11. Drugs for Termination of Ventricular Tachycardia

Drug	Loading Dose	Maintenance Dose
Procainamide	12–17 mg/kg IV, no faster than 20 mg/minute	1–4 mg/minute continuous infusion
Lidocaine	0.5–0.75 mg/kg IV bolus Repeat every 5–10 minutes to a total of 3 mg/kg	1–4 mg/minute continuous infusion
Amiodarone	150 mg IV over 10 minutes	1 mg/minute continuous infusion for 6 hours, 0.5 mg/minute for 18 hours

IV, intravenously.

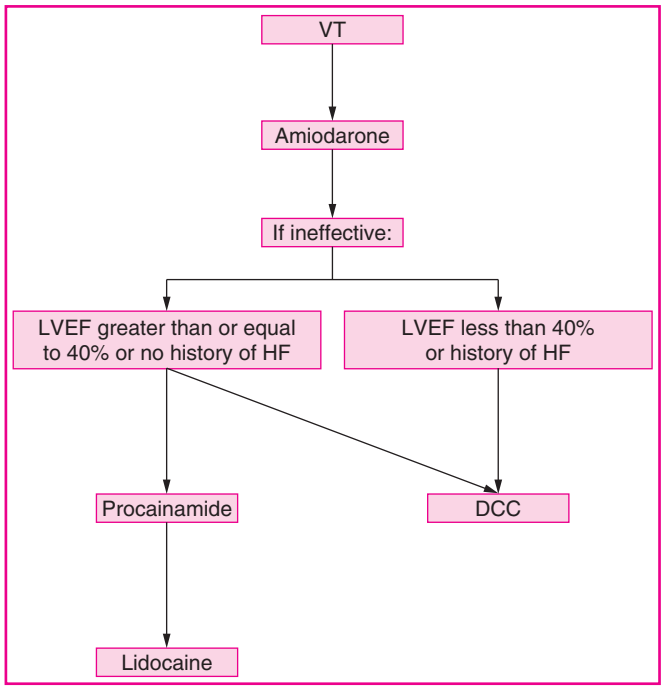


FIGURE 6–11. Decision algorithm for termination of hemodynamically stable ventricular tachycardia.
DCC, direct current cardioversion; HF, heart failure; LVEF, left ventricular ejection fraction; VT, ventricular tachycardia.
(Algorithm adapted with permission from Tisdale JE, Moser LR. Tachyarrhythmias. In: Mueller BA, Bertch KE, Dunsworth TS, et al. (eds.) *Pharmacotherapy Self-Assessment Program*, 4th ed. Kansas City: American College of Clinical Pharmacy; 2001:217–267.)[50]

an increased risk of hypotension and drug-induced torsades de pointes and due to negative inotropic activity.[14]

Nonpharmacologic Therapy: Prevention of Sudden Cardiac Death

❸ *In patients who have experienced VT and are at risk for sudden cardiac death, implantation of an* ***implantable cardioverter-defibrillator*** *(ICD) is the treatment of choice.*[44] An ICD is a device that provides internal electrical cardioversion of VT or defibrillation of VF; the ICD does not prevent the patient from developing the arrhythmia, but it reduces the risk that the patient will die of sudden cardiac death as a result of the arrhythmia. Whereas in the past ICD implantation required a thoracotomy, these devices now may be implanted transvenously, similarly to pacemakers, markedly reducing the complication rate.

ICDs have been found to be significantly more effective than antiarrhythmic agents such as amiodarone or sotalol for reducing the risk of sudden cardiac death;[45,46] therefore, ICDs are preferred therapy.[44] However, many patients with ICDs receive concurrent antiarrhythmic drug therapy to reduce the frequency with which patients experience the discomfort of shocks and to prolong battery life of the devices. Combined pharmacotherapy with amiodarone and a β-blocker is more effective than monotherapy with sotalol or β-blockers for reduction in the frequency of ICD shocks.[47]

Outcome Evaluation

- Monitor patients for termination of VT and restoration of normal sinus rhythm.
- Monitor patients for adverse effects of antiarrhythmic drugs administered (Table 6–6).

Ventricular Fibrillation

Ventricular fibrillation is irregular, disorganized, chaotic electrical activity in the ventricles resulting in absence of ventricular depolarizations, and, consequently, lack of pulse, cardiac output, and blood pressure.

Epidemiology and Etiology

Approximately 400,000 people die of sudden cardiac death annually in the United States. While some of these deaths occur as a result of asystole, the majority occur as a result of primary VF or VT that degenerates into VF. Etiologies of VF are presented in Table 6–10 and are similar to those of VT.

Treatment

Desired Outcomes

The desired outcomes for treatment are to: (1) terminate VF, (2) achieve return of spontaneous circulation, and (3) achieve patient survival to hospital admission (in those with out-of-hospital cardiac arrest) and to hospital discharge.

Pharmacologic and Nonpharmacologic Therapy

Ventricular fibrillation is by definition hemodynamically unstable, due to the absence of pulse and blood pressure. Initial management includes provision of basic life support, including calling for help and initiation of cardiopulmonary resuscitation (CPR).[48] Oxygen should be administered as soon



Clinical Presentation and Diagnosis: Ventricular Fibrillation

Symptoms

- VF results in immediate loss of pulse and blood pressure. Patients who are in the standing position at the onset of VF suddenly immediately collapse to the ground.

Diagnosis

- The absence of a pulse does not guarantee VF, as the pulse may also be absent in patients with asystole, VT, or pulseless electrical activity.
- Confirmation of the diagnosis with an ECG is necessary in order to determine appropriate treatment. ECG reveals no organized, recognizable QRS complexes. If treatment is not initiated within a few minutes, death will occur, or at best, resuscitation of the patient with permanent anoxic brain injury.

as it is available. Most importantly, defibrillation should be performed as soon as possible. It is critically important to understand that the only means of successfully terminating VF and restoring sinus rhythm is electrical defibrillation. Defibrillation should be attempted using 200 J, after which CPR should be resumed immediately while the defibrillator charges; if the first shock was unsuccessful, subsequent defibrillation shocks should be 360 J.[48]

If VF persists following one or two defibrillation shocks, drug therapy may be administered. ❾ *The purpose of drug administration for treatment of VF is to facilitate successful defibrillation. Drug therapy alone will not result in termination of VF. Drugs that are used for facilitation of defibrillation in patients with VF are listed in Table 6–12.* Drug administration should occur during CPR, before or after delivery of a defibrillation shock. The vasopressor agents epinephrine or vasopressin are administered initially, because it has been shown that a critical factor in successful defibrillation is maintenance of coronary perfusion pressure, which is achieved via the vasoconstricting effects of these drugs. A decision algorithm for the treatment of VF is presented in Fig. 6–12. Epinephrine and vasopressin are equally effective for facilitation of defibrillation leading to survival to hospital admission in patients with out-of-hospital cardiac arrest due to VF. Amiodarone is more effective than lidocaine for facilitation of defibrillation leading to survival to hospital admission in patients with VF,[49] which is the reason that amiodarone administration is recommended earlier than lidocaine administration in the decision algorithm.[48] Note that the amiodarone doses recommended for administration during a resuscitation attempt for VF (Table 6–12) are different than those recommended for administration for termination of VT (Table 6–11).

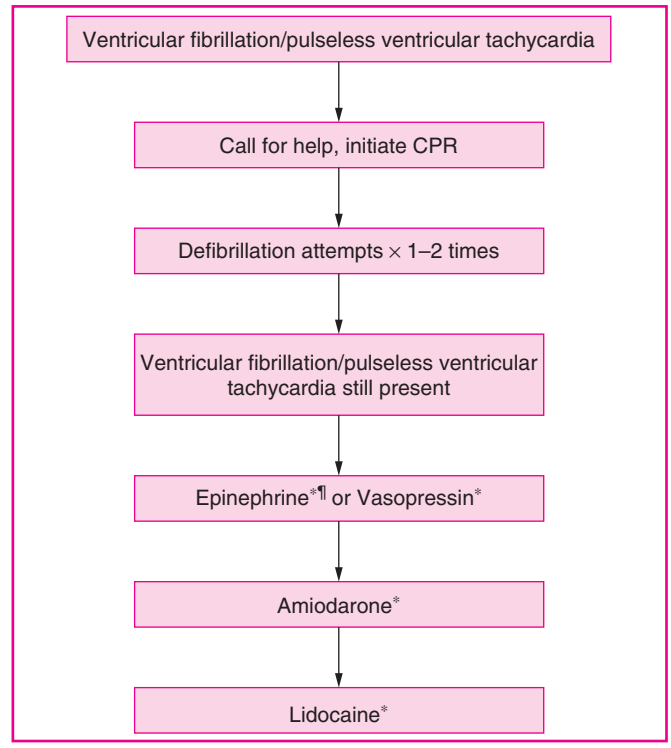


FIGURE 6–12. Decision algorithm for resuscitation of ventricular fibrillation or pulseless ventricular tachycardia.
CPR, cardiopulmonary resuscitation.
*A defibrillation attempt should be made after every dose of drug.
¶If epinephrine is selected, the drug should continue to be administered every 3 to 5 minutes throughout the remainder of the resuscitation attempt.

Outcome Evaluation

- Monitor the patient for return of pulse and blood pressure, and for termination of VF and restoration of normal sinus rhythm.
- After successful resuscitation, monitor the patient for adverse effects of drugs administered (Table 6–6).

TABLE 6–12. Drugs for Facilitation of Defibrillation in Patients with Ventricular Fibrillation

Drug	Dose
Epinephrine	1 mg IV every 3–5 minutes
Vasopressin	40 units IV single dose
Amiodarone	300 mg IV diluted in 20–30 mL D_5W One subsequent dose of 150 mg IV may be administered
Lidocaine	1–1.5 mg/kg IV bolus Follow with additional IV boluses of 0.5–0.75 mg/kg up to total of 3 mg/kg

IV, intravenous.

Torsades de Pointes

Torsades de pointes is a specific polymorphic VT that is associated with prolongation of the QT interval in the sinus beats that precede the arrhythmia.[13]

Epidemiology and Etiology

The incidence of torsades de pointes in the population at large is unknown. The incidence of torsades de pointes associated with specific drugs ranges from less than 1% to as high as 8% to 10%, depending on dose and plasma concentration of the drug and the presence of other risk factors for the arrhythmia.

Torsades de pointes may be inherited or acquired. Patients with specific genetic mutations may have the inherited long QT syndrome, in which the QT interval is prolonged, and these patients are at risk for torsades de pointes. Acquired torsades de pointes may be caused by numerous drugs (Table 6–13); the list of drugs that are known to cause torsades de pointes continues to expand.

TABLE 6–13. Drugs That Have Been Reported to Cause Torsades de Pointes[13]

Amiodarone	Ibutilide
Amitriptyline	Indapamide
Arsenic	Levofloxacin
Bepridil	Levomethadyl
Chloroquine	Loratadine
Chlorpromazine	Methadone
Ciprofloxacin	Metoclopramide
Clarithromycin	Pentamidine
Disopyramide	Pimozide
Dofetilide	Procainamide
Doxepin	Propafenone
Droperidol	Quinidine
Erythromycin	Sertraline
Famotidine	Sotalol
Flecainide	Tacrolimus
Fluconazole	Thioridazine
Fluoxetine	Trazodone
Gatifloxacin	Trimethoprim-sulfamethoxazole
Haloperidol	

Pathophysiology

Torsades de pointes is caused by circumstances, often drugs, that lead to prolongation in the repolarization phase of the ventricular action potential (Fig. 6–2) manifested on the ECG by prolongation of the QT interval. Prolongation of ventricular repolarization occurs via inhibition of efflux of potassium through potassium channels; therefore, drugs that inhibit conductance through potassium channels may cause QT interval prolongation and torsades de pointes. ❶ *Prolongation of ventricular repolarization likely promotes the development of early ventricular afterdepolarizations during the relative refractory period, which may provoke reentry leading to torsades de pointes.*

❿ *Drug-induced torsades de pointes rarely occurs in patients without specific risk factors for the arrhythmia (Table 6–14).* In most cases, administration of a drug known to cause torsades de pointes is unlikely to cause the arrhythmia; however, the likelihood of the arrhythmia increases markedly in patients with concomitant risk factors.

The onset of torsades de pointes associated with oral drug therapy is somewhat variable and in some cases may be delayed; often, a patient can be taking a drug known to cause torsades de pointes for months or longer without problem, until another risk factor for the arrhythmia becomes present, which then may trigger the arrhythmia.

In some patients, torsades de pointes may be of short duration and may terminate spontaneously. However, torsades de pointes may not terminate on its own, and if left untreated, may degenerate into VF and result in sudden cardiac death.[13] Several drugs, including terfenadine, astemizole, and cisapride have been withdrawn from the United States market as a result of causing deaths due to torsades de pointes.

TABLE 6–14. Risk Factors for Drug-Induced Torsades de Pointes[13]

QTc interval greater than 500 milliseconds
Increase in QTc interval by more than 60 milliseconds compared with the pretreatment value
Female gender
Heart failure
Electrolyte abnormalities: hypokalemia and hypomagnesemia
Bradycardia
Elevated plasma concentrations of QT interval-prolonging drugs due to drug interactions or absence of dose adjustment for organ dysfunction
Rapid intravenous infusion of torsades-inducing drugs
Concomitant administration of more than one agent known to cause QT interval prolongation/torsades de pointes
Possible genetic predisposition
Previous history of drug-induced torsades de pointes

QTc, corrected QT interval



Clinical Presentation and Diagnosis: Torsades de pointes

Symptoms

- As with other tachyarrhythmias, symptoms associated with torsades de pointes are dependent primarily on heart rate and include palpitations, dizziness, lightheadedness, shortness of breath, chest pain (if underlying CAD is present), near-syncope, and syncope.
- Torsades de pointes may be hemodynamically unstable if the rate is sufficiently rapid.
- Like sustained monomorphic VT, torsades de pointes may result in the absence of a pulse, or may rapidly degenerate into VF, resulting in the syndrome of sudden cardiac death.

Diagnosis

- Diagnosis of torsades de pointes requires examination of the arrhythmia on ECG.
- Torsades de pointes, or "twisting of the points," appears on ECG as apparent twisting of the wide QRS complexes around the isoelectric baseline.
- The arrhythmia is associated with heart rates from 150 to 300 bpm.
- Characteristic feature: a "long-short" initiating sequence, which occurs as a result of a ventricular premature beat followed by a compensatory pause, which is followed by the first beat of the torsades de pointes.
- Episodes of torsades de pointes may self-terminate, with frequent recurrence.

Prevention and Treatment

Desired Outcomes

The desired outcomes for treatment include the: (1) prevention of torsades de pointes, (2) termination of torsades de pointes, (3) prevention of recurrence, and (4) prevention of sudden cardiac death.

Pharmacologic and Nonpharmacologic Therapy

⑩ *In patients with risk factors for torsades de pointes, drugs with the potential to cause QT interval prolongation and torsades de pointes should be avoided or used with extreme caution, and diligent QT interval monitoring should be performed.*

Management of drug-induced torsades de pointes includes discontinuation of the potentially causative agent. Patients with hemodynamically unstable torsades de pointes should undergo immediate synchronized DCC. In patients with hemodynamically stable torsades de pointes, electrolyte abnormalities such as hypokalemia and hypomagnesemia should be corrected. Hemodynamically stable torsades de pointes is often treated with intravenous magnesium, irrespective of whether the patient is hypomagnesemic; magnesium has been shown to terminate torsades de pointes in normomagnesemic patients. Intravenous magnesium may be administered in doses of 1 to 2 g, diluted in 50 to 100 mL D_5W, administered over 5 to 10 minutes; doses may be repeated to a total of 12 g.

Alternatively, a continuous magnesium infusion may be initiated after the first bolus, at a rate of 0.5 to 1 g/hour. Alternative treatments include: transvenous insertion of a temporary pacemaker for overdrive pacing, which shortens the QT interval and may terminate torsades de pointes; intravenous isoproterenol 2 to 10 mcg/minute, to increase the heart rate and shorten the QT interval; intravenous lidocaine, which may shorten the duration of ventricular repolarization; or intravenous phenytoin, which may also shorten the duration of ventricular repolarization, administered at a dose of 10 to 15 mg/kg infused at a rate of 25 to 50 mg/minute.

Outcome Evaluation

- Monitor vital signs (heart rate and blood pressure).
- Monitor the ECG to determine the QTc interval (maintain less than 450 milliseconds) and for the presence of torsades de pointes.
- Monitor serum potassium and magnesium concentrations.
- Monitor for symptoms of tachycardia.



Patient Care and Monitoring

1. Perform a thorough medication history to determine whether the patient is receiving any prescription or non-prescription drugs that may cause or contribute to the development of an arrhythmia.
2. Evaluate the patient for the presence of drug-induced diseases, drug allergies, and drug interactions.
3. Determine and monitor the patient's serum electrolyte concentrations to determine the presence or absence of hypokalemia, hyperkalemia, hypomagnesemia, or hypermagnesemia.
4. Consider the patient's heart rate, blood pressure, and symptoms to determine whether he or she is hemodynamically stable or unstable.
5. Monitor the patient's 12-lead ECG or single rhythm strips to determine if an arrhythmia is present and to identify the specific arrhythmia, and evaluate and monitor the patient's symptoms.
6. Develop drug therapy treatment plans for management of the specific arrhythmia that the patient is experiencing: sinus bradycardia, AV nodal blockade, AF, PSVT, VPDs, VT (including torsades de pointes), or VF.
7. Develop specific drug therapy monitoring plans for the treatment plan implemented. Monitoring includes assessment of symptoms, ECG, adverse effects of drugs, and potential drug interactions.
8. In those receiving warfarin for AF, determine whether the patient's INR is therapeutic.
9. Provide information regarding safe and effective warfarin therapy:
   - Notify appropriate clinicians in the event of severe bruising, blood in urine or stool, or frequent nosebleeds;
   - Avoid radical changes in diet;
   - Avoid alcohol;
   - Do not take non-prescription medications or herbal/alternative/complementary medicines without notifying your physician, pharmacist, and/or health care team members.
10. Stress the importance of adherence to the therapeutic regimen.
11. Provide patient education regarding disease state and drug therapy.

ABBREVIATIONS

AF:	Atrial fibrillation
ATPase:	adenosine triphosphatase
AV:	atrioventricular
BP:	blood pressure
bpm:	beats per minute
Ca:	calcium
CAD:	coronary artery disease
CAST:	Cardiac Arrhythmia Suppression Trial
CCB:	calcium channel blocker
CPR:	cardiopulmonary resuscitation
DCC:	direct current cardioversion
ECG:	electrocardiogram
ED:	emergency department
HF:	heart failure
ICD:	implantable cardioverter-defibrillator
INR:	International Normalized Ratio
IV:	intravenous
J:	Joules
K:	potassium
LV:	left ventricular
LVEF:	left ventricular ejection fraction
Na:	sodium
NYHA:	New York Heart Association
PO:	oral
PSVT:	paroxysmal supraventricular tachycardia
PTT:	partial thromboplastin time
PVC:	premature ventricular contraction
QTc:	corrected QT interval
RR:	respiratory rate
SA:	sinoatrial
TEE:	transesophageal echocardiogram
VPB:	ventricular premature beat
VPC:	ventricular premature contraction
VPD:	ventricular premature depolarization
VF:	ventricular fibrillation
VT:	ventricular tachycardia

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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7 Venous Thromboembolism

Stuart T. Haines and Edith A. Nutescu



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Identify risk factors and signs and symptoms of deep vein thrombosis and pulmonary embolism.
2. Describe the processes of hemostasis and thrombosis, including the role of the vascular endothelium, platelets, coagulation cascade, and thrombolytic proteins.
3. Determine a patient's relative risk (low, moderate, high, or very high) of developing venous thrombosis.
4. State at least two potential advantages of the low-molecular-weight heparins and fondaparinux over unfractionated heparin.
5. Formulate an appropriate prevention strategy for a patient at risk for deep vein thrombosis.
6. Identify factors that place a patient at high risk of bleeding while receiving antithrombotic drugs.
7. Select and interpret laboratory test(s) to monitor antithrombotic drugs.
8. Identify and analyze warfarin drug-drug and drug-food interactions.
9. Manage a patient with an elevated International Normalized Ratio (INR) with or without bleeding.
10. Formulate an appropriate treatment plan for a patient who develops a deep vein thrombosis or pulmonary embolism, and develop a comprehensive education plan for a patient who is receiving an antithrombotic drug.

Key Concepts

❶ Antithrombotic therapies require meticulous and systematic monitoring, as well as ongoing patient education. Well-organized anticoagulation management services improve the quality of patient care and reduce the overall cost.

❷ The risk of venous thromboembolism (VTE) is related to several easily identifiable factors including age, prior history of VTE, major surgery (particularly orthopedic procedures of the lower extremities), trauma, malignancy, pregnancy, estrogen use, and hypercoagulable states. These risks are additive.

❸ The diagnosis of VTE must be confirmed by an objective test.

❹ At the time of hospital admission, all patients should be evaluated for their risk of VTE, and strategies to prevent VTE appropriate for each patient's level of risk should be routinely employed. Prophylaxis should be continued throughout the period of risk.

❺ In the absence of contraindications, the treatment of VTE should initially include a rapid-acting anticoagulant (e.g., unfractionated heparin, low-molecular-weight heparin, or fondaparinux) overlapped with warfarin for at least 5 days and until the patient's INR is greater than 2. Anticoagulation therapy should be continued for a minimum of 3 months. However, the duration of anticoagulation therapy should be based on the patient's risk of VTE recurrence and major bleeding.

❻ Bleeding is the most common adverse effect associated with antithrombotic drugs. A patient's risk of major hemorrhage is related to the intensity and stability of therapy, age, concurrent drug use, history of gastrointestinal bleeding, risk of falls or trauma, and recent surgery.

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❼ Most patients with an uncomplicated deep vein thrombosis (DVT) can be managed safely at home.
❽ Warfarin is prone to numerous clinically important drug-drug and drug-food interactions.

Venous thromboembolism (VTE) is one of the most common cardiovascular disorders in the United States. VTE is manifested as **deep vein thrombosis** (DVT) and **pulmonary embolism** (PE) resulting from **thrombus** formation in the venous circulation (Fig. 7–1).[1] It is often provoked by prolonged immobility and vascular injury and is most frequently seen in patients who have been hospitalized for a serious medical illness, trauma, or major surgery. VTE can also occur with little or no provocation in patients who have an underlying hypercoagulable disorder.

While VTE may initially cause few or no symptoms, the first overt manifestation of the disease may be sudden death.[2] Death from PE can occur within minutes, before effective treatment can be given. In addition to the symptoms produced by the acute event, the long-term sequelae of VTE such as the post-thrombotic syndrome (PTS; a complication of VTE occurring due to damage to the vein caused by a blood clot) and recurrent thromboembolic events cause long-term pain and suffering.

The treatment of VTE is fraught with substantial risks.[3] ❶ *Antithrombotic drugs require precise dosing and meticulous monitoring, as well as ongoing patient education.*[4,5] *Well organized anticoagulation management services improve the quality of patient care and reduce the overall cost.* A systematic approach to drug therapy management substantially reduces these risks, but bleeding remains a common and serious complication.[6] Therefore, preventing VTE is paramount to improving outcomes. When VTE is suspected, a rapid and accurate diagnosis is critical to making appropriate treatment decisions. The optimal use of antithrombotic drugs requires not only an in-depth knowledge of their pharmacology and pharmacokinetic properties, but also a comprehensive approach to patient management.[7]

EPIDEMIOLOGY AND ETIOLOGY

The true incidence of VTE in the general population is unknown because many patients, perhaps more than 50%, have no overt symptoms or go undiagnosed.[8] An estimated

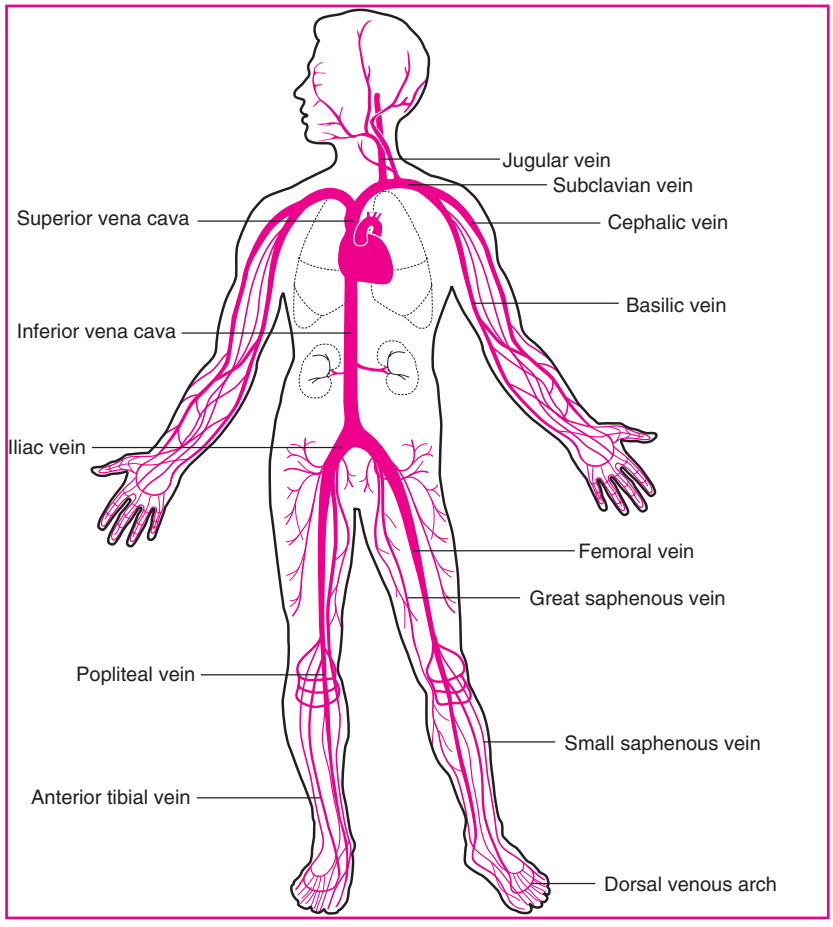


FIGURE 7–1. Venous circulation. (Reproduced from Haines ST, Zeolla M, Witt DM. Venous thromboembolism. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 374, with permission.)

2 million people in the United States develop VTE each year; 600,000 are hospitalized and 60,000 die. The estimated annual direct medical costs of managing the disease are well over $1 billion. The best available data indicate the age-adjusted incidence of symptomatic VTE in Caucasians is 117 per 100,000 per year.[9] The incidence of VTE nearly doubles in each decade of life over the age of 50 and is slightly higher in men. The age-adjusted incidence of PE has declined slightly in recent years, presumably because of heightened awareness of VTE, effective prevention strategies, early diagnosis, and prompt treatment. However, as the population ages, the total number of cases of DVT and PE continues to rise.

❷ *The risk of VTE is related to several easily identifiable factors including age, prior history of VTE, major surgery (particularly orthopedic procedures of the lower extremities), trauma, malignancy, pregnancy, estrogen use, and hypercoagulable state (Table 7–1).*[2] *These risk factors are additive and can be easily identified in clinical practice. A prior history of venous* ***thrombosis*** *is perhaps the strongest risk factor for recurrent VTE, presumably because of the destruction of venous valves and obstruction of blood flow caused by the initial event.* Rapid blood flow has an inhibitory effect on thrombus formation, but a slow rate of flow reduces the clearance of activated clotting factors in the zone of injury and slows the influx of regulatory substances. Stasis tips the delicate balance of procoagulation and anticoagulation in favor of **thrombogenesis**. The rate of blood flow in the venous circulation, particularly in the deep veins of the lower extremities, is relatively slow. Valves in the deep veins of the legs, as well as contraction of the calf and thigh muscles, facilitate the flow of blood back to the heart and lungs. Damage to the venous valves and periods of prolonged immobility result in venous stasis. Vessel obstruction, either from a thrombus or external compression, promotes clot propagation. Numerous medical conditions and surgical procedures are associated with reduced venous blood flow and increase the risk of VTE (Table 7–1). Greater than normal blood viscosity, seen in myeloproliferative disorders like polycythemia vera, for example, may also contribute to slowed blood flow and thrombus formation.

TABLE 7–1. Risk Factors for Venous Thromboembolism

Risk Factor	Example
Age	Risk doubles with each decade after age 50
Prior history of VTE	Strongest known risk factor for DVT and PE
Venous stasis	Major medical illness (e.g., congestive heart failure) Major surgery (e.g., general anesthesia for greater than 30 minutes) Paralysis (e.g., due to stroke or spinal cord injury) Polycythemia vera Obesity Varicose veins
Vascular inujury	Major orthopedic surgery (e.g., knee and hip replacement) Trauma (esp. fractures of the pelvis, hip, or leg) Indwelling venous catheters
Hypercoagulable states	Malignancy, diagnosed or occult Activated protein C resistance/factor V Leiden Prothrombin (20210A) gene mutation Protein C deficiency Protein S deficiency Antithrombin deficiency Factor VIII excess (greater than 90th percentile) Factor XI excess (greater than 90th percentile) Antiphospholipid antibodies Dysfibrinogenemia PAI-l excess Pregnancy/postpartum
Drug therapy	Estrogen-containing oral contraceptive pills Estrogen replacement therapy SERMs HIT

DVT, deep vein thrombosis; HIT, heparin-induced thrombocytopenia; PAI-l, plasminogen activator inhibitor; PE, pulmonary embolism; SERM, selective estrogen receptor modulator; VTE, venous thromboembolism.

A growing list of hereditary deficiencies, gene mutations, and acquired diseases have been linked to hypercoagulability (Table 7–1).[10] Activated protein C resistance is the most common genetic disorder of hypercoagulability, found in nearly 5% of individuals of northern European descent and in as many as 40% of those who suffer an idiopathic DVT. Although these patients have normal plasma concentrations of protein C, they have a mutation on factor V that renders it resistant to degradation by activated protein C. This mutation is known as factor V Leiden, named after the city of Leiden, Holland, where the defect was initially reported. The prothrombin 20210A mutation is also a relatively common defect, occurring in as many as 3% of healthy individuals of southern European descent and 16% of those with an idiopathic DVT. Although less common, inherited deficiencies of the natural **anticoagulants** protein C, protein S, and antithrombin place patients at a high lifetime risk for VTE. Conversely, high concentrations of factors VIII, IX, and XI also increase the risk of VTE. Some patients have multiple genetic defects.

Acquired disorders of hypercoagulability include malignancy, antiphospholipid antibodies, estrogen use, and pregnancy.[2] The strong link between cancer and thrombosis has been recognized since the late 1800s.[11] Tumor cells secrete a number of procoagulant substances that activate the clotting cascade. Furthermore, patients with cancer often have suppressed levels of protein C, protein S, and antithrombin. Antiphospholipid antibodies, commonly found in patients with autoimmune disorders such as systemic lupus erythematosus and inflammatory bowel disease, can cause venous and arterial thrombosis.[12] The antiphospholipid antibody syndrome is associated with repeated pregnancy loss. The precise mechanism by which these antibodies provoke thrombosis is unclear, but they activate the coagulation cascade and platelets, as well as inhibit the anticoagulant

activity of proteins C and S. Estrogen-containing contraceptives, estrogen replacement therapy, and many of the selective estrogen receptor modulators (SERMs) increase the risk of venous thrombosis.[2,13] While the mechanisms are not clearly understood, estrogens increase serum **clotting factor** concentrations and induce activated protein C resistance. Increased serum estrogen concentrations may explain, in part, the increased risk of VTE during pregnancy and the postpartum period.[14]

PATHOPHYSIOLOGY

The arrest of bleeding following vascular injury, or hemostasis, is essential to life.[15] Within the vascular system, blood remains in a fluid state, transporting oxygen, nutrients, plasma proteins, and waste. With vascular injury, a dynamic interplay between **thrombogenic** (activating) and antithrombotic (inhibiting) forces result in the local formation of a hemostatic plug that seals the vessel wall and prevents further blood loss (Figs. 7–2, 7–3, and 7–4). A disruption of this delicate system of checks and balances may lead to inappropriate clot formation within the blood vessel that can obstruct blood flow or embolize to a distant vascular bed.

Under normal circumstances, the endothelial cells that line the inside of blood vessels maintain blood flow by producing a number of substances that inhibit platelet adherence, prevent the activation of the coagulation cascade, and facilitate **fibrinolysis**.[15,16] Vascular injury exposes the subendothelium (Fig. 7–3). Platelets readily adhere to the subendothelium, using glycoprotein Ib receptors found on their surfaces and facilitated by von Willebrand factor. This causes platelets to become activated, releasing a number of procoagulant substances that stimulate circulating platelets to expose glycoprotein IIb-IIIa receptors and allow platelets to adhere to one another, resulting in platelet aggregation. The damaged vascular tissue releases tissue factor which activates the extrinsic pathway of the coagulation cascade (Fig. 7–4).

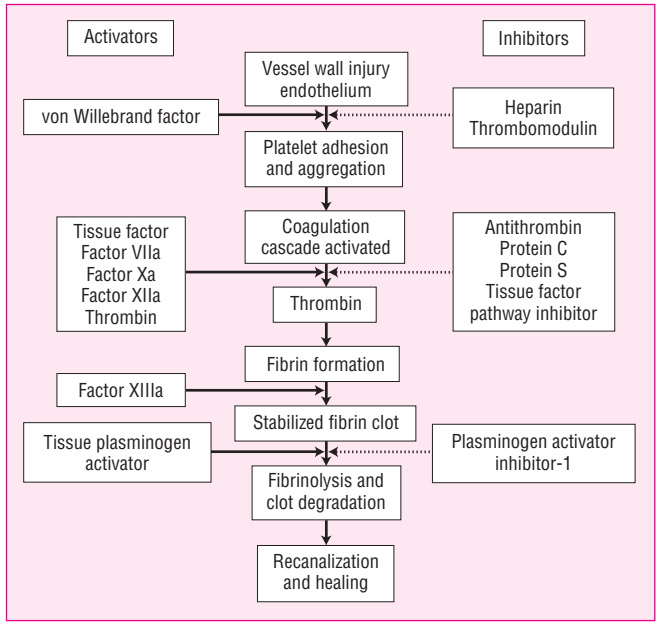


FIGURE 7–2. Hemostasis and thrombosis. (Reproduced from Haines ST, Zeolla M, Witt DM. Venous thromboembolism. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 376, with permission.)

The **clotting cascade** is a stepwise series of enzymatic reactions that result in the formation of a fibrin mesh.[15,16] Clotting factors circulate in the blood in inactive forms. Once a precursor is activated by specific stimuli, it activates the next precursor in the sequence. The final steps in the cascade are the conversion of **prothrombin** to **thrombin** and fibrinogen to **fibrin**. Thrombin plays a key role in the coagulation cascade; it is responsible not only for the production of fibrin, but also for the conversion of factors V and VIII, creating a positive feedback loop that greatly accelerates the entire cascade. Thrombin also enhances platelet aggregation. Traditionally, the coagulation cascade has been divided into three distinct parts: the intrinsic, the extrinsic, and the common pathways (Fig. 7–4). This artificial division is misleading because there are numerous interactions between the three pathways.

A number of tempering mechanisms control coagulation (Fig. 7–2).[15,16] Without effective self-regulation, the coagulation cascade would proceed unabated until all the clotting factors and platelets are consumed. The intact endothelium adjacent to the damaged tissue actively secretes several antithrombotic substances including heparan sulfate, thrombomodulin, protein C, and protein S. Activated protein C inhibits factor Va and VIIIa activity. Antithrombin and heparin cofactor II (HCII) are circulating proteins that inhibit thrombin and factor Xa. Heparan sulfate exponentially accelerates antithrombin and HCII activity. Tissue factor pathway inhibitor (TFPI) inhibits the extrinsic coagulation pathway. When these self-regulatory mechanisms are intact, the formation of the fibrin clot is limited to the zone of tissue injury. However, disruptions in the system often result in inappropriate clot formation.

The fibrinolytic protein plasmin degrades the fibrin mesh into soluble end products collectively known as fibrin split products or fibrin degradation products.[15,16] The fibrinolytic system is also under the control of a series of stimulatory and inhibitory substances. Tissue plasminogen activator (t-PA) and urokinase plasminogen activator (u-PA) convert plasminogen to plasmin. Plasminogen activator inhibitor-1 (PAI-1) inhibits the plasminogen activators and α_2-antiplasmin inhibits plasmin activity. Aberrations in the fibrinolytic system have also been linked to hypercoagulability.

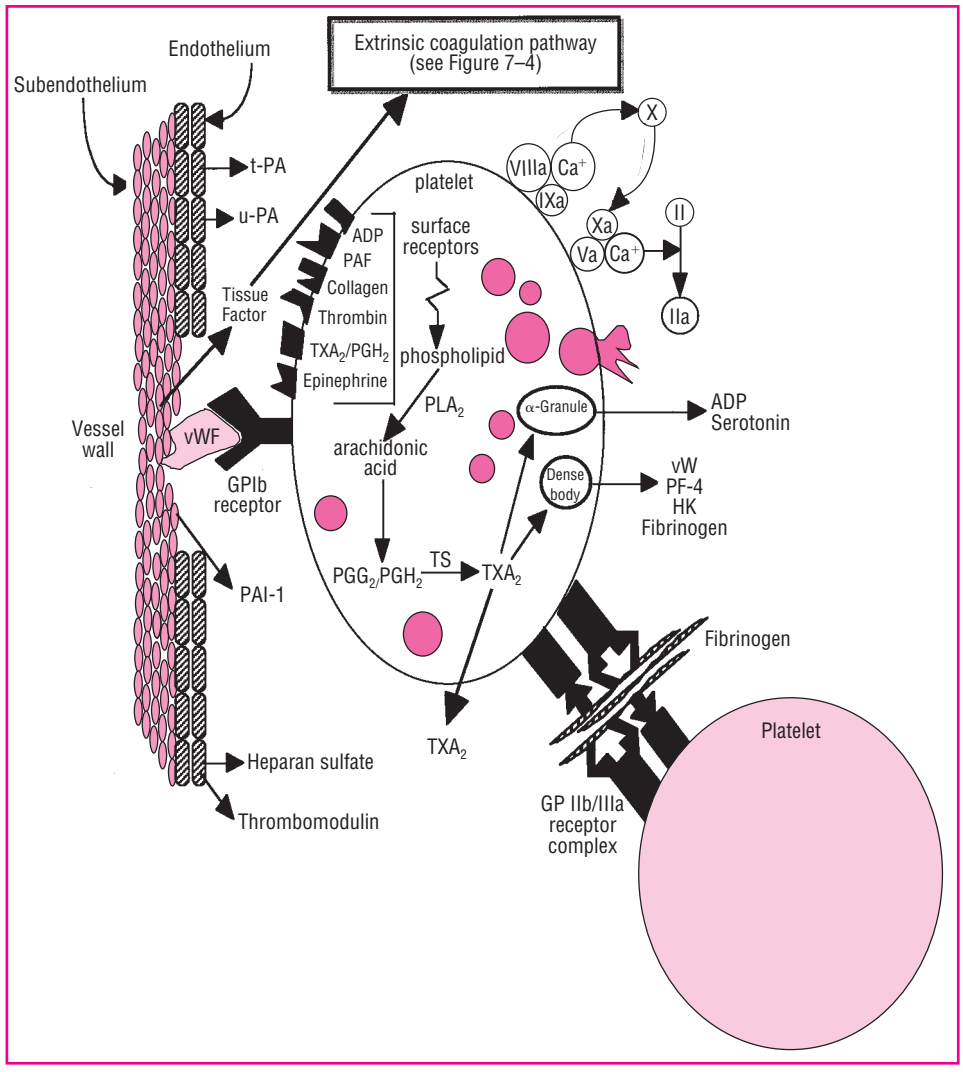


FIGURE 7–3. Vascular injury and thrombosis. ADP, adenosine diphosphate; CO, cyclooxygenase; GP Ib, glycoprotein Ib; GP IIb/IIa, glycoprotein IIb/IIa; HK, high-molecular-weight kininogen; PAF, platelet-activating factor-1; PAI-1, plasminogen activator inhibitor; PF-4 platelet factor-4; PGG/PGH, prostaglandins; PGI, prostacyclin; PLA, phospholipase A; TS, thromboxane synthetase; TXA_2, thromboxane A_2; t-PA, tissue plasminogen activator; u-PA, urokinase plasminogen activator; vWF, von Willebrand factor. (Reproduced from Haines ST, Zeolla M, Witt DM. Venous thromboembolism. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 376, with permission.)

CLINICAL PRESENTATION AND DIAGNOSIS

Although a thrombus can form in any part of the venous circulation, the majority begin in the lower extremities. Once formed, a venous thrombus may behave in several ways including: (1) remain asymptomatic, (2) spontaneously lyse, (3) obstruct the venous circulation, (4) propagate into more proximal veins, (5) embolize, and/or (6) slowly incorporate into the endothelial layer of the vessel.[15] The majority of patients with VTE never develop symptoms.[2] However, even those who initially experience no symptoms may suffer long-term consequences, such as the postthrombotic syndrome and recurrent VTE. ❸ *The symptoms of DVT or PE are nonspecific, and it is extremely difficult to distinguish VTE from other disorders.*[17] *Therefore, objective tests are required to confirm or exclude the diagnosis.* Patients with deep vein thrombosis often present with unilateral leg pain and swelling. Similarly, the postthrombotic syndrome, a long-term complication of DVT caused by damage to the venous valves, produces chronic lower extremity swelling, pain, tenderness, skin discoloration, and ulceration. The D-dimer test, a quantitative measure of fibrin breakdown in the serum, is a marker of acute thrombotic activity and may help to distinguish between an acute DVT and the post-thrombotic syndrome. Symptomatic PE often produces shortness of breath, tachypnea, and tachycardia. **Hemoptysis**, while distressing, occurs in less than one-third of patients. The physical exam may reveal diminished breath sounds, crackles, wheezes, or a pleural friction rub during auscultation of the lungs. Cardiovascular collapse, characterized by cyanosis, shock, and oliguria, is an ominous sign.[18]

Given that VTE can be debilitating or fatal, it is important to treat it quickly and aggressively.[8] On the other hand, because major bleeding induced by antithrombotic drugs can be equally harmful, it is important to avoid treatment when the diagnosis is not reasonably certain. Assessment of the patient's status should focus on the search for risk factors in the patient's medical history

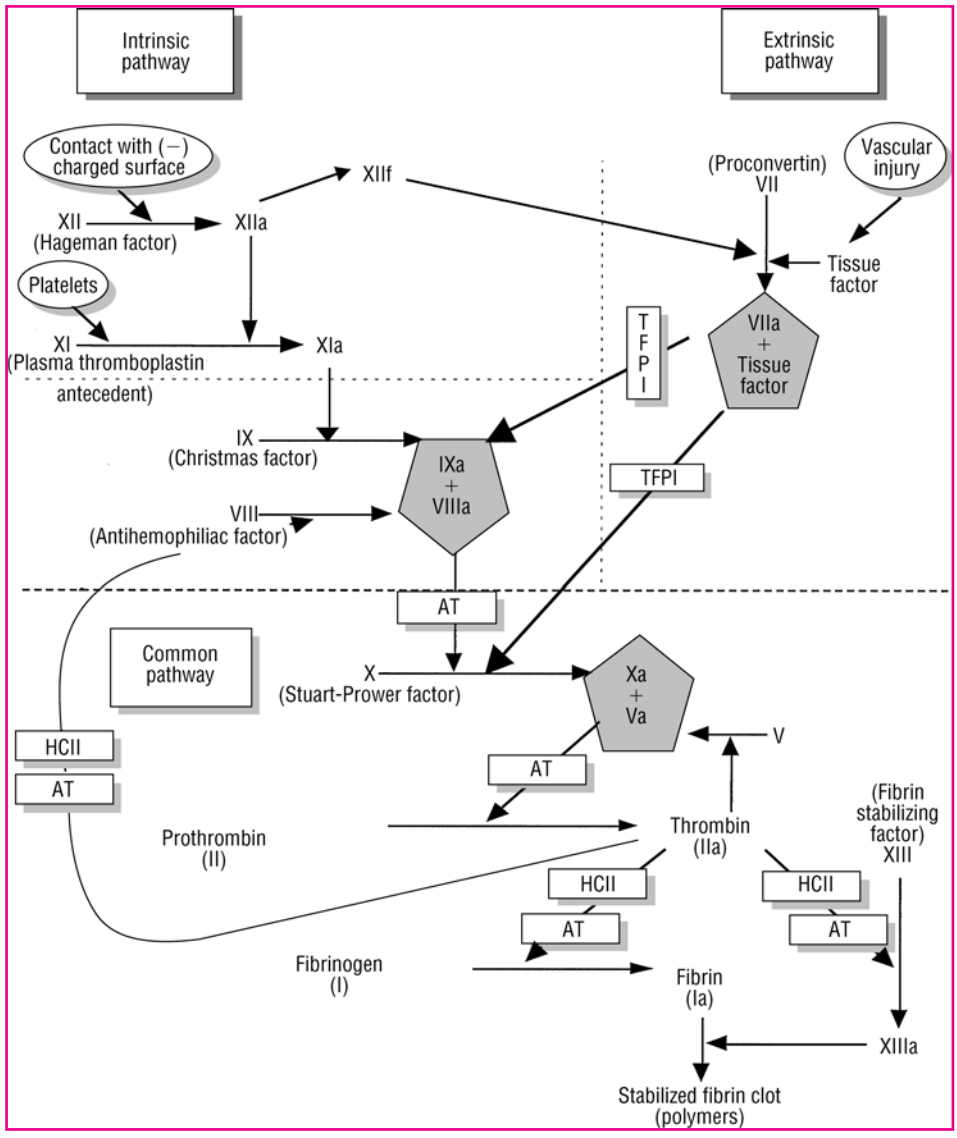


FIGURE 7–4. Coagulation cascade. AT, antithrombin; HCII, heparin cofactor II; TFPI, tissue factor pathway inhibitor. (Reproduced from Haines ST, Zeolla M, Witt DM. Venous thromboembolism. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 377, with permission.)

(Table 7–1).[17] Venous thrombosis is uncommon in the absence of risk factors, and the effects of these risks are additive. Conversely, even in the absence of symptoms, VTE should be strongly suspected in those with multiple risk factors.

Because radiographic contrast studies are the most accurate and reliable methods for the diagnosis of VTE, they are considered the gold standards in clinical trials.[17] Contrast venography allows visualization of the entire venous system in the lower extremities and abdomen. Pulmonary angiography allows the visualization of the pulmonary arteries. The diagnosis of VTE can be made if there is a persistent intraluminal filling defect observed on multiple x-ray films. Contrast studies are expensive, invasive procedures that are technically difficult to perform and evaluate. Severely ill patients often are unable to tolerate the procedure, and many develop hypotension and cardiac arrhythmias. Furthermore, the contrast medium is irritating to vessel walls and toxic to the kidneys. For these reasons, non-invasive tests, such as ultrasonography, computed tomography (CT) scans, and the ventilation/perfusion (V/Q) scan are frequently used in clinical practice for the initial evaluation of patients with suspected VTE.

PREVENTION OF VENOUS THROMBOEMBOLISM

Given that VTE is often clinically silent and potentially fatal, prevention strategies have the greatest potential to improve patient outcomes.[2] To rely on the early diagnosis and treatment of VTE is unacceptable because many patients will die before treatment can be initiated. Furthermore, even clinically silent disease is associated with long-term morbidity from the postthrombotic syndrome and predisposes the patient to future thromboembolic events. Despite an immense body of literature that overwhelmingly supports the widespread use of



Clinical Presentation and Diagnosis of Deep Vein Thrombosis

General

Venous thromboembolism most commonly develops in patients with identifiable risk factors (Table 7–1) during or following a hospitalization. Many, perhaps the majority of patients, have asymptomatic disease. Patients may die suddenly of pulmonary embolism.

Symptoms

- The patient may complain of leg swelling, pain, or warmth. Symptoms are non-specific and objective testing must be performed to establish the diagnosis.

Signs

- The patient's superficial veins may be dilated and a "palpable cord" may be felt in the affected leg.
- The patient may experience pain in back of the knee in the affected leg when the examiner dorsiflexes the foot while the knee is slightly bent.

Laboratory Tests

- Serum concentrations of D-dimer, a by-product of thrombin generation, is usually elevated. The patient may have an elevated erythrocyte sedimentation rate (ESR) and white blood cell (WBC) count.

Diagnostic Tests

- Duplex ultrasonography is the most commonly used test to diagnosis DVT. It is a non-invasive test that can measure the rate and direction of blood flow and visualize clot formation in proximal veins of the legs. It cannot reliably detect small blood clots in distal veins. Coupled with a careful clinical assessment, it can rule in or out (include or exclude) the diagnosis in the majority of cases.
- Venography (also known as phlebography) is the gold standard for the diagnosis of DVT. However, it is an invasive test that involves injection of radiopaque contrast dye into a foot vein. It is expensive and can cause anaphylaxis and nephrotoxicity.



Clinical Presentation and Diagnosis of Pulmonary Embolism

General

Pulmonary embolism most commonly develops in patients with risk factors for VTE (Table 7–2) during or following a hospitalization. While many patients will have symptoms of DVT prior to developing a PE, many do not. Patients may die suddenly before effective treatment can be initiated.

Symptoms

- The patient may complain of cough, chest pain, chest tightness, shortness of breath, or palpitations.
- The patient may spit or cough up blood (hemoptysis).
- The patient may complain of dizziness or lightheadedness.
- Symptoms may be confused for a myocardial infarction and objective testing must be performed to establish the diagnosis.

Signs

- The patient may have tachypnea (increased respiratory rate) and tachycardia (increased heart rate).
- The patient may appear diaphoretic (sweaty).
- The patient's neck veins may be distended.
- The examiner may hear diminished breath sounds, crackles, wheezes, or pleural friction rub during auscultation of the lungs.
- In massive PE, the patient may appear cyanotic and may become hypotensive. In such cases, oxygen saturation by pulse oximetry or arterial blood gas will likely indicate that the patient is hypoxic.
- In the worst cases, the patient may go into circulatory shock and die within minutes.

Laboratory Tests

- Serum concentrations of D-dimer, a by-product of thrombin generation, is usually elevated. The patient may have an elevated ESR and WBC count.

Diagnostic tests

- V/Q scan and CT scans are the most commonly used tests to diagnose PE. A V/Q scan measures the distribution of blood and air flow in the lungs. When there is a large mismatch between blood and air flow in one area of the lung, there is a high probability that the patient has a PE. Spiral CT scans can detect emboli in the pulmonary arteries.
- Pulmonary angiography is the gold standard for the diagnosis of PE. However, it is an invasive test that involves injection of radiopaque contrast dye into the pulmonary artery. The test is expensive and associated with a significant risk of mortality.

pharmacologic and nonpharmacologic strategies to prevent VTE, prophylaxis is underutilized in most hospitals. Even when prophylaxis is given, many patients receive prophylaxis that is less than optimal. Educational programs and computerized clinical decision support systems have been shown to improve the appropriate use of VTE prevention methods.[2]

The goal of an effective VTE prophylaxis program is to identify all patients at risk, determine each patient's level of risk, and select and implement regimens that provide sufficient protection for the level of risk. ❹ *At the time of hospital admission, all patients should be evaluated for their risk of VTE, and strategies to prevent VTE appropriate for each patient's level of risk should be routinely employed. Prophylaxis should be continued throughout the period of risk.* The risk classification criteria and recommended prophylaxis strategies published by the American College of Chest Physicians (ACCP) Conference on Antithrombotic Therapy are widely used in North America (Table 7–2).[2] Several pharmacologic and nonpharmacologic methods are effective for preventing VTE, and these can be used alone or in combination. Nonpharmacologic methods improve venous blood flow by

TABLE 7–2. Risk Classification and Consensus Guidelines for VTE Prevention[2]

Level of Risk	Calf Vein Thrombosis (%)	Symptomatic PE (%)	Fatal PE (%)	Prevention Strategies
Low				
Minor surgery, age less than 40 years, and no clinical risk factors	2	0.2	0.002	Ambulation
Moderate				
Major or minor surgery, age 40–60 years, and no clinical risk factors Major surgery, age less than 40 years, and no clinical risk factors Minor surgery, with clinical risk factor(s) Acutely ill (e.g., myocardial infarction, ischemic stroke, heart failure exacerbation), and no clinical risk factors	10–20	1–2	0.1–0.4	UFH 5000 units SC every 12 hours Dalteparin 2500 units SC every 24 hours Enoxaparin 40 mg SC every 24 hours Tinzaparin 3500 units SC every 24 hours IPC Graduated compression stockings
High				
Major surgery, age greater than 60 years, and no clinical risk factors Major surgery, age 40–60 years, with clinical risk factor(s) Acutely ill (e.g., myocardial infarction, ischemic stroke, heart failure exacerbation), with clinical risk factor(s)	20–40	2–4	0.4–1	UFH 5000 units SC every 8 hours Dalteparin 5000 units SC every 24 hours Enoxaparin 40 mg SC every 24 hours Fondaparinux 2.5 mg SC every 24 hours Tinzaparin 75 units/kg SC every 24 hours IPC
Highest				
Major lower extremity orthopedic surgery Hip fracture Multiple trauma Major surgery, age greater than 40 years, and prior history of VTE Major surgery, age greater than 40 years, and malignancy Major surgery, age greater than 40 years, and hypercoagulable state Spinal cord injury or stroke with limb paralysis	40–80	4–10	0.2–5	Adjusted dose UFH SC every 8 hours (aPTT greater than 36 seconds) Dalteparin 5000 units SC every 24 hours Desirudin 15 mg SC every 12 hours Enoxaparin 30 mg SC every 12 hours Fondaparinux 2.5 mg SC every 24 hours Tinzaparin 75 units/kg SC every 24 hours Warfarin (target INR = 2–3) IPC with UFH 5000 units SC every 8 hours

aPTT, activated partial thromboplastin time; INR, International Normalized Ratio; IPC, intermittent pneumatic compression; PE, pulmonary embolism; SC, subcutaneous; UFH, unfractionated heparin; VTE, venous thromboembolism.

mechanical means, while drug therapy prevents thrombus formation by inhibiting the coagulation cascade.

Nonpharmacologic Therapy

Ambulation as soon as possible following surgery lowers the incidence of VTE in low-risk patients.[2] Walking increases venous blood flow and promotes the flow of natural antithrombotic factors into the lower extremities. Graduated compression stockings (GCS) reduce the incidence of VTE by approximately 60% following general surgery, neurosurgery, and stroke. Compared with anticoagulant drugs, graduated compression stockings are relatively inexpensive and safe. They are a good choice in low- to moderate-risk patients when pharmacologic interventions are contraindicated. When combined with pharmacologic interventions, graduated compression stockings have an additive effect. However, some patients are unable to wear compression stockings because of the size or shape of their legs.

Similar to graduated compression stockings, intermittent pneumatic compression (IPC) devices increase the velocity of blood flow in the lower extremities.[2] These devices sequentially inflate a series of cuffs wrapped around the patient's legs from the ankles to the thighs and then deflate in 1- to 2-minute cycles. IPC has been shown to reduce the risk of VTE by more than 60% following general surgery, neurosurgery, and orthopedic surgery. Although IPC is well tolerated and safe to use in patients who have contraindications to pharmacologic therapies, it does have a few drawbacks: it is more expensive than the use of graduated compression stockings, it is a relatively cumbersome technique, and some patients may have difficulty sleeping while using it. Continuous passive motion devices, electrical calf muscle stimulation, and plantar compression system devices are also used in some institutions,

but they have not been shown to be as effective as other mechanical methods.

Inferior vena cava (IVC) filters, also known as Greenfield filters, provide short-term protection against pulmonary embolism in very-high-risk patients by preventing the **embolization** of a thrombus formed in the lower extremities into the pulmonary circulation.[2] Insertion of a filter into the IVC is a minimally invasive procedure. Despite the widespread use of IVC filters, there are very limited data regarding their effectiveness and long-term safety. The evidence suggests that IVC filters, particularly in the absence of effective antithrombotic therapy, increase the long-term risk of recurrent DVT. In the only randomized clinical trial examining the short- and long-term effectiveness of the filters in patients with a documented proximal DVT, treatment with IVC filters reduced the risk of pulmonary embolism by more than 75% during the first 12 days following insertion.[19] However, this benefit was not sustained during 2 years of follow-up and the long-term risk of recurrent deep vein thrombosis was nearly two-fold higher in those who received a filter. Although IVC filters can reduce the short-term risk of PE in patients at highest risk, they should be reserved for patients in whom other prophylactic strategies cannot be used. To further reduce the long-term risk of VTE in association with IVC filters, pharmacologic prophylaxis is necessary and warfarin therapy should begin as soon as the patient is able to tolerate it.

Pharmacologic Therapy

Numerous randomized clinical trials have extensively evaluated pharmacologic strategies for VTE prophylaxis.[2] Appropriately selected drug therapies can dramatically reduce the incidence of VTE following hip replacement, knee replacement, general surgery, myocardial infarction, and ischemic stroke (Table 7–2). The choice of medication and dose to use for VTE prevention must be based on the patient's level of risk for thrombosis and bleeding complications, as well as the cost and availability of an adequate drug therapy monitoring system.

The ACCP Conference on Antithrombotic Therapy recommended against the use of aspirin as the primary method of VTE prophylaxis.[2] Antiplatelet drugs clearly reduce the risk of coronary artery and cerebrovascular events in patients with arterial disease, but aspirin produces a very modest reduction in VTE following orthopedic surgeries of the lower extremities. The relative contribution of venous stasis in the pathogenesis of venous thrombosis compared with that of platelets in arterial thrombosis likely explains the reason for this difference.

The most extensively studied drugs for the prevention of VTE are unfractionated heparin (UFH), the low-molecular-weight heparins (LMWHs; dalteparin, enoxaparin, and tinzaparin), fondaparinux, and warfarin.[2] The LMWHs and fondaparinux provide superior protection against VTE when compared to low-dose unfractionated heparin after hip and knee replacement surgery and in other very-high-risk populations. Even so, unfractionated heparin remains a highly effective, cost-conscious choice for many patient populations, provided that it is given in the appropriate dose (Table 7–2). Low-dose UFH (5000 units every 8 or 12 hours) given subcutaneously (SC) has been shown to reduce the risk of VTE by 55% to 70% both in patients undergoing a wide range of general surgical procedures and following a myocardial infarction or stroke. For the prevention of VTE following hip and knee replacement surgery, the effectiveness of low-dose UFH is considerably lower. Adjusted-dose UFH therapy provided subcutaneously, which requires dose adjustments to maintain the activated partial thromboplastin time (aPTT) at the high end of the normal range, may be used in the highest-risk patient populations. However, adjusted-dose UFH has been studied in only a few, relatively small clinical trials and requires frequent laboratory monitoring. The LMWHs and fondaparinux appear to provide a high degree of protection against VTE in most high-risk populations. The appropriate prophylactic dose for each LMWH product is indication-specific (Table 7–2). There is no evidence that one LMWH is superior to another for the prevention of VTE. Fondaparinux was significantly more effective than enoxaparin in several clinical trials that enrolled patients undergoing high-risk orthopedic procedures, but has not been shown to reduce the incidence of symptomatic pulmonary embolism or mortality.[20] To provide optimal protection, some experts believe that the LMWHs should be initiated prior to surgery.[2]

Warfarin is another commonly used option for the prevention of VTE following orthopedic surgeries of the lower extremities.[2] Warfarin appears to be as effective as the LMWHs for the prevention of symptomatic VTE events in the highest-risk populations. When used to prevent VTE, the dose of warfarin must be adjusted to maintain an **International Normalized Ratio** (INR) between 2 and 3. Oral administration and low drug cost give warfarin some advantages over the LMWHs and fondaparinux. However, warfarin does not achieve its full antithrombotic effect for several days, requires frequent monitoring and periodic dosage adjustments, and carries a substantial risk of major bleeding. Warfarin should only be used when a systematic patient monitoring system is available.

The optimal duration for VTE prophylaxis following surgery is not well established.[2] Prophylaxis should be given throughout the period of risk. For general surgical procedures and medical conditions, once the patient is able to ambulate regularly and other risk factors are no longer present, prophylaxis can be discontinued. The risk of VTE in the first month following hospital discharge among patients who have undergone total hip replacement or hip fracture repair is very high. Therefore, extended prophylaxis for 21 to 35 days following hospital discharge with an LMWH, fondaparinux, or warfarin is recommended.



Patient Encounter 1, Part 1

KK is a 69-year-old obese female who fell on her way to church and fractured her right hip. She is hospitalized and will undergo surgery to repair her fractured right hip.

PMH
Hypertension × 12 years; dyslipidemia × 10 years; obesity × 20 years; degenerative joint disease × 5 years; recurrent urinary tract infections

FH
Non-significant

SH
Smoke one-half pack per day for 25 years; occasional alcohol use
The patient has Medicare, but due to her fixed income, has difficulty paying for medications, leading to occasional periods of non-compliance.

Current Meds
Metoprolol 100 mg by mouth twice daily
Hydrochlorothiazide 25 mg by mouth daily
Vytorin 10/40 (ezetimibe 10 mg/simvastatin 40 mg) by mouth daily
Salsalate 750 mg by mouth twice daily
Trimethoprim-sulfamethoxazole SS tablets by mouth twice daily for 7 days (last treatment was 1 month ago)
Shark cartilage 3 tablets by mouth daily
Enteric-coated aspirin 81 mg by mouth daily
Ginseng 2 tablets by mouth daily

Allergies
No known drug allergies

PE
VS: blood pressure 145/90 mm Hg; heart rate, 72; respiratory rate, 16; temperature , 37.4ºC (99.3°F); weight 280 lb (127.3 kg); body mass index (BMI) 40 kg/m^2

Labs
Within normal limits; estimated glomerular filtration rate = 74 mL/minute

- Which risk factor(s) predispose KK to VTE?
- What is KK's estimated risk for developing VTE?
- Given KK's presentation and history, create an appropriate VTE prophylaxis plan including the pharmacologic agent, dose, route and frequency of administration, duration of therapy, monitoring parameters, and patient education.

TREATMENT OF VENOUS THROMBOEMBOLISM

Desired Therapeutic Outcomes

The goal of VTE treatment is to prevent short- and long-term complications of the disease. In the short-term (i.e., the first few days to 6 months), the aim of therapy is to prevent propagation or local extension of the clot, embolization, and death. In the long-term (i.e., more than 6 months after the first event), the aim of therapy is to prevent complications, such as the postthrombotic syndrome, pulmonary hypertension, and recurrent VTE.[8, 21]

General Treatment Principles

Anticoagulant drugs are considered the mainstay of therapy for patients with VTE, and the therapeutic strategies for DVT and PE are essentially identical.[8, 22] ❺ *In the absence of contraindications, the treatment of VTE should initially include a rapid-acting anticoagulant (e.g., unfractionated heparin, low-molecular-weight heparin, or fondaparinux) overlapped with warfarin for at least 5 days and until the patient's International Normalized Ratio (INR) is greater than 2. Anticoagulation therapy should be continued for a minimum of 3 months. However, the duration of anticoagulation therapy should be based on the patient's risk of VTE recurrence and major bleeding.* The treatment of VTE can be divided into acute, subacute, and chronic phases (Fig. 7–5).[23,24] The acute treatment phase of VTE is typically accomplished by administering a fast-acting parenteral anticoagulant (Table 7–3). The subacute and chronic phase treatments of VTE are usually accomplished using oral anticoagulant agents, such as warfarin.[8,24] In certain populations, such as patients with cancer and women who are pregnant, the LMWHs are the preferred agents during subacute and chronic treatment phases.[8] In the last decade, several novel anticoagulants, such as direct thrombin inhibitors and factor Xa inhibitors have emerged as potential alternatives for the acute, subacute, and chronic phases of treatment. As data from clinical trials using these new agents in VTE treatment continue to emerge, their role in clinical practice will be better understood.[8,21]

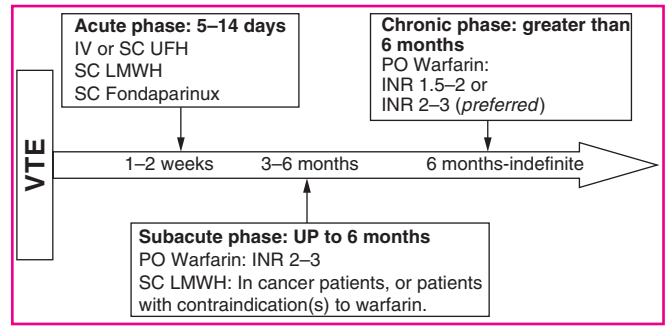


FIGURE 7–5. Treatment approach for patients with VTE. INR, International Normalized Ratio; IV, intravenous; LMWH, low-molecular-weight heparin; PO, oral; SC, subcutaneous; UFH, unfractionated heparin; VTE, venous thromboembolism. (Adapted from Nutescu EA. Emerging options in the treatment of venous thromboembolism. Am J Health Syst Pharm 2004;61(Suppl 7):S16, with permission.)

TABLE 7–3. Pharmacologic Options for the Initial Treatment of Acute VTE[21,24,34]

Unfractionated Heparin

IV administration:[a] use weight-based dosing nomogram (Table 7–5)
or
SC administration: 17,500 units given every 12 hours (an initial 5000 unit IV bolus dose is recommended to obtain rapid anticoagulation)
Adjust subsequent doses to attain a goal aPTT based on the institution-specific therapeutic range

Low-Molecular-Weight Heparins

Dalteparin:[b] 200 units/kg SC once daily **or** 100 units/kg SC twice daily
Enoxaparin: 1.5 mg/kg SC once daily **or** 1 mg/kg SC twice daily; if CrCl is less than 30 mL/minute: 1 mg/kg SC once daily
Tinzaparin: 175 units/kg SC once daily

Factor Xa Inhibitor

Fondaparinux:
For body weight less than 50 kg (110 lb) use 5 mg SC once daily
For body weight 50–100 kg (110–220 lb) use 7.5 mg SC once daily
For body weight greater than 100 kg (220 lb) use 10 mg SC once daily

[a]IV administration preferred due to improved dosing precision.
[b]Not FDA approved for treatment of VTE.
aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; FDA, Food and Drug Administration; IV, intravenous; SC, subcutaneous; VTE, venous thromboembolism.

TABLE 7–4. Thrombolysis for the Treatment of VTE

- Thrombolytic therapy should be reserved for patients who present with shock, hypotension, right ventricular strain, or massive DVT with limb gangrene
- Diagnosis must be objectively confirmed before initiating thrombolytic therapy
- Thrombolytic therapy is most effective when administered as soon as possible after PE diagnosis, but benefit may extend up to 14 days after symptom onset
- Approved PE thrombolytic regimens:
  - Streptokinase 250,000 units intravenously over 30 minutes followed by 100,000 units/hour for 24 hours[a]
  - Urokinase 4400 units/kg intravenously over 10 minutes followed by 4400 units/kg/hour for 12–24 hours[a]
  - Alteplase 100 mg intravenously over 2 hours
- Factors that increase the risk of bleeding must be evaluated before thrombolytic therapy is initiated (i.e., recent surgery, trauma or internal bleeding, uncontrolled hypertension, recent stroke, or intracranial hemorrhage)
- Baseline labs should include CBC and blood typing in case transfusion is needed
- Unfractionated heparin should not be used during thrombolytic therapy. Neither the aPTT nor any other anticoagulation parameter should be monitored during the thrombolytic infusion
- aPTT should be measured following the completion of thrombolytic therapy:
  - If aPTT less than 2.5 times the control value, unfractionated heparin infusion should be started and adjusted to maintain aPTT in therapeutic range
  - If aPTT greater than 2.5 times the control value, remeasure every 2–4 hours and start unfractionated heparin infusion when aPTT is less than 2.5
- Avoid phlebotomy, arterial puncture, and other invasive procedures during thrombolytic therapy to minimize the risk of bleeding

[a]2-Hour infusions of streptokinase and urokinase are as effective and safe as alteplase. aPTT, activated partial thromboplastin time; CBC, complete cell blood count; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Treatment Options

Pharmacologic Therapy

Thrombolytics

The role of **thrombolysis** in the treatment of VTE is controversial. **Thrombolytic** agents are proteolytic enzymes that have the ability to dissolve, or lyse, the fibrin clot. Thrombolytics are administered systemically or directly into the thrombus using a catheter-directed infusion.[8] Compared to anticoagulants, thrombolytics restore venous patency more quickly; however, the bleeding risk associated with their use is significantly higher.[25] In patients with DVT, thrombolytics decrease short-term pain and swelling and prevent destruction of the venous valves. It is not clear if thrombolytics decrease the incidence and severity of postthrombotic syndrome. Clinical trials have failed to show any long-term benefits from the routine use of thrombolytics; therefore, their use in the majority of patients is not recommended.[8,25] In a select group of high-risk patients with massive iliofemoral DVT who are at risk of limb gangrene, thrombolysis may be considered[8] (Table 7–4).

In patients with acute PE, the use of thrombolytics provides short-term benefits such as restoring pulmonary artery patency and hemodynamic stability.[8,26] A recent meta-analysis of nine small randomized clinical trials showed a slightly lower risk of death or recurrent PE in patients treated with thrombolytics when compared to those treated with heparin alone. However, this small benefit was offset by a higher risk of major bleeding.[27] Tissue plasminogen activator (t-PA), streptokinase, and urokinase have all been studied and are Food and Drug Administration (FDA) approved in the treatment of PE. All three agents have comparable thrombolytic capacity but t-PA has the potential advantage of a shorter infusion time. Reteplase is not currently FDA-approved for the treatment of PE, but it has also been studied. Reteplase is administered as two 10 unit IV boluses given 30 minutes apart.[8,28] Given the relative lack of data to support their routine use, thrombolytics should be reserved for select high risk circumstances (Table 7–4). Candidates for thrombolytic therapy are patients with acute massive **embolism** who are hemodynamically unstable [systolic blood pressure (SBP) less than 90 mm Hg] and at low risk for bleeding.[8] The use of thrombolytics in hemodynamically stable patients with right ventricular dysfunction is controversial but some experts support their use.

Unfractionated Heparin

Unfractionated heparin has traditionally been the drug of choice for indications requiring a rapid anticoagulation, including the acute treatment of VTE. Commercially available UFH preparations are isolated from porcine intestinal mucosa or bovine lung. Unfractionated heparin is composed of a heterogeneous mixture of glycosaminoglycans with variable length, molecular weight, and pharmacologic properties. Unlike thrombolytics, UFH and other anticoagulants will not dissolve a formed clot but prevent its propagation and growth.[5,29] Heparin exerts its anticoagulant effect by augmenting the natural anticoagulant antithrombin (AT). A specific pentasaccharide sequence on the heparin molecule binds to AT and causes a conformational change that greatly accelerates its activity (Fig. 7–6). This complex inhibits thrombin (factor IIa), as well as factors Xa, IXa, XIa, and XIIa. Thrombin and factor Xa are most sensitive to this inhibition and are inactivated in an equal 1:1 ratio. In order to inactivate thrombin, the UFH molecule needs to form a ternary complex by binding to both AT and thrombin. Only UFH molecules that are at least 18 saccharide units long are able to form this bridge between AT and thrombin. In contrast, inhibition of factor Xa does not require the formation of a ternary complex. Unfractionated heparin molecules as short as five saccharide units can catalyze the inactivation of factor Xa. Due to its nonspecific binding to cellular proteins, UFH has several limitations, including poor bioavailability when given subcutaneously and significant intra- and interpatient variability in anticoagulant response.[5,22]

Unfractionated heparin can be administered via the intravenous (IV) or subcutaneous (SC) route. When rapid anticoagulation is required, unfractionated heparin should be administered intravenously and an initial bolus dose should be given. For the treatment of VTE, UFH is generally given as a continuous IV infusion. Intermittent IV bolus dosing is associated with a higher risk of bleeding and is therefore not recommended. When given SC, the bioavailability of UFH ranges from 30% to 70%, depending on the dose given. Therefore, higher doses of unfractionated heparin must be given if the SC route of administration is used. Onset of anticoagulation is delayed by 1 to 2 hours after the SC injection. Due to the risk of hematomas and erratic absorption, intramuscular (IM) administration is not recommended. The half-life of UFH is dose dependent and ranges from 30 to 90 minutes, but may be significantly longer, up to 150 minutes, with high doses. Unfractionated heparin is eliminated by two mechanisms: (1) enzymatic degradation via a saturable zero-order process, and (2) renally via a first-order process. Lower UFH doses are primarily cleared via enzymatic processes, while higher doses are primarily renally eliminated. Clearance

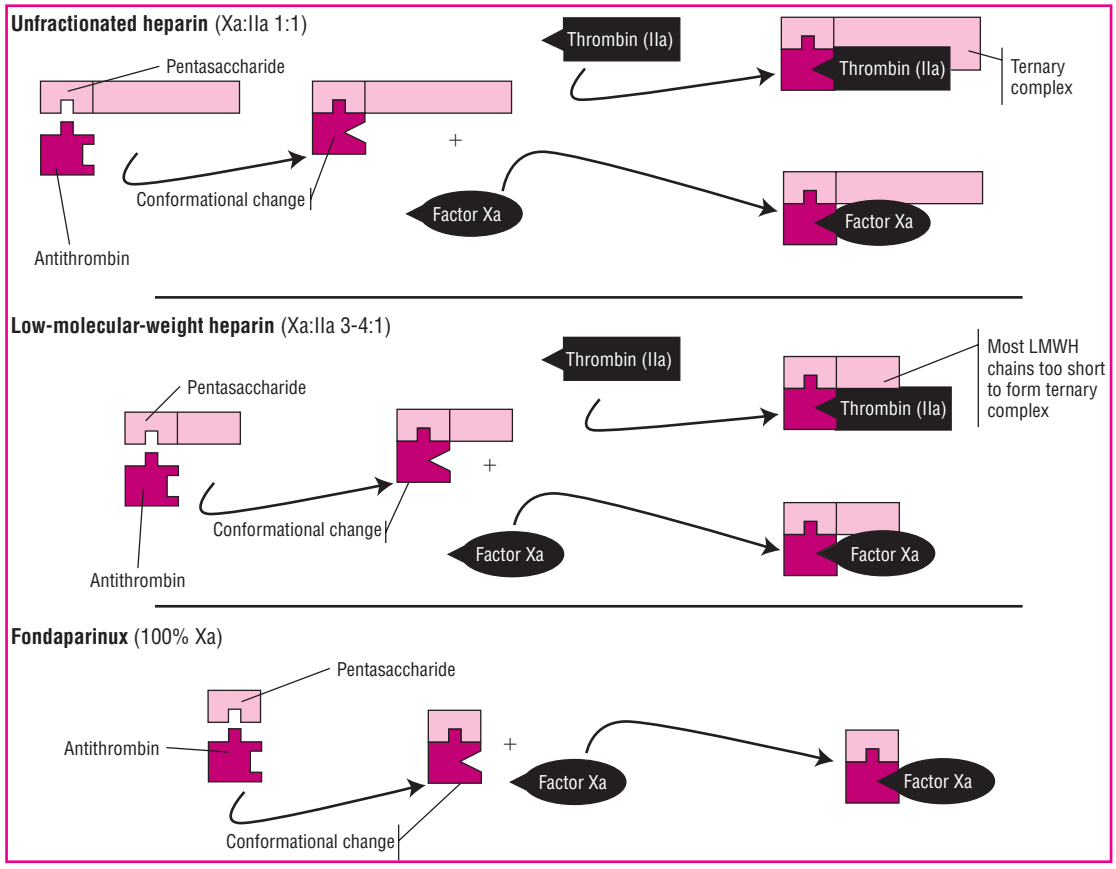


FIGURE 7–6. Mechanism of action of unfractionated heparin, low-molecular-weight heparin (LMWH), and fondaparinux. (Reproduced from Haines ST, Zeolla M, Witt DM. Venous thromboembolism. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 381, with permission.)

of UFH can be impaired in patients with renal and hepatic dysfunction. Patients with active thrombosis may require higher UFH doses due to a more rapid elimination or variations in the plasma concentrations of heparin-binding proteins. Antithrombin deficiency and elevated factor VIII levels that are common in pregnant patients have also been linked to higher UFH dose requirements. The requirement of these higher UFH doses is termed "heparin resistance."[5,15]

The dose of UFH required to achieve a therapeutic anticoagulant response is correlated to the patient's weight. Traditional dosing regimens consist of a 5000 unit bolus dose followed by an infusion administered at 1000 to 1200 units/hour.[5] However, weight-based dosing regimens are more likely to exceed the therapeutic threshold in the first 24 hours after initiating treatment.[30] Achieving a therapeutic aPTT in the first 24 hours after initiating unfractionated heparin is critical because this has been shown to lower the risk of recurrent VTE.[5,30] For non-obese patients, the actual body weight should be used to calculate the initial UFH dose (Table 7–5). For obese patients, using the actual body weight to calculate the initial dose is controversial. Some experts recommend using an adjusted body weight instead. The infusion rate is then adjusted based on laboratory monitoring of the patient's response. Unfractionated heparin can also be administered via the SC route; however, IV infusion is preferred by most clinicians because it can be dosed more precisely. If the SC route is selected, an initial 5000 unit IV bolus should be given followed by 17,500 units given SC every 12 hours. Subsequent doses of SC unfractionated heparin need to be adjusted based on the patient's response.[5,8]

TABLE 7–5. Weight-Based[a] Dosing for UFH Administered by Continuous Intravenous Infusion for Venous Thromboembolism

Initial Loading Dose	Initial Infusion Rate
80–100 units/kg (maximum = 10,000 units)	17–20 units/kg/hour (maximum = 2300 units/hour)
	Maintenance Infusion Rate
aPTT (seconds)	**Dose Adjustment**
Less than 37 (or less than 12 seconds below institution-specific therapeutic range)	80 units/kg bolus then increase infusion by 4 units/kg/hour
37–47 (or 1–12 seconds below institution-specific therapeutic range)	40 units/kg bolus then increase infusion by 2 units/kg/hour
48–71 (within institution-specific therapeutic range)	No change
72–93 (or 1–22 seconds above institution-specific therapeutic range)	Decrease infusion by 2 units/kg/hour
Greater than 93 (or greater than 22 seconds above institution-specific therapeutic range)	Hold infusion for 1 hour then decrease by 3 units/kg/hour

[a]Use actual body weight for all calculations. Adjusted body weight (ABW) may be used for obese patients (greater than 130% of IBW). ABW = IBW + (actual body weight − IBW) × 0.7.
aPTT, activated partial thromboplastin time; IBW, ideal body weight; UFH, unfractionated heparin.

❶ *Due to significant variability in interpatient response and changes in patient response over time, unfractionated heparin requires close monitoring and periodic dose adjustment.* The response to unfractionated heparin can be monitored using a variety of laboratory tests including the aPTT, the whole blood clotting time, activated clotting time (ACT), anti–factor Xa activity, and the plasma heparin concentration.[5,31] Although it has several limitations, the aPTT is the most widely used test in clinical practice to monitor UFH. Traditionally, therapeutic aPTT range is defined as 1.5 to 2.5 times the control aPTT value. However, due to variations in the reagents and instruments used to measure the aPTT in different laboratories, each institution should establish a therapeutic range for UFH. The institution-specific therapy range should correlate with a plasma heparin concentration of 0.2 to 0.4 units/mL by protamine titration or 0.3 to 0.7 units/mL by an amidolytic anti–factor Xa assay.[5,31] An aPTT should be obtained at baseline, 6 hours after initiating the heparin infusion, and 6 hours after each dose change, as this is the time required to reach steady state. The UFH dose is then adjusted based on the aPTT measurement and the institutional-specific therapeutic range. (Table 7–5) In patients with "heparin resistance," anti–factor Xa concentrations may be a more accurate method of monitoring the patient's response.[5,31]

Side effects associated with UFH include bleeding, thrombocytopenia, hypersensitivity reactions, and with prolonged use, alopecia, hyperkalemia, and osteoporosis.[22,29] ❻ *Bleeding is the most common adverse effect associated with antithrombotic drugs, including UFH therapy. A patient's risk of major hemorrhage is related to the intensity and stability of therapy, age, concurrent drug use, history of gastrointestinal bleeding, risk of falls or trauma, and recent surgery.* Several risk factors can increase the risk of unfractionated heparin–induced bleeding (Table 7–6). The risk of bleeding is related to the intensity of anticoagulation.

TABLE 7–6. Risk Factors for Major Bleeding While Taking Anticoagulation Therapy

Anticoagulation intensity (e.g., INR greater than 5, aPTT greater than 120 seconds)
Initiation of therapy (first few days and weeks)
Unstable anticoagulation response
Age greater than 65 years
Concurrent antiplatelet drug use
Concurrent non-steroidal anti-inflammatory drug or aspirin use
History of gastrointestinal bleeding
Recent surgery or trauma
High risk for fall/trauma
Heavy alcohol use
Renal failure
Cerebrovascular disease
Malignancy

aPTT, activated partial thromboplastin time; INR, International Normalized Ratio.

Higher aPTT values are associated with an increased risk of bleeding. The risk of major bleeding is 1% to 5% during the first few days of treatment. [3] In addition to the aPTT, hemoglobin, hematocrit, and blood pressure should also be monitored. Concurrent use of UFH with other antithrombotic agents, such as thrombolytics and antiplatelet agents, also increases the risk of bleeding. Patients receiving UFH therapy should be closely monitored for signs and symptoms of bleeding, including epistaxis, hemoptysis, hematuria, bright red blood per rectum, tarry stools, severe headache, and joint pain. If major bleeding occurs, UFH should be stopped immediately and the source of bleeding treated.[3,5] If necessary, use protamine sulfate to reverse the effects of UFH. The usual dose is 1 mg protamine sulfate per 100 units of UFH, up to a maximum of 50 mg, given as a slow IV infusion over 10 minutes. The effects of UFH are neutralized in 5 minutes, and the effects of protamine persist for 2 hours. If the bleeding is not controlled or the anticoagulant effect rebounds, repeated doses of protamine may be administered.[5]

Heparin-induced thrombocytopenia (HIT) is a very serious adverse effect associated with UFH use. Platelet counts should be monitored every 2 to 3 days during the course of UFH therapy.[5] HIT should be suspected if the platelet count drops by more than 50% from baseline or to below 120,000. In patients with contraindications to anticoagulation therapy, UFH should not be administered (Table 7–7).

Unfractionated heparin is an FDA pregnancy category C drug and may be used to treat VTE during pregnancy. Unfractionated heparin should be used with caution in the peripartum period due to the risk of maternal hemorrhage. Unfractionated heparin is not secreted into the breast milk and is safe for use by women who wish to breastfeed.[14] For the treatment of VTE in children, the UFH dose is 50 units/kg bolus followed by an infusion of 20,000 units/m^2/24 hours. Alternatively, a loading dose of 75 units/kg followed by an infusion of 28 units/kg/hour if less than 12 months old and 20 units/kg/hour if greater than 1 year old may be considered.[32]

Low-Molecular-Weight Heparins

The LMWHs are smaller heparin fragments obtained by chemical or enzymatic depolymerization of UFH. Low-molecular-weight heparins are heterogeneous mixtures of glycosaminoglycans and each product has slightly different molecular weight distributions and pharmacologic properties.[5] Compared with unfractionated heparin, LMWHs have improved pharmacodynamic and pharmacokinetic properties. They exhibit less binding to plasma and cellular proteins, resulting in a more predictable anticoagulant response. Consequently, routine monitoring of anticoagulation activity and dose adjustments are not required in the majority of patients. Low-molecular-weight heparins have longer plasma half-lives, allowing once- or twice-daily administration, improved subcutaneous bioavailability, and dose-independent renal clearance. In addition, LMWHs have a more favorable side-effect profile than UFH. They are also associated with a lower incidence of HIT and osteopenia. Three LMWHs are currently available in the United States: dalteparin, enoxaparin, and tinzaparin.[5,29]

Like UFH, LMWHs prevent the propagation and growth of formed thrombi. The anticoagulant effect is mediated through a specific pentasaccharide sequence that binds to AT. The primary difference in the pharmacologic activity of UFH and LMWH is their relative inhibition of thrombin (factor IIa) and factor Xa. Smaller heparin fragments cannot bind AT and thrombin simultaneously (Fig. 7–6). Due to their smaller chain length, LMWHs have relatively greater activity against factor Xa and inhibit thrombin to a lesser degree. The anti–factor Xa:IIa activity ratio for the LMWHs range from 2:1 to 4:1. The SC bioavailability of the LMWHs is greater

TABLE 7–7. Contraindications to Anticoagulation Therapy

General
Active bleeding
Hemophilia or other hemorrhagic tendencies
Severe liver disease with elevated baseline PT
Severe thrombocytopenia (platelet count less than 20,000)
Malignant hypertension
Inability to meticulously supervise and monitor treatment
Product-Specific Contraindications
UFH
Hypersensitivity to unfractionated heparin
History of HIT
LMWHs
Hypersensitivity to low-molecular-weight heparin, unfractionated heparin, pork products, methylparaben, or propylparaben
History of HIT or suspected HIT
Fondaparinux
Hypersensitivity to fondaparinux
Severe renal insufficiency (creatinine clearance less than 30 mL/minute)
Body weight less than 50 kg (110 lb)
Bacterial endocarditis
Thrombocytopenia with a positive in vitro test for antiplatelet antibodies in the presence of fondaparinux
Lepirudin
Hypersensitivity to hirudins
Argatroban
Hypersensitivity to argatroban
Warfarin
Hypersensitivity to warfarin
Pregnancy
History of warfarin-induced skin necrosis
Inability to obtain follow-up PT/INR measurements
Inappropriate medication use or lifestyle behaviors

HIT, heparin-induced thrombocytopenia; INR, International Normalized Ratio; LMWHs, low-molecular-weight heparins; PT, prothrombin time; UFH, unfractionated heparin.

than 90%. The peak anticoagulant effect of the LMWHs is reached 3 to 5 hours after a SC dose. The elimination half-life is 3 to 6 hours and is agent-specific. In patients with renal impairment, the half-life of LMWHs is prolonged.[5,21,29]

The dose of LMWHs for the treatment of VTE is determined based on the patient's weight and administered subcutaneously once or twice daily (Table 7–3). Once-daily dosing of enoxaparin appears to be as effective as twice-daily dosing; however, some data suggest that twice-daily dosing may be more effective in patients who are obese or have cancer.[8,21] The dose of enoxaparin is expressed in milligrams, whereas the doses of dalteparin and tinzaparin are expressed in units of anti–factor Xa activity. Due to their predictable anticoagulant effect, routine monitoring is not necessary in the majority of patients.[5] Low-molecular-weight heparins have been evaluated in a large number of randomized trials and have been shown to be at least as safe and effective as UFH for the treatment of VTE.[8,21] Indeed, the rate of mortality was lower in patients treated with a LMWH in clinical trials. This mortality benefit was primarily seen in patients with cancer.[33]

Prior to initiating treatment with a LMWH, baseline laboratory tests should include PT (**prothrombin time**)/INR, aPTT, complete blood cell count (CBC), and serum creatinine. Monitor the CBC every 3 to 4 days during the first 2 weeks of therapy, and every 2 to 4 weeks with extended use.[5] Use LMWHs cautiously in patients with renal impairment. Specific dosing recommendations for patients with a creatinine clearance (CrCl) less than 30 mL/minute are currently available for enoxaparin but lacking for other agents of the class (Table 7–3). Current guidelines recommend the use of UFH over LMWH in patients with severe renal dysfunction (CrCl less than 30 mL/minute).[8]

❼ *Most patients with an uncomplicated DVT can be managed safely at home.* LMWHs can be easily administered in the outpatient setting, thus enabling the treatment of VTE at home. Several large clinical trials have demonstrated the efficacy and safety of LMWHs used for outpatient treatment of DVT.[8,34,35] Acceptance of this treatment approach has increased tremendously over the last several years among clinicians. Patients who can be treated safely at home are stable and have normal vital signs, have low bleeding risk, and have no other comorbid conditions requiring hospitalization.[34,35] Although the treatment of patients with PE in the outpatient setting is controversial, patients with submassive PE who are hemodynamically stable can be safely treated in the outpatient setting as well.[36] Patients considered for outpatient therapy need to be reliable or have adequate caregiver support and must be able to strictly adhere to the prescribed treatment regimen and recommended follow-up visits. Close patient follow-up is critical to the success of any outpatient DVT treatment program.[35] Home DVT treatment results in cost savings and improved patient satisfaction and quality of life.[8]

Laboratory methods of measuring a patient's response to LMWH may be warranted in certain situations.[5] Although controversial, measurement of anti–factor Xa activity has been the most widely used method in clinical practice and is recommended by the College of American Pathologists.[37] Monitoring of anti–factor Xa activity may be considered in adult patients who are morbidly obese (weight greater than 150 kg [330 lb] or BMI greater than 50 kg/m^2), weigh less than 50 kg (110 lb), or have significant renal impairment (CrCl less than 30 mL/minute). Laboratory monitoring may also be useful in children and pregnant women. When monitoring anti–factor Xa activity, the sample should be obtained approximately 4 hours after the SC dose is administered, when peak concentration is anticipated. The therapeutic range for anti–factor Xa activity has not been clearly defined, and there is a limited correlation between anti–factor Xa activity and safety or efficacy. For the treatment of VTE, an acceptable anti–factor Xa activity range is 0.6 to 1 unit/mL with twice-daily dosing. In patients treated with once-daily LMWH regimens, a target level between 1 and 2 units/mL is recommended by some experts.[8,37]

Similar to UFH, bleeding is the major complication associated with LMWHs. The frequency of major bleeding appears to be numerically lower with LMWHs than with UFH.[33] The incidence of major bleeding reported in clinical trials is less than 3%.[8] Minor bleeding, especially bruising at the injection site, occurs frequently. Protamine sulfate will partially reverse the anticoagulant effects of the LMWHs and should be administered in the event of major bleeding. Due to its limited binding to LMWH chains, protamine only neutralizes 60% of their antithrombotic activity. If the LMWH was administered within the previous 8 hours, give 1 mg protamine sulfate per 1 mg of enoxaparin or 100 anti–factor Xa units of dalteparin or tinzaparin. If the bleeding is not controlled, give 0.5 mg of protamine sulfate for every anti–factor Xa 100 units of LMWH. Give smaller protamine doses if more than 8 hours have lapsed since the last LMWH dose.[5]

The incidence of HIT is lower with LMWHs than with UFH. However, LMWHs cross-react with heparin antibodies in vitro and should not be given as an alternative anticoagulant in patients with a diagnosis or history of HIT.[5] Monitor platelet counts every few days during the first 2 weeks and periodically thereafter.[5]

Low-molecular-weight heparins are an excellent alternative to UFH for the treatment of VTE in pregnant women.[34] The LMWHs do not cross the placenta, and they are FDA pregnancy category B. Because the pharmacokinetics of LMWHs may change during pregnancy, monitor anti–factor Xa activity every 3 to 4 weeks to make dose adjustments.[34] Low-molecular-weight heparins have also been used to treat

VTE in pediatric patients. Children less than 1 year old require higher doses (e.g., enoxaparin 1.5 mg/kg SC every 12 hours). Monitor anti–factor Xa activity to guide dosing in children.[32]

Factor Xa Inhibitors

Fondaparinux, the first agent in this class, is an indirect inhibitor of factor Xa, and exerts its anticoagulant activity by accelerating AT. Fondaparinux contains the specific 5-saccharide sequence found in unfractionated heparin that is responsible for its pharmacologic activity. Due to its small size, fondaparinux exerts inhibitory activity specifically against factor Xa and has no effect on thrombin (factor IIa)[38] (Fig. 7–6). Fondaparinux is currently the only agent of the class that is commercially available in the United States. Idraparinux and razaxaban are anti–factor Xa inhibitors currently undergoing Phase III clinical trials. Fondaparinux and idraparinux are administered SC; razaxaban is administered orally. After SC administration, fondaparinux is completely absorbed, and peak plasma concentrations are reached within 2 to 3 hours.[38]

As synthetic drugs (unlike UFH and the LMWHs), factor Xa inhibitors cannot transmit animal pathogens, are consistent from batch-to-batch, and are available in an unlimited supply. Other favorable attributes of the anti–factor Xa inhibitors include a predictable and linear dose-response relationship, rapid onset of activity, and long half-life.[29] Factor Xa inhibitors do not require routine coagulation monitoring or dose adjustments. Fondaparinux has a half-life of 17 to 21 hours, permitting once-daily administration, but the anticoagulant effects of fondaparinux will persist for 2 to 4 days after stopping the drug. In patients with renal impairment, the anticoagulant effect persists even longer. Idraparinux has a significantly longer duration of activity and is being developed for once-weekly injection. Neither fondaparinux nor idraparinux are metabolized in the liver and therefore have few drug interactions. However, concurrent use with other antithrombotic agents will increase the risk of bleeding. Unlike the heparins, factor Xa inhibitors do not affect platelet function and do not react with the heparin platelet factor-4 (PF-4) antibodies seen in patients with HIT. Some centers use fondaparinux in patients with a history of HIT who require anticoagulation therapy.[29,38,39]

Fondaparinux has been used for the treatment of DVT and PE in two large Phase III trials and is approved by the FDA for these indications. Fondaparinux is as safe and effective as IV UFH for the treatment of PE and SC LMWH for DVT treatment.[36,40] The recommended dose for fondaparinux in the treatment of VTE is based on the patient's weight (Table 7–3). Fondaparinux is renally eliminated and accumulation can occur in patients with renal dysfunction. Due to the lack of specific dosing guidelines, fondaparinux is contraindicated in patients with severe renal impairment (CrCl less than 30 mL/minute). Baseline renal function should be measured and monitored closely during the course of therapy. Monitoring anti–factor Xa activity to guide fondaparinux dosing is not recommended.[29,38,39]

As with other anticoagulants, the major side effect associated with fondaparinux is bleeding. Fondaparinux should be used with caution in elderly patients because their risk of bleeding is higher. Patients receiving fondaparinux should be carefully monitored for signs and symptoms of bleeding. A CBC should be obtained at baseline and monitored periodically to detect the possibility of occult bleeding. In the event of major bleeding, fresh frozen plasma and factor concentrates should be given. In the case of a life-threatening bleed, recombinant factor VIIa may be considered, but this is a very costly option and it can also increase the risk of thrombosis. Fondaparinux is not reversed by protamine.[29,38,39]

Fondaparinux is pregnancy category B, but there are very limited data regarding its use during pregnancy. Use in pediatric patients has not been studied.[29,38,39]

Direct Thrombin Inhibitors (DTIs)

Given that thrombin is the central mediator of coagulation and amplifies its own production, it is a natural target for pharmacologic intervention. Direct thrombin inhibitors (DTIs) bind thrombin and prevent interactions with its substrates (Fig. 7–7). Several injectable DTIs are approved for use in the United States including lepirudin, bivalirudin, argatroban, and desirudin. Several oral DTIs are currently in

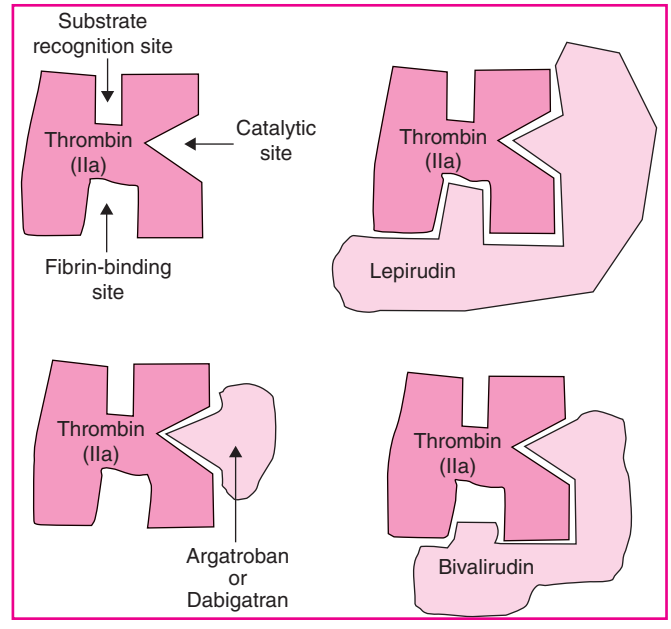


FIGURE 7–7. Mechanism of action of direct thrombin inhibitors. (Reproduced from Haines ST, Zeolla M, Witt DM. Venous thromboembolism. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 387, with permission.)

development. These agents differ in terms of their chemical structure, molecular weight, and binding to the thrombin molecule. Potential advantages of DTIs include a targeted specificity for thrombin, the ability to inactivate clot-bound thrombin, and an absence of platelet interactions that can lead to HIT. Unlike heparins, DTIs do not require antithrombin as a co-factor and do not bind to plasma proteins. Therefore they produce a more predictable anticoagulant effect. DTIs are considered the drugs of choice for the treatment of VTE in patients with a diagnosis or history of HIT.[29,38,41]

The prototype of this class is hirudin, which was originally isolated from the salivary glands of the medicinal leech, *Hirudo medicinalis*. Hirudin itself is not commercially available, but recombinant technology has permitted production of hirudin derivatives, namely lepirudin and desirudin.[29,38,41] Lepirudin has a short half-life of approximately 40 minutes after IV administration and 120 minutes when given SC. Elimination of lepirudin is primarily renal; therefore, doses must be adjusted based on the patient's renal function. The dose should be monitored and adjusted to achieve an aPTT ratio of 1.5 to 2.5 times the baseline measurement. Lepirudin is currently approved for use in patients with HIT and related thrombosis. Up to 40% of patients treated with lepirudin will develop antibodies to the drug.[29,38,41]

Bivalirudin, a smaller-molecular-weight DTI, is given by IV infusion. Bivalirudin has a shorter elimination half-life (~25 minutes) than lepirudin and is only partially eliminated renally. Unlike lepirudin, bivalirudin is a reversible inhibitor of thrombin and provides transient antithrombotic activity. Patients with moderate or severe renal impairment (CrCl less than 60 mL/minute) may require dose adjustment because clearance of bivalirudin is reduced by approximately 20% in these patients. Bivalirudin is approved for use in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty. The activated clotting time is used to monitor the anticoagulant effect of bivalirudin during percutaneous coronary intervention (PCI).[29,38,41]

Desirudin is a SC administered DTI approved for VTE prevention after hip replacement surgery but is not yet commercially available in the United States. Desirudin has an elimination half-life of 2 to 3 hours and is typically dosed every 12 hours. It is primarily eliminated through the kidneys, so dose reduction is needed in patients with renal impairment. The aPTT should be used to measure desirudin's anticoagulant activity.[29,38,41]

Argatroban is a small synthetic molecule that binds reversibly to the active site of thrombin (Fig. 7–7). Argatroban is IV administered and has a 40 to 50 minute elimination half-life. The aPTT must be monitored to assess its anticoagulant activity. Argatroban is hepatically metabolized; therefore, dose reductions and careful monitoring are recommended in patients with hepatic dysfunction. Renal impairment has no influence on the elimination half-life or dosing of argatroban. Argatroban is approved for prevention and treatment of thrombosis in patients with HIT and in patients with HIT undergoing PCI.[29,38,41]

Small-molecule direct thrombin inhibitors have been structurally modified for oral administration. Approximately 10 oral DTIs are in development. There was considerable excitement about ximelagatran, the first oral DTI to complete several large Phase III clinical trials.[29,38,41] Ximelagatran was given in fixed doses without laboratory monitoring for VTE prophylaxis and acute and long-term VTE treatment. While these studies showed that ximelagatran was as effective as standard treatment regimens, the FDA denied its approval due to concerns regarding liver toxicity. Dabigatran is another promising oral DTI that is currently undergoing Phase III clinical trials for the treatment of VTE.

Contraindications to the use of DTIs and risk factors for bleeding are similar to those of other antithrombotic agents (Tables 7–6 and 7–7). Bleeding is the most common side effect reported with the use of DTIs. Concurrent use of DTIs with thrombolytics significantly increases bleeding complications. Currently, there are no known antidotes to reverse the effects of the DTIs. Fresh frozen plasma, factor concentrates, or recombinant factor VIIa should be given in the event of a major bleed. DTIs can increase the PT/INR and can interfere with the accuracy of monitoring and dosing of warfarin therapy. Data on the use of DTIs in pregnancy and pediatric patients are very limited.[29,38,41]

Warfarin

Warfarin has been the primary oral anticoagulant used in the United States for the past 60 years. Warfarin is the anticoagulant of choice when long-term or extended anticoagulation is required. Warfarin is FDA-approved for the prevention and treatment of VTE, as well as the prevention of thromboembolic complications in patients with myocardial infarction, atrial fibrillation, and heart valve replacement. While very effective, warfarin has a narrow therapeutic index, requiring frequent dose adjustments and careful patient monitoring.[15,29]

Warfarin exerts its anticoagulant effect by inhibiting the production of the vitamin K–dependent coagulation factors II (prothrombin), VII, IX, and X, as well as the anticoagulant proteins C and S (Fig. 7–8). Warfarin has no effect on circulating coagulation factors that have been previously formed, and its full antithrombotic activity is delayed for 7 to 15 days. This delay is related to half-lives of the clotting factors: 60 to 100 hours for factor II (prothrombin), 6 to 8 hours for factor VII, 20 to 30 hours for factor IX, and 24 to 40 hours for factor X. Proteins C and S, the natural anticoagulants, are inhibited more rapidly due to their shorter half-lives, 8 to 10 hours and 40 to 60 hours, respectively. Reductions in the concentration of natural anticoagulants before the clotting factors are depleted can lead to a paradoxical **hypercoagulable state** during the first few days of warfarin therapy. It is for this reason that patients with acute thrombosis should receive a fast-acting anticoagulant

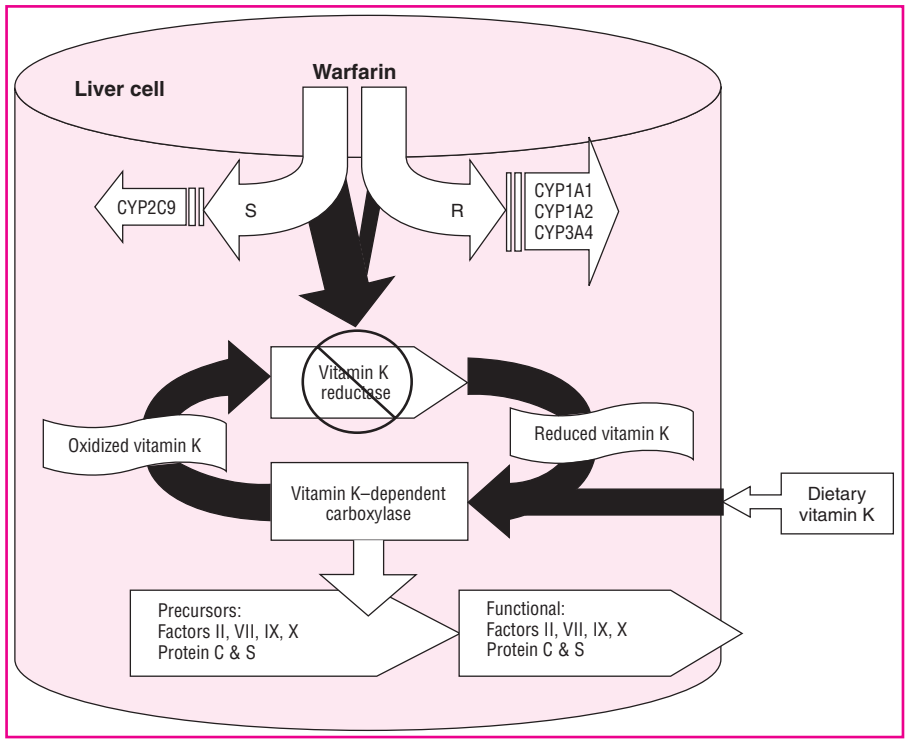


FIGURE 7–8. Pharmacologic activity and metabolism of warfarin. CYP, cytochrome P-450 isoenzyme**.** (Reproduced from Haines ST, Zeolla M, Witt DM. Venous thromboembolism. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 389, with permission.)

(heparin, LMWH, or fondaparinux) while transitioning to warfarin therapy.[4,29,34]

Warfarin is a racemic mixture of two isomers, the S and the R forms. The S-isomer is two to five times more potent than the R-isomer. Both isomers are extensively bound to albumin. The two isomers are metabolized in the liver via several isoenzymes including cytochrome P-450 (CYP)1A2, 2C9, 2C19, 2C18, and 3A4 (Fig. 7–8). Hepatic metabolism of warfarin varies greatly among patients, leading to very large interpatient differences in dose requirements and genetic variations in these isoenzymes; specifically, polymorphisms in the CYP2C9*2, CYP2C9*3, and the VKORC1 haplotypes result in a significantly lower warfarin dose requirement to achieve a therapeutic response.[4,42]

Warfarin does not follow linear kinetics. Small dose adjustments can lead to large changes in anticoagulant response. The dose of warfarin is determined by each patient's individual response to therapy and the desired intensity of anticoagulation. In addition to hepatic metabolism, warfarin dose requirements are influenced by diet, drug-drug interactions, and health status. Therefore, the dose of warfarin must be determined by frequent clinical and laboratory monitoring.[4,22,34] While there are conflicting data regarding the optimal warfarin induction regimen, most patients can start with 5 mg daily and subsequent doses are determined based on INR response (Fig. 7–9). When initiating therapy, it is difficult to predict the precise warfarin maintenance dose that a patient will require. Patients who are younger (less than 55 years of age) and otherwise healthy can safely use higher warfarin "initiation" doses (e.g., 7.5 or 10 mg). A more conservative "initiation" dose (e.g., 5 mg or less) should be given to elderly patients (greater than 75 years of age); patients with heart failure, liver disease, or poor nutritional status; and patients who are taking interacting medications or are at high risk of bleeding.[4,21] Loading doses of warfarin (e.g., 15 to 20 mg) are not recommended. These large doses can lead to the false impression that a therapeutic INR has been achieved in 2 to 3 days and also increases the risk of bleeding.[4] Before initiating therapy, screen the patient for any contraindications to anticoagulation therapy and risk factors for major bleeding (Tables 7–6 and 7–7). In addition, conduct a thorough medication history including the use of prescription and over-the-counter drugs, and any herbal supplements to detect interactions that may affect warfarin dosing requirements. In patients with acute VTE, a rapid-acting anticoagulant (UFH, LMWH, or fondaparinux) should be overlapped with warfarin for a minimum of 5 days and until the INR is greater than 2 and stable. This is important because the full antithrombotic effect will not be reached until 5 to 7 days or even longer after initiating warfarin therapy.[4,8] The typical maintenance dose of warfarin for most patients will be between 25 and 55 mg per week, although some patients require higher or lower doses. Adjustments in the maintenance warfarin dose should be determined on the total weekly dose and by reducing or increasing the weekly dose by 5% to 25%. When adjusting the maintenance dose, wait at least 7 days to ensure that a steady state has been attained on the new dose before checking the INR again. Checking the INR too soon can lead to inappropriate dose adjustments and unstable anticoagulation status.[4]

❶ *Warfarin requires frequent laboratory monitoring to ensure optimal outcomes and minimize complications.* The prothrombin

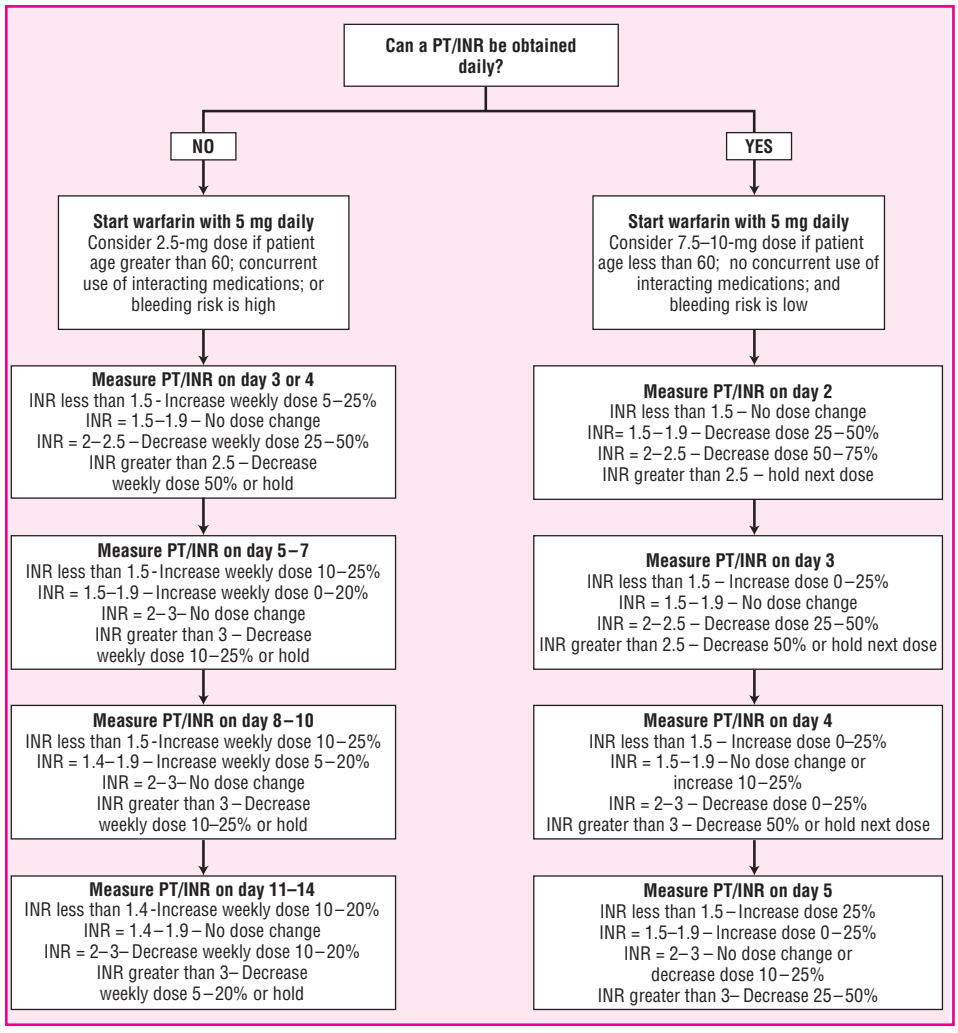


FIGURE 7–9. Initiation of warfarin therapy. INR, International Normalized Ratio; PT, prothrombin time. (Reproduced from Haines ST, Zeolla M, Witt DM. Venous thromboembolism. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 391, with permission.)

time is the most frequently used test to monitor warfarin's anticoagulant effect. The PT measures the biological activity of factors II, VII, and X. Due to wide variation in reagent sensitivity, different **thromboplastins** will result in different PT results, potentially leading to inappropriate dosing decisions.[4,22] In order to standardize result reporting, the World Health Organization (WHO) developed a reference thromboplastin and recommended the INR to monitor warfarin therapy. The INR corrects for the differences in thromboplastin reagents and uses the following formula: $INR = (PT^{Patient}/PT^{Control})_{ISI}$. The International Sensitivity Index (ISI) is a measure of the thromboplastin's responsiveness compared to the WHO reference.[4] The goal or target INR for each patient is based on the indication for warfarin therapy. For the treatment and prevention of VTE, the INR target is 2.5 with an acceptable range of 2 to 3. In certain high-risk patients (e.g., mechanical heart valves), a higher target INR of 3 with a range of 2.5 to 3.5 is recommended.[4] Before initiating warfarin therapy, a baseline PT/INR and CBC should be obtained. After initiating warfarin therapy, the INR should be monitored at least every 2 to 3 days during the first week of therapy. Once a stable response to therapy is achieved, INR monitoring is performed less frequently, weekly for the first 1 to 2 weeks, then every 2 weeks, and monthly thereafter.[4] At each encounter, carefully question the patient regarding any factors that may influence the INR result. These factors include adherence to therapy, the use of interacting medications, consumption of vitamin K–rich foods, alcohol use, and general health status. Patients should also be questioned about symptoms related to bleeding and thromboembolic events. Warfarin dose adjustments should take into account not only the INR result, but also patient-related factors that influence the result. Structured anticoagulation therapy management services (anticoagulation clinics) have been demonstrated to improve the efficacy and safety of warfarin therapy when compared to "usual" medical care. Some patients engage in self-testing and self-management by using a point of care PT/INR device approved for home use. Highly motivated and well-trained patients are good candidates for self-testing or self-management.[4,7,22,34]

❻ *Similar to other anticoagulants, warfarin's primary side effect is bleeding.* Warfarin can "unmask" an existing lesion. The incidence of warfarin-related bleeding appears to be highest during the first few weeks of therapy. The annual incidence of major bleeding ranges from 1% to 10% depending on the quality of warfarin therapy management. Bleeding in the gastrointestinal tract is most common. Intracranial hemorrhage (ICH) is one of the most serious complications, as it often causes severe disability and death. The intensity of anticoagulation therapy is related to bleeding risk. Higher INRs result in higher bleeding risk, and the risk of ICH increases when the INR exceeds 4.[3,4] Instability and wide fluctuations in the INR are also associated with higher bleeding risk. In cases of warfarin overdose or over-anticoagulation, vitamin K may be used to reverse warfarin's effect (Fig. 7–10).[4] Vitamin K can be given by the IV or oral route; the SC route is no longer recommended. When given SC, vitamin K is erratically absorbed and frequently ineffective. The IV route is reserved for cases of severe warfarin overdose (e.g., INR greater than 20) or major bleeding. Anaphylactoid reactions have been reported with rapid IV administration, therefore slow infusion is recommended. An oral dose of vitamin K will reduce the INR within 24 hours. If the INR is still elevated after 24 hours, another dose of oral vitamin K can be given. The dose of vitamin K should be based on the INR elevation. A dose of 1 to 2.5 mg is sufficient when the INR is between 5 and 9, but 5 mg may be

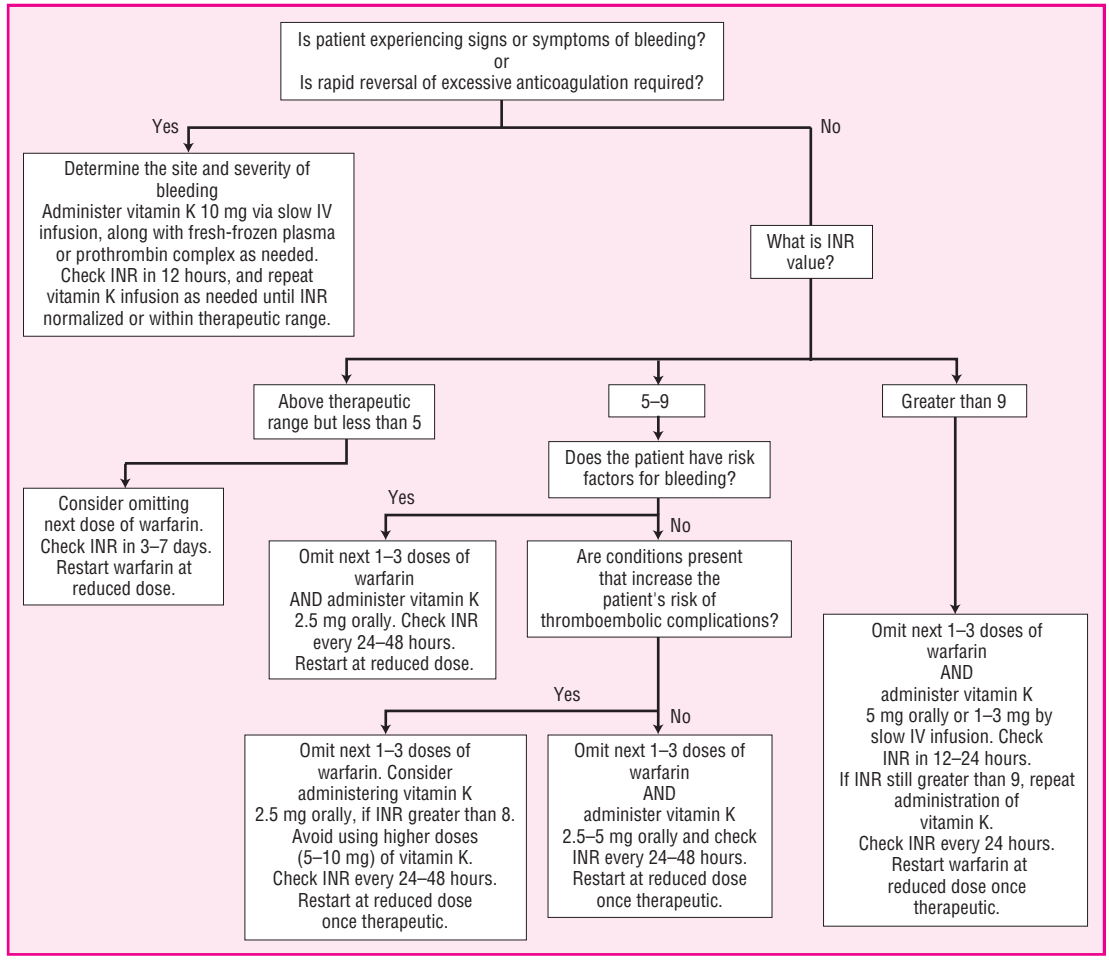


FIGURE 7–10. Management of an elevated INR in patients taking warfarin. Dose reductions should be made by determining the weekly warfarin dose and reducing the weekly dose by 10% to 25% based on the degree of INR elevation. Conditions that increase the risk of thromboembolic complications include history of hypercoagulability disorders (e.g., protein C or S deficiency, presence of antiphospholipid antibodies, antithrombin deficiency, or activated protein C resistance), arterial or venous thrombosis within the previous month, thromboembolism associated with malignancy, mechanical mitral valve in conjunction with atrial fibrillation, previous stroke, poor ventricular function, or co-existing mechanical aortic valve. INR, International Normalized Ratio; IV, intravenous. (Reproduced from Haines ST, Zeolla M, Witt DM. Venous thromboembolism. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 394, with permission.)

required for INRs greater than 9. Higher doses (e.g., 10 mg) can lead to prolonged warfarin resistance. In cases of life-threatening bleeding, fresh frozen plasma or clotting factor concentrates should be administered, in addition to IV vitamin K. In cases in whom the INR is less than 9 and there is no active bleeding or imminent risk of bleeding, simply withholding warfarin until the INR decreases to within therapeutic range and reducing the weekly dose with more frequent monitoring is appropriate.[4]

Non-hemorrhagic side effects related to warfarin are rare but can be severe when they occur. Warfarin-induced skin necrosis presents as an eggplant-colored skin lesion or a maculopapular rash that can progress to necrotic gangrene. It usually manifests in fatty areas such as the abdomen, buttocks, and breasts. The incidence is less than 0.1%, and it generally appears during the first week of therapy. Patients with protein C or S deficiency or those who receive large loading doses of warfarin are at greatest risk. The mechanism is thought to be due to imbalances between procoagulant and anticoagulant proteins early in the course of warfarin therapy. Warfarin-induced purple toe syndrome is another rare side effect; patients present with a purplish discoloration of their toes. If these side effects are suspected, warfarin therapy should be discontinued immediately and an alternative anticoagulant given. There is a theoretical risk that warfarin may cause accelerated bone loss with long-term use, but to date there is no evidence to support this concern. Warfarin is teratogenic and is FDA pregnancy category X. It should be avoided during pregnancy, and women of child-bearing potential should be instructed to use an effective form of contraception. Unfractionated heparin and LMWH are the agents of choice for the treatment of VTE during pregnancy.[4,22]

❽ *Warfarin is prone to numerous clinically significant drug-drug and drug-food interactions (Tables 7–8, 7–9, and 7–10)* Patients on warfarin should be questioned at every encounter to assess for any potential interactions with foods, drugs, herbal products, and nutritional supplements. When an interacting drug is initiated or discontinued, more frequent monitoring should be instituted. In addition, the dose of warfarin can be modified (increased or decreased) in anticipation of the expected impact on the INR.[4,43] Warfarin-related drug interactions can generally be divided into two major categories: pharmacokinetic and pharmacodynamic. Pharmacokinetic interactions are most commonly due to changes in hepatic metabolism or binding to plasma proteins. Drugs that affect the CYP2C9, CYP3A4, and CYP1A2 have the greatest impact on warfarin metabolism. Interactions that impact the metabolism of the S-isomer result in greater changes in the INR than interactions affecting the R-isomer. Pharmacodynamic drug interactions enhance or diminish the anticoagulant effect of warfarin, increasing the risk of bleeding or clotting, but may not alter the INR.[4,43] There are increasing reports regarding dietary supplements, nutraceuticals, and vitamins that can interact with warfarin.[44] Patients on warfarin may experience changes in the INR due to fluctuating intake of dietary vitamin K. Patients should be instructed to maintain a consistent diet and avoid large fluctuations in vitamin K intake rather than strictly avoiding vitamin K–rich foods.[45]

TABLE 7–8. Clinically Significant Warfarin Drug Interactions

Increase Anticoagulation Effect (↑ INR)	Decrease Anticoagulation Effect (↓ INR)	Increase Bleeding Risk
Acetaminophen	Amobarbital	Argatroban
Alcohol binge	Butabarbital	Aspirin
Allopurinol	Carbamazepine	Clopidogrel
Amiodarone	Cholestyramine	Danaparoid
Cephalosporins (with MTP side chain)	Dicloxacillin	Dipyridamole
Chloral hydrate	Griseofulvin	Low-molecular-weight heparins
Chloramphenicol	Nafcillin	Non-steroidal anti-inflammatory drugs
Cimetidine	Phenobarbital	Ticlopidine
Ciprofloxacin	Phenytoin	Unfractionated heparin
Clofibrate	Primidone	
Danazol	Rifampin	
Disulfiram	Secobarbital	
Doxycycline	Sucralfate	
Erythromycin	Vitamin K	
Fenofibrate		
Fluconazole		
Fluorouracil		
Fluoxetine		
Fluvoxamine		
Gemfibrozil		
Influenza vaccine		
Isoniazid		
Itraconazole		
Lovastatin		
Metronidazole		
Miconazole		
Moxalactam		
Neomycin		
Norfloxacin		
Ofloxacin		
Omeprazole		
Phenylbutazone		
Piroxicam		
Propafenone		
Propoxyphene		
Quinidine		
Sertraline		
Sulfamethoxazole		
Sulfinpyrazone		
Tamoxifen		
Testosterone		
Vitamin E		
Zafirlukast		

INR, International Normalized Ratio; UFH, unfractionated heparin.

TABLE 7–9. Potential Warfarin Interactions with Herbal and Nutritional Products

Increased Anticoagulation Effect (Increase Bleeding Risk or ↑ INR)	Decreased Anticoagulation Effect (↓ INR)
Amica flower	Coenzyme Q_{10}
Angelica root	Ginseng
Anise	Green tea
Asafoetida	St. John's wort
Bogbean	
Borage seed oil	
Bromelain	
Capsicum	
Celery	
Chamomile	
Clove	
Danshen	
Devil's claw	
Dong quai	
Fenugreek	
Feverfew	
Garlic	
Ginger	
Ginkgo	
Horse chestnut	
Licorice root	
Lovage root	
Meadowsweet	
Onion	
Papain	
Parsley	
Passionflower herb	
Poplar	
Quassia	
Red clover	
Rue	
Sweet clover	
Turmeric	
Vitamin E	
Willow bark	

INR, International Normalized Ratio.

Nonpharmacologic

Thrombectomy

Most cases of VTE can be successfully treated with anticoagulation. In some cases, removal of the occluding thrombus by surgical intervention may be warranted. Surgical thrombectomy can be considered in patients with massive iliofemoral DVT when there is a risk of limb gangrene due to venous occlusion. The procedure can be complicated by recurrence of thrombus formation. In patients who present with massive PE, pulmonary embolectomy can be performed in emergency cases when conservative measures have failed. Patients who are hemodynamically unstable and have a contraindication to thrombolysis are candidates for pulmonary embolectomy. Administer heparin by IV infusion to achieve a therapeutic aPTT during the operation and postoperatively. Thereafter, give warfarin for the usual recommended duration.[8,21]

TABLE 7–10. Vitamin K Content of Select Foods[a]

Very High (greater than 200 mcg)	High (100–200 mcg)	Medium (50–100 mcg)	Low (less than 50 mcg)
Brussels sprouts	Basil	Apple, green	Apple, red
Chickpea	Broccoli	Asparagus	Avocado
Collard greens	Canola oil	Cabbage	Beans
Coriander	Chive	Cauliflower	Breads and grains
Endive	Coleslaw	Mayonnaise	Carrot
Kale	Cucumber (w/peel)	Pistachios	Celery
Lettuce, red leaf	Green onion/ scallion	Squash, summer	Cereal
Parsley	Lettuce, butterhead		Coffee
Spinach	Mustard greens		Corn
Swiss Chard	Soybean oil		Cucumber (w/o peel)
Tea, black			Dairy products
Tea, green			Eggs
Turnip greens			Fruit (varies)
Watercress			Lettuce, iceberg
			Meats, fish, poultry
			Pasta
			Peanuts
			Peas
			Potato
			Rice
			Tomato

[a]Approximate amount of vitamin K per 100-g (3.5-oz) serving.



Patient Encounter 1, Part 2

KK has been hospitalized for right hip fracture repair. Two weeks after her discharge from the hospital, she presents to the emergency department with complaints of swelling, redness, and pain in her right lower extremity. KK states her symptoms started 3 days ago and have gotten progressively worse. During your interview, the patient states that she was sent home with a prescription for fondaparinux 2.5 mg SC daily. A duplex ultrasound shows a proximal DVT in her right lower extremity. All of her other laboratory values are within normal limits.

- Which of KK's symptoms are consistent with an acute DVT?
- Design an appropriate treatment plan for KK. Your plan should include acute and chronic therapy—specify the drug(s), dose(s), route, frequency of administration, and duration of each therapy, as well monitoring parameters, patient education, and follow-up plan.
- Assuming KK continues to take the prescription and over-the-counter medications listed in her medication history obtained during her hospitalization, should any of these medications be discontinued or changed? If changed, what alternative therapy would you recommend?
- Is KK a candidate for outpatient treatment of her DVT?

Vena Cava Interruption

Inferior vena cava (IVC) interruption is indicated in patients with PE who have a contraindication to anticoagulation therapy and in patients who have recurrent VTE while taking anticoagulation therapy.[8,46] IVC interruption is accomplished by inserting a filter through the internal jugular vein or femoral vein and advancing it into the IVC using ultrasound or fluoroscopic guidance. IVC filters reduce the short-term risk of PE, but this benefit is not sustained in the long term. The incidence of DVT at 1 year after IVC filter insertion is higher when compared to patients without filters. Survival after a PE is no different in patients with filters versus patients without filters.[19] Therefore, anticoagulation therapy should be resumed as soon as possible after filter insertion and continued as long as the filter is in place due to the high risk of DVT.[8,46] Temporary or removable filters are currently under study, and these may replace the permanent filters now used in practice.[8,46]

Compression Stockings

Postthrombotic syndrome occurs in 20% to 50% of patients within 8 years after a DVT. Wearing graduated compression stockings (GCS) after a DVT reduces the risk of PTS by as much as 50%. Current guidelines recommend the use of GCS with an ankle pressure of 30 to 40 mm Hg for 2 years after a DVT. To be effective, GCS must fit properly. Traditionally, strict bed rest has been recommended after a DVT, but this approach has now been refuted and patients should be encouraged to ambulate as tolerated.[8,34]



Patient Encounter 2, Part 1

BA is a 38-year-old female who presents to the emergency department complaining of chest pain, shortness of breath, and lightheadedness. The patient states that her symptoms started with some mild left calf pain approximately 5 days ago. She started feeling short of breath and experiencing chest pain last evening. She could not sleep and her shortness of breath has gotten progressively worse in the last several hours. BA was hospitalized because she was suspected to have a pulmonary embolism.

PMH
Obesity × 12 years; asthma

FH
Mother died of a stroke; paternal grandmother had clots in her legs

SH
The patient is a school teacher

Current meds
Albuterol (salbutamol) metered-dose inhaler as needed
Ortho-Tri-Cyclen Lo by mouth daily
Echinacea 1 to 2 tablets by mouth daily as needed
Multivitamin 1 tablet by mouth daily

Allergies
Shellfish, no known drug allergies

PE
VS: blood pressure 104/64 mm Hg; heart rate 102; respiratory rate 20; temperature 38ºC (100.4°F); weight 211 lb (96 kg); height 65 inches (165 cm)

Labs
Within normal limits; estimated glomerular filtration rate (GFR) 101 mL/minute

Procedures/Tests
Electrocardiograph: normal sinus rhythm
Chest x-ray: slightly enlarged heart
Ventilation/perfusion (V/Q) scan: high probability of PE

- What signs and symptoms are consistent with the diagnosis of PE in BA's case? What are the most likely etiologies for pulmonary embolism in this case?
- What are appropriate initial and chronic treatment options for BA?
- If unfractionated heparin is chosen as the initial anticoagulation treatment option, what is the goal aPTT?
- What is BA's goal INR for warfarin therapy?
- How long should BA remain on anticoagulation therapy?
- Given the list of medications BA took prior to hospitalization, should any of these medications be discontinued or changed? If changed, what alternative therapy would you recommend?

APPROACH TO TREATING PATIENTS WITH VENOUS THROMBOEMBOLISM

❺ *Once the diagnosis of VTE has been confirmed with an objective test, promptly start anticoagulation therapy in full therapeutic doses. If there is high clinical suspicion of VTE, anticoagulation therapy can be initiated while waiting for the results of diagnostic tests.[8] Initiate therapy with a quick-acting anticoagulant such as UFH (given IV), an LMWH (given SC), or fondaparinux (given SC) (Figs. 7–5 and 7–11). In patients with adequate renal function, the LMWHs are preferred over UFH.[8] Recent evidence also supports the use of SC fondaparinux as an alternative option to UFH or LMWH for the initial treatment of VTE.[8,21] For the long-term treatment phase, warfarin is the preferred approach except for patients with cancer, in whom an LMWH is recommended. Initiate warfarin on the first day of therapy after the first dose of UFH, LMWH, or fondaparinux is given. Overlap the injectable agent with warfarin therapy for a minimum of 5 days. Warfarin should be dosed to achieve a goal INR range of 2 to 3. Once the INR is stable and above 2, the injectable anticoagulant should be discontinued. Anticoagulation therapy is continued for a minimum of 3 months but should be given longer depending on the underlying etiology of the VTE and the patient's risk factors (Table 7–11).[8,21,34] Use a thrombolytic only if the patient has a massive iliofemoral DVT and is at risk of limb gangrene. In patients with PE, use a thrombolytic if the patient is hemodynamically unstable (i.e., SBP less than 90 mm Hg). If there is a contraindication to anticoagulation therapy or the patient has failed therapy with an anticoagulant, a vena cava filter should*

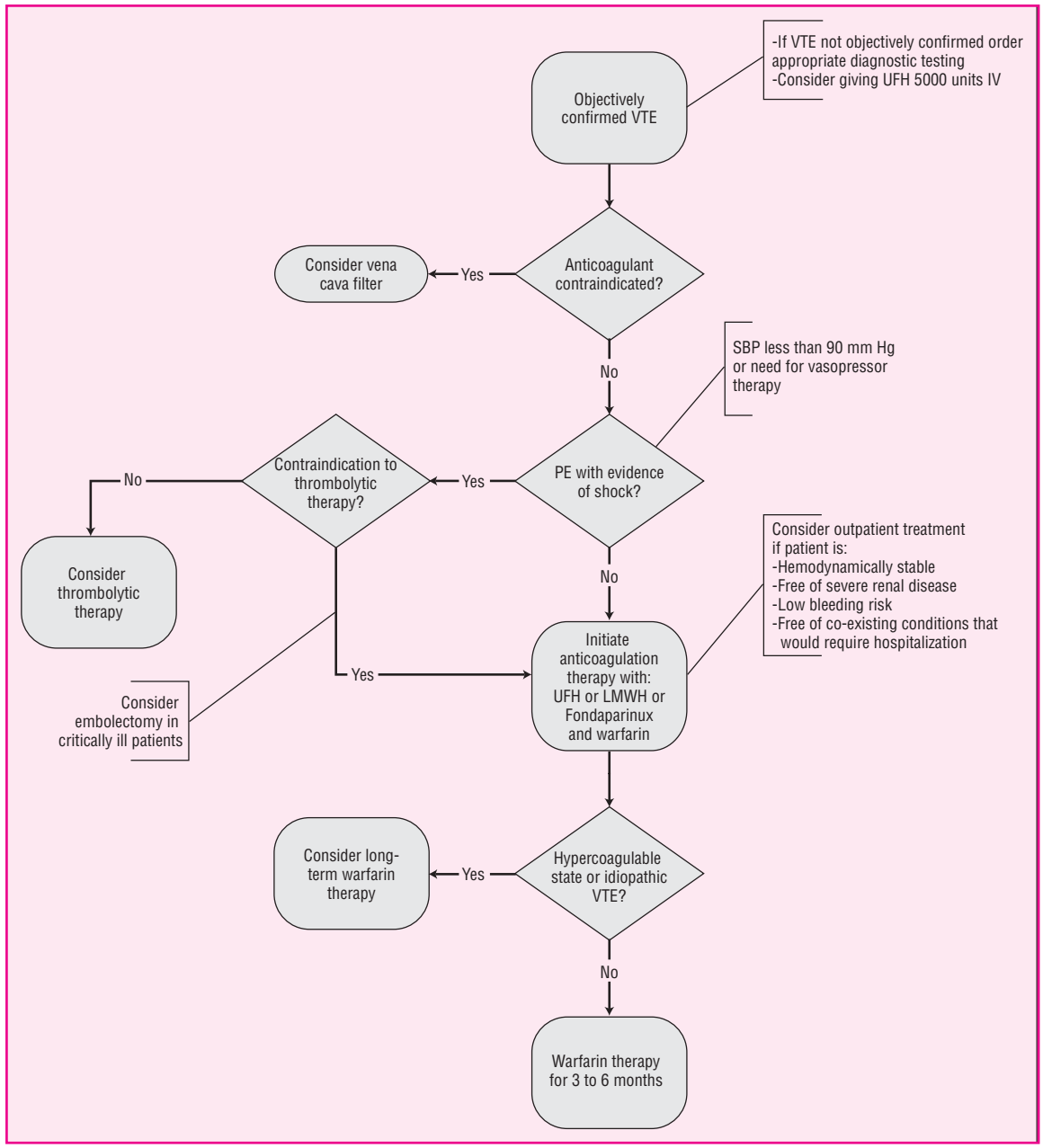


FIGURE 7–11. Treatment of venous thromboembolism. LMWH, low-molecular-weight heparin; PE, pulmonary embolism; SBP, systolic blood pressure; UFH, unfractionated heparin; VTE, venous thromboembolism. (Reproduced from Haines ST, Zeolla M, Witt DM. Venous thromboembolism. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 398, with permission.)

be inserted. Encourage early ambulation as tolerated by the patient during the initial treatment phase.[8,21]

OUTCOME EVALUATION

- Achieve optimal outcomes by (1) preventing the occurrence of VTE in patients who are at risk, (2) administering effective treatments in a timely manner to patients who develop VTE, (3) preventing treatment-related complications, and (4) reducing the likelihood of long-term complications including recurrent events.
- Given that VTE is often clinically silent and potentially fatal, strategies to increase the widespread use of prophylaxis have the greatest potential to improve patient outcomes.
- Relying on the early diagnosis and treatment of VTE is unacceptable because many patients will die before treatment can be initiated.

- Effective VTE prophylaxis programs screen and identify all patients at risk, determine each patient's level of risk, and select and implement regimens that provide sufficient protection for the level of risk.
- Periodically evaluate patients who receive prophylaxis during the course of treatment for signs and symptoms of VTE, such as swelling, pain, warmth, and redness of lower extremities, and for DVT, as well as chest pain, shortness of breath, palpitations, and hemoptysis.
- Providing effective treatment in a timely manner is the primary goal for patients who develop VTE. Treat DVT and PE quickly and aggressively with effective doses of anticoagulant drugs.
- The short-term aim of therapy is to prevent propagation or local extension of the clot, embolization, and death.
- Regularly monitor patients for the development of new symptoms or worsening of existing symptoms.
- Anticoagulant drugs require precise dosing and meticulous monitoring. Closely monitor patients receiving anticoagulant therapy for signs and symptoms of bleeding, including epistaxis, hemoptysis, hematuria, bright red blood per rectum, tarry stools, severe headache, and joint pain. If major bleeding occurs, stop therapy immediately and treat the source of bleeding. In addition, closely monitor patients for potential drug-drug and drug-food interactions and adherence with the prescribed regimen.
- The long-term (i.e., more than 3 months after the first event) goals of therapy are to prevent complications such as the postthrombotic syndrome, pulmonary hypertension, and recurrent VTE.
- Encourage all patients who have had DVT to wear graduated compression stockings.
- Continue warfarin therapy for an appropriate duration based on the presence of ongoing risk factors.



Patient Encounter 2, Part 2

BA is a 38-year-old female with acute PE discharged home on warfarin therapy. She was referred to a local area antithrombosis center for monitoring of her oral anticoagulation therapy and has been maintained on warfarin 6 mg daily for the last 3 months. The patient presents today for a routine visit for anticoagulation monitoring and her INR is 8.3. She reports that 6 days ago she was started on metronidazole 500 mg by mouth twice daily, which was prescribed by her primary care physician for a vaginal infection. In addition, the primary care physician told the patient that her thyroid gland was enlarged and ordered some lab tests to determine if she has a thyroid problem. The patient has not heard what the results are. She also reports that her intake of vitamin K–rich foods (spinach, broccoli, and cabbage) has increased significantly over the last month because she is trying to lose weight. BA has no other complaints today and denies any signs or symptoms of bleeding.

- What is the most likely explanation for elevated INR in BA's case?
- Should BA be given vitamin K? If yes, discuss the dose, route of administration, and an appropriate patient monitoring plan.
- How will you manage BA's warfarin therapy? Outline a plan including specific dose changes, timing of monitoring, and patient education.

TABLE 7–11. Duration of Anticoagulation Therapy for the Treatment of VTE

Patient Characteristics	Drug	Duration of Therapy (Months)	Comments
First episode of VTE secondary to a transient (reversible) risk factor	Warfarin	3	Recommendation applies to both proximal and calf vein thrombosis
First episode of VTE and cancer	Low-molecular-weight heparin	6	Low-molecular-weight heparin is recommended over warfarin
First episode of idiopathic VTE with or without a documented hypercoagulable abnormality	Warfarin	12	Continue warfarin therapy after 12 months if patient is at low risk for bleeding
First episode of VTE with documented antiphospholipid antibodies or two or more hypercoagulable abnormalities	Warfarin	24+	Continue warfarin therapy after 24 months if patient is at low risk for bleeding
Second episode of VTE	Warfarin	24+	Continue warfarin therapy after 24 months if patient is at low risk for bleeding

VTE, venous thromboembolism.



Patient Care and Monitoring

Day 1

1. It is critical to first confirm diagnosis of VTE
- Clinical assessment: look for risk factors for VTE
- If DVT symptoms are present, obtain a venous ultrasound
- If PE is suspected, obtain a V/Q or computed tomography scan
- D-dimer: this test may be a helpful adjunct to either a venous ultrasound or V/Q scan

2. Obtain baseline laboratory tests. These tests must be obtained prior to initiating anticoagulation therapy:
- Prothrombin time (PT) and calculated International Normalized Ratio (INR)
- Activated partial thromboplastin time (aPTT)
- Serum creatinine
- Complete blood cell count (CBC) with platelets

3. Medications:
- Screen the patient's pharmacy profile for potential drug-drug interactions with anticoagulation therapy
- Initiate unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) or fondaparinux by injection (see Table 7–3 for dosing guidelines)
- Start warfarin sodium orally every evening (see Fig. 7–9 for dosing guidelines)
- Start pain medication if necessary (avoid non-steroidal anti-inflammatory drugs)

4. Patient Education:
- Educate the patient regarding the purpose of therapy and importance of proper monitoring of anticoagulant drugs. Assist the patient to determine an appropriate provider for long-term monitoring of anticoagulation therapy.
- If LMWH or fondaparinux is selected, teach the patient how to self-administer (if the patient or a family member is unwilling or unable to self-administer, visiting nurse services should be arranged). Initial injection should be administered in the medical office or hospital.
- Inform patient about the effects of vitamin K–rich foods on warfarin therapy. Moderate intake (less than 500 to 1000 mcg) of vitamin K is acceptable. Provide patient with written material regarding vitamin K content of foods.
- Inform the patient about the potential drug-drug interactions with warfarin, including over-the-counter medications and dietary supplements (Tables 7–8, 7–9, and 7–10). Instruct the patient to call the health care practitioner responsible for monitoring warfarin therapy before starting any new medications or dietary supplements.
- Instruct the patient regarding nonpharmacologic strategies including elevation of the affected extremity and anti-embolic exercises such as flexion/extension of the ankle (for lower extremity VTE) or hand squeezing/relaxation (for upper extremity VTE).

5. Next steps:
- If the patient is to be treated at home, dispense to the patient a 5- to 7-day supply of prefilled LMWH or fondaparinux syringes in patient-specific dose.
- If the patient is to be treated with UFH, measure aPTT (or anti–factor Xa activity) 6 hours after initiating the IV infusion. Adjust dose if necessary (Table 7–5) and measure aPTT (or anti–factor Xa activity) every 6 hours after each dose change until therapeutic. Measure aPTT (or anti–factor Xa activity) daily thereafter.
- Arrange for follow-up and long-term anticoagulation therapy management. Communicate with the patient's primary care physician and/or refer to a local antithrombosis service, if available. If the patient is to be treated primarily in the hospital, these arrangements can be made 1 to 2 days prior to hospital discharge.

6. Document all activities in medical record.

Day 2

1. If the patient is being treated with UFH, remeasure aPTT (or anti–factor Xa activity), and adjust dose if necessary. If patient is being treated with LMWH or fondaparinux, continue therapy.
2. Interview the patient to determine if there is worsening or new symptoms related to VTE. Ask the patient about overt bruising or bleeding, particularly at the injection site, as well as changes in stool or urine color.
3. Advise the patient to limit physical activity if pain persists and to elevate the extremity; increase activity as tolerated.
4. Document activities in medical record.

Days 3 to 5

1. Measure PT/INR every 1 to 2 days.
2. Interview the patient to determine if there is worsening or new symptoms related to VTE. Inquire about and evaluate patient adherence to therapy. Ask the patient about overt bruising or bleeding, particularly at the injection site, as well as changes in stool or urine color. Advise the patient to limit physical activity if pain persists and to elevate the extremity; increase activity as tolerated. Reinforce previous patient education regarding vitamin K intake and potential drug-drug interactions with warfarin.
3. Hold or adjust warfarin dose as necessary. If the patient is being treated with UFH, measure aPTT daily (or anti–factor Xa activity), and adjust dose if necessary. If the patient is being treated with an LMWH or fondaparinux, continue therapy.
4. Document activities in medical record.

Days 6 to 8

1. Measure PT/INR every 2 to 3 days. Obtain CBC or platelet count.
2. Interview the patient to determine if there is worsening or new symptoms related to VTE. Inquire about and evaluate patient adherence to therapy. Ask the patient about overt bruising or bleeding, particularly at the injection site, as well as changes in stool or urine color. Advise the patient to limit physical activity if pain persists and to elevate the extremity; increase activity as tolerated. Reinforce previous patient education regarding vitamin K intake and potential drug-drug interactions with warfarin.

(*Continued*)

3. Hold or adjust warfarin dose as necessary. Discontinue UFH, LMWH, or fondaparinux if INR is greater than 2 on two consecutive occasions. If the patient requires continued treatment with UFH, measure aPTT, and adjust dose if necessary.
4. If the patient is treated with UFH or LMWH and platelet count has dropped by more than 50% from baseline or is less than $120 \times 10^3/\mu L$, evaluate the patient for heparin-induced thrombocytopenia (HIT).
5. Document activities in medical record.

Days 9 to 14

1. Measure PT/INR every 3 to 5 days.
2. Interview the patient to determine if there is worsening or new symptoms related to VTE. Inquire about and evaluate patient adherence to therapy. Ask the patient about overt bruising or bleeding, particularly at the injection site, as well as changes in stool or urine color. Advise the patient to elevate the extremity and increase activity as tolerated. Reinforce previous patient education regarding vitamin K intake and potential drug-drug interactions with warfarin.
3. Hold or adjust warfarin dose as necessary. Discontinue UFH, LMWH, or fondaparinux if INR is greater than 2 on two consecutive occasions. If the patient requires continued treatment with UFH, re-measure aPTT, and adjust dose if necessary.
4. Obtain CBC or platelet count. If the patient is treated with UFH or LMWH and platelet count has dropped by more than 50% from baseline or is less than $120 \times 10^3/\mu L$, evaluate the patient for HIT.
5. Document activities in medical record.

Days 15 to 90

1. Measure PT/INR every 1 to 4 weeks based on the stability of the INR and patient's health status.
2. Interview the patient to determine if there is worsening or new symptoms related to VTE. Inquire about and evaluate patient adherence to therapy. Ask the patient about overt bruising or bleeding as well as changes in stool or urine color. Encourage the patient to increase activity as tolerated. Reinforce previous patient education regarding vitamin K intake and potential drug-drug interactions with warfarin.
3. Adjust warfarin dose as necessary. Consider restarting LMWH or fondaparinux if INR drops below 1.5.
4. Document activities in medical record.

Three Months and Beyond

1. Measure PT/INR every 1 to 4 weeks based on the stability of the INR and patient's health status.
2. Interview the patient to determine if there is worsening or new symptoms related to VTE. Inquire about and evaluate patient adherence to therapy. Ask the patient about overt bruising or bleeding as well as changes in stool or urine color. Reinforce previous patient education regarding vitamin K intake and potential drug-drug interactions with warfarin.
3. Re-evaluate the risks and benefits of continuing warfarin therapy.
4. Document activities in medical record.

ABBREVIATIONS

ABW:	adjusted body weight
ACCP:	American College of Chest Physicians
ACT:	activated clotting time
ADP:	adenosine diphosphate
aPTT:	activated partial thromboplastin time
AT:	antithrombin
BMI:	body mass index
CBC:	complete blood count
CO:	cyclooxygenase
CrCl:	creatinine clearance
CT:	computed tomography
CYP:	cytochrome P-450 isoenzyme
DTI:	direct thrombin inhibitor
DVT:	deep vein thrombosis
ESR:	erythrocyte sedimentation rate
FDA:	Food and Drug Administration
GCS:	graduated compression stockings
GFR:	glomerular filtration rate
GP:	glycoprotein
HCII:	heparin co-factor II
HIT:	heparin-induced thrombocytopenia
HMWK:	high-molecular-weight kininogen
IBW:	ideal body weight
ICH:	intracranial hemorrhage
IM:	intramuscular
INR:	International Normalized Ratio
IPC:	intermittent pneumatic compression (device)
ISI:	International Sensitivity Index
IV:	intravenous
IVC:	inferior vena cava
LMWH:	low-molecular-weight heparin
PAF:	platelet activating factor
PAI-1:	plasminogen activator inhibitor-1
PCI:	percutaneous coronary inhibitor
PE:	pulmonary embolism
PF-4:	platelet factor-4
PGG/PGH:	prostaglandins
PGI:	prostacyclin
PLA:	phospholipase A
PO:	oral
PT:	prothrombin time
PTS:	postthrombotic syndrome
SBP:	systolic blood pressure
SC:	subcutaneous
SERM:	selective estrogen receptor modulator
TFPI:	tissue factor pathway inhibitor
t-PA:	tissue plasminogen activator
TS:	thromboxane synthetase
TXA:	thromboxane A
UFH:	unfractionated heparin

u-PA: urokinase plasminogen activator
V/Q: ventilation/perfusion (scan)
VTE: venous thromboembolism
vWF: von Willebrand factor
WBC: white blood cell (count)
WHO: World Health Organization

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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8 Stroke

Susan R. Winkler



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Understand the types of cerebrovascular disease including transient ischemic attack, cerebral infarction, and cerebral hemorrhage.
2. Understand the pathophysiology of cerebral ischemia and cerebral hemorrhage.
3. Identify the modifiable and non-modifiable risk factors associated with ischemic stroke and hemorrhagic stroke.
4. Identify risk factors for ischemic stroke in a patient and provide the appropriate patient education.
5. Discuss the various treatment options for acute ischemic stroke and hemorrhagic stroke.
6. Determine whether thrombolytic therapy is indicated in a patient with acute ischemic stroke.
7. Develop an appropriate patient-specific therapeutic plan for acute ischemic stroke.
8. Develop an appropriate therapeutic plan for outpatient management of a patient with ischemic stroke, including an appropriate agent to prevent stroke recurrence.

Key Concepts

❶ Strokes can either be ischemic (88%) or hemorrhagic (12%).

❷ Ischemic stroke is the abrupt development of a focal neurologic deficit that occurs due to inadequate blood supply to an area of the brain. Most often, this is due to a thrombotic or embolic arterial occlusion leading to cerebral infarction.

❸ Hemorrhagic stroke is a result of bleeding into the brain and other spaces within the central nervous system and includes subarachnoid hemorrhage, intracerebral hemorrhage, and subdural hematomas.

❹ There are two main classifications of cerebral ischemic events: transient ischemic attacks and cerebral infarction.

❺ A major goal in the long-term treatment of ischemic stroke involves the prevention of a recurrent stroke through the reduction and modification of risk factors.

❻ All patients should have a brain computed tomography scan or magnetic resonance imaging scan to differentiate an ischemic stroke from a hemorrhagic stroke, as the treatment will differ accordingly and thrombolytic (fibrinolytic) therapy must be avoided until a hemorrhagic stroke is ruled out.

❼ In carefully selected patients, alteplase is effective in limiting the infarct size and protecting brain tissue from ischemia and cell death by restoring blood flow. Treatment must be given within 3 hours of the onset of symptoms and offers no benefit if given beyond this time period.

❽ Early aspirin therapy is recommended in most patients with acute ischemic stroke within the first 24 to 48 hours after stroke onset and should be continued for at least 2 weeks.

❾ Aspirin is typically considered to be the first-line secondary prevention agent for ischemic stroke and decreases the risk of subsequent stroke by approximately 25% in both men and women with previous transient ischemic attacks or stroke.

❿ There is no proven treatment for intracerebral hemorrhage. Management is based on neurointensive care treatment and prevention of complications. Oral nimodipine is recommended in subarachnoid hemorrhage to prevent delayed cerebral ischemia.

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EPIDEMIOLOGY AND ETIOLOGY

Cerebrovascular disease (CVD), or stroke, is the third leading cause of death in the United States and the second most common cause of death worldwide. Over 700,000 strokes occur in the United States each year. ❶ *Strokes can either be ischemic (88% of all strokes) or hemorrhagic (12% of all strokes).* Figure 8–1 provides a classification of stroke by mechanism. New strokes account for 500,000 of this total, while recurrent strokes account for the remaining 200,000 strokes each year. Stroke is the leading cause of long-term disability in adults, with 90% of survivors having residual deficits. Moderate to severe disability is seen in 70% of survivors. The American Heart Association estimates that there are 4.7 million survivors of stroke in the United States. The societal impact and economic burden is great, with costs exceeding $57 billion per year in the United States. Stroke mortality has declined due to improved recognition and treatment of risk factors; however, risk factor management is still inadequate today. Stroke incidence increases with age, especially after age 55, resulting in an increased stroke incidence due to aging of the population.[1]

❷ *Ischemic stroke is the abrupt development of a focal neurologic deficit that occurs due to inadequate blood supply to an area of the brain. Most often, this is due to a thrombotic or embolic arterial occlusion leading to cerebral infarction.* A thrombotic occlusion occurs when a **thrombus** forms inside an artery in the brain. An embolism refers to a clot originating outside of the brain in which a piece of the clot breaks loose and is carried to the brain.

❸ *Hemorrhagic stroke is a result of bleeding into the brain and other spaces within the central nervous system and includes subarachnoid hemorrhage, intracerebral hemorrhage, and subdural hematomas.* Subarachnoid hemorrhage (SAH) results from sudden bleeding into the space between the inner layer and middle layer of the **meninges**, most often due to trauma or rupture of a cerebral aneurysm or arteriovenous malformation (AVM). Intracerebral hemorrhage (ICH) is bleeding directly into the brain parenchyma, often as a result of chronic, uncontrolled hypertension. Subdural hematomas result from bleeding under the dura which covers the brain and most often occur as a result of head trauma.

PATHOPHYSIOLOGY

Classification of Cerebral Ischemic Events

❹ *There are two main classifications of ischemic events,* ***transient ischemic attack*** *(TIA) and cerebral infarction.* A TIA is a temporary reduction in perfusion to a focal region of the brain causing a short-lived disturbance of function. TIAs have a rapid onset (5 minutes) and short duration (2 to 15 minutes, up to 24 hours). The symptoms vary depending on the area of the brain affected; however, no deficit remains after the attack. A TIA may be the only warning of an impending stroke, with the greatest risk occurring in the first several weeks. Cerebral infarction is similar to a TIA; however, symptoms last longer than 24 hours, and in 90% of patients residual deficits remain after the event.

Classification of Hemorrhagic Events

A sudden severe headache, nausea and vomiting, and **photophobia** may be the first signs and symptoms of hemorrhagic stroke. Neck pain and **nuchal rigidity** may also be experienced at the time of the hemorrhage. Patients may complain that the headache is "the worst headache of my life," especially if the cause is an SAH. It is important to note that a diagnosis of the type of stroke cannot be made solely on signs and

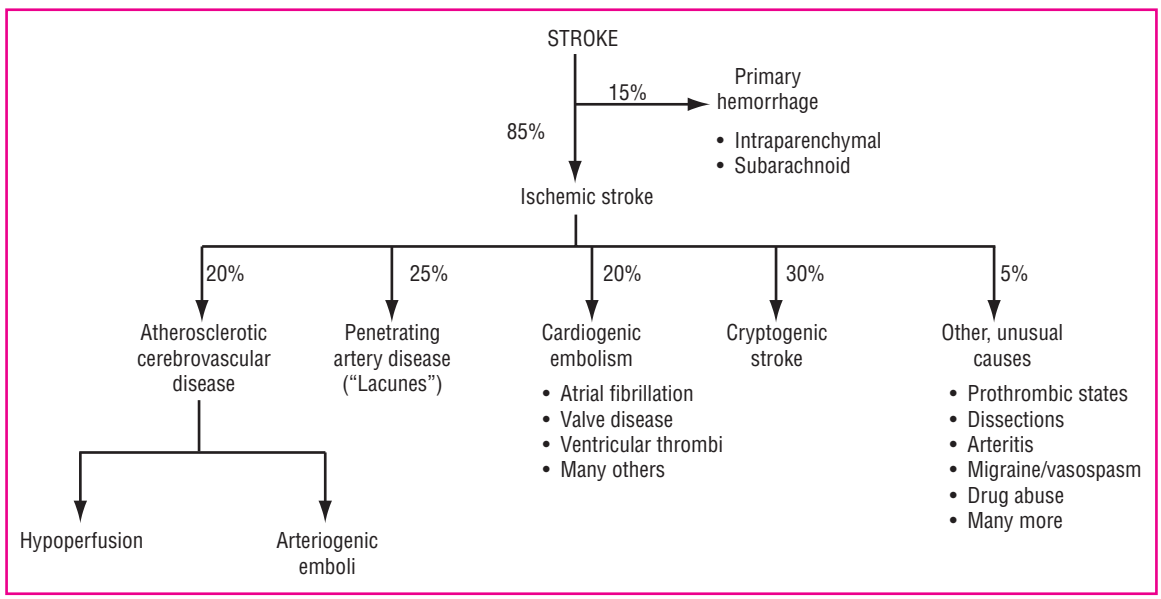


FIGURE 8–1. Classification of stroke. (Adapted from Fagan SC, Hess DC. Stroke. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 416, with permission.)

TABLE 8–1. Signs and Symptoms of Stroke

Sudden weakness, numbness, or paralysis of the face, arm, or leg (especially on one side of the body)
Loss of speech or trouble talking or understanding language
Sudden loss of vision
Sudden severe headache
Unexplained dizziness or loss of balance or coordination

symptoms, as many of these overlap between the types of stroke. Table 8–1 identifies the signs and symptoms of stroke.

Pathophysiology of Ischemic Stroke

There are three major pathophysiologic mechanisms underlying the occurrence of ischemic stroke including large-vessel disease, small-vessel disease, and embolism. In ischemic stroke, there is an interruption of the blood supply to an area of the brain either due to thrombus formation or an embolism. Loss of cerebral blood flow results in a failure of energy production in the affected brain cells. This lack of blood flow results in tissue hypoperfusion, tissue hypoxia, and cell death. Lipid deposits in the vessel wall cause turbulent blood flow and lead to vessel injury, exposing vessel collagen to blood. This vessel injury initiates the platelet aggregation process due to the exposed subendothelium. Platelets release adenosine diphosphate (ADP), which causes platelet aggregation and consolidation of the platelet plug. Thromboxane A_2 is released, contributing to platelet aggregation and vasoconstriction. The vessel injury also activates the coagulation cascade, which leads to thrombin production. Thrombin converts fibrinogen to fibrin, leading to clot formation as fibrin molecules, platelets, and blood cells aggregate. Figures 8–2 and 8–3 depict these processes.

Once the initial event occurs, secondary events occur at the cellular level that contribute to cell death. Regardless of the specific initiating event, the cellular processes that follow may be similar. Excitatory amino acids such as glutamate accumulate within the cells, causing intracellular calcium accumulation. Inflammation occurs and oxygen free radicals are formed ending in the common pathway of cell death.

Often, there is a core of ischemia containing unsalvageable brain cells. Surrounding this core is an area often termed the ischemic penumbra. In this area, cells are still salvageable; however, this is a time-sensitive endeavor, as without restoration of adequate perfusion, cell death continues throughout a larger area of the brain. This process ultimately leads to neurologic deficits. No agents have been shown to be effective at providing neuroprotection at this time.

Pathophysiology of Hemorrhagic Stroke

The pathophysiology of hemorrhagic stroke is not as well studied as that of ischemic stroke; however, it is a more complex process than previously thought. Much of the process is related to the presence of blood in the brain tissue and/or surrounding

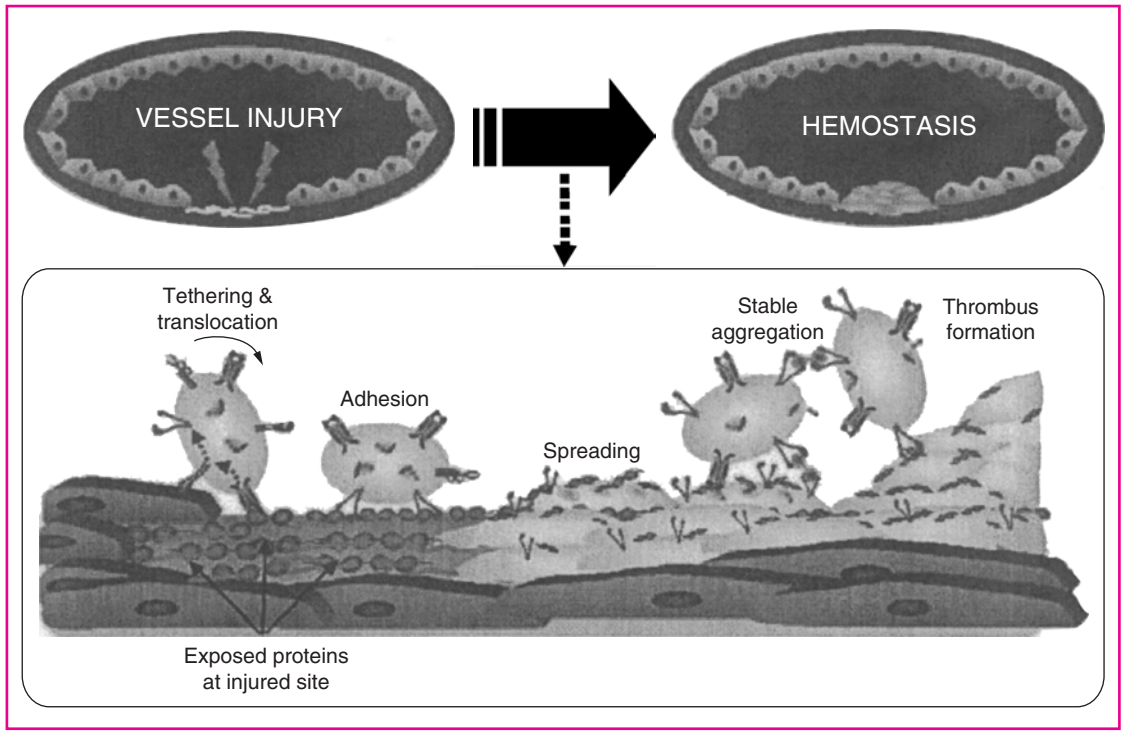


FIGURE 8–2. Platelet aggregation. This figure shows the process of platelet aggregation. Vessel injury occurs resulting in adhesion of the platelets to the vessel wall. This leads to continued adhesion and aggregation of platelets resulting in thrombus formation.

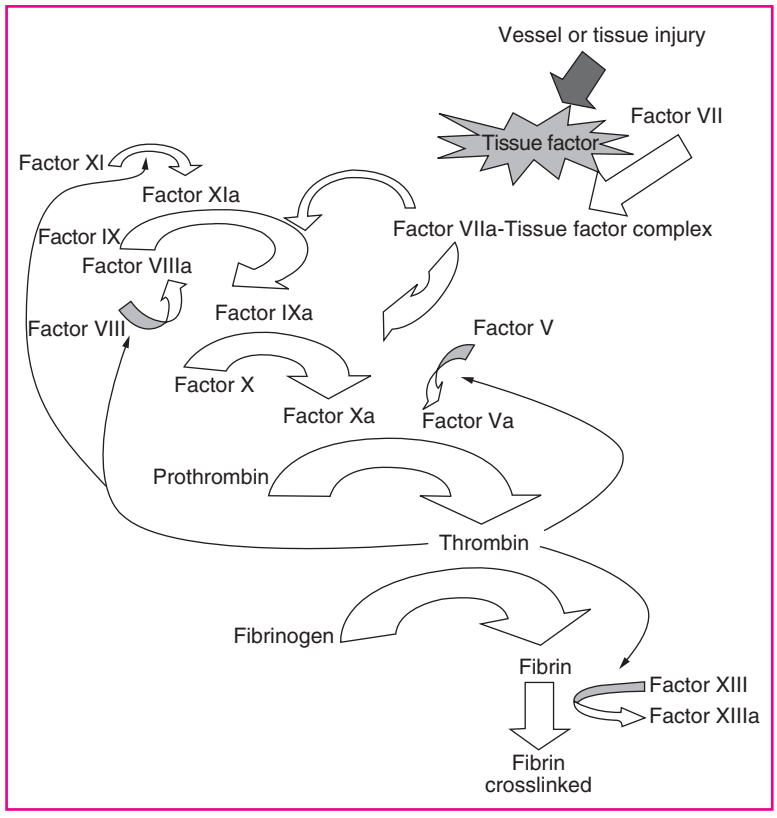


FIGURE 8–3. The physiologic clotting cascade. Clot formation beginning with vessel or tissue injury. Tissue injury starts the complex process involving clotting factors and resulting in cross-linked fibrin. This is a schematic of the factors and steps involved in the process.

spaces resulting in compression. It is now known that the hematoma that forms may continue to grow and enlarge after the initial bleed and that early growth of the hematoma is associated with a poor outcome. Brain tissue swelling and injury is a result of inflammation caused by thrombin and other blood products. This can lead to increased intracranial pressure and **herniation**.[2,3]

Risk Factors

Assessment of risk factors for ischemic stroke as well as for hemorrhagic stroke is an important component of the diagnosis and treatment of patients. ❺ *A major goal in the long-term treatment of ischemic stroke involves the prevention of a recurrent stroke through the reduction and modification of risk factors.* The major focus of primary prevention (prevention of the first stroke) is also reduction and modification of risk factors. Risk factors for ischemic stroke can be divided into modifiable and non-modifiable factors. Every patient should have risk factors assessed and treated, if possible, as management of risk factors can decrease the occurrence and/or recurrence of stroke.[4]

Non-modifiable risk factors include age, gender, race/ethnicity, and heredity. Ischemic stroke risk is increased in those greater than 55 years of age, in men, and in African-Americans, Hispanics, and Asian-Pacific Islanders. It is also increased in those with a family history of stroke. Modifiable risk factors include a number of treatable disease states and lifestyle factors that can greatly influence overall stroke risk. Hypertension is one of the major risk factors for both ischemic and hemorrhagic stroke. For ICH specifically, uncontrolled hypertension is thought to be the cause of hemorrhage in 60% to 70% of patients.[5] Other risk factors for hemorrhagic stroke include trauma, cigarette smoking, cocaine use, heavy alcohol use, and cerebral aneurysm and AVM rupture. Tables 8–2 and 8–3 provide a listing of risk factors in ischemic stroke.

DESIRED TREATMENT OUTCOMES

The short-term goals of treatment for acute ischemic stroke include reducing secondary brain damage by re-establishing and maintaining adequate perfusion to marginally ischemic areas of the brain and to protect these areas from the effects of ischemia (i.e., neuroprotection). The long-term goals of treatment include prevention of a recurrent stroke through reduction and modification of risk factors and by use of appropriate treatments.

TABLE 8–2. Non-modifiable Risk Factors for Ischemic Stroke

Age (greater than 55 years of age)
Gender (males greater than females)
Race (African-American, Hispanic, or Asian-Pacific Islander)
Ethnicity
Heredity



Clinical Presentation and Diagnosis

General

- The patient may not be able to reliably report the history owing to cognitive or language deficits. A reliable history may have to come from a family member or another witness.

Symptoms

- The patient may complain of weakness on one side of the body, inability to speak, loss of vision, **vertigo**, or falling. Stroke patients may complain of headache; however, with hemorrhagic stroke, the headache can be severe.

Signs

- Patients usually have multiple signs of neurologic dysfunction, and the specific deficits are determined by the area of the brain involved.
- **Hemiparesis** or **monoparesis** occur commonly, as does a **hemisensory deficit**.
- Patients with vertigo and double vision are likely to have posterior circulation involvement.
- **Aphasia** is seen commonly in patients with anterior circulation strokes.
- Patients may also suffer from **dysarthria**, visual field defects, and altered levels of consciousness.

Laboratory Tests

- There are no specific laboratory tests for stroke.
- Tests for hypercoagulable states, such as protein C deficiency and antiphospholipid antibody, should be done only when the cause of stroke cannot be determined based on the presence of well-known risk factors for stroke.

Other Diagnostic Tests

- A computed tomography (CT) scan of the head will reveal an area of hyperintensity (white) identifying that a hemorrhage has occurred. The CT scan will either be normal or hypointense (dark) in an area where an infarction has occurred. The CT scan may take 24 hours (rarely longer) to reveal the area of infarction.
- Magnetic resonance imaging (MRI) of the head will reveal areas of ischemia earlier and with better resolution than a CT scan. Some types of imaging can reveal an evolving infarct within minutes.
- Carotid Doppler studies will determine whether the patient has a high degree of stenosis in the carotid arteries supplying blood to the brain (extracranial disease).
- The electrocardiogram will determine whether the patient has atrial fibrillation, which is a major risk factor for stroke.
- A transthoracic echocardiogram will identify whether there are heart valve abnormalities or problems with wall motion resulting in emboli to the brain.



Patient Encounter, Part 1

GR is a 68-year-old African-American male who presents to the emergency department with dizziness and loss of speech that began 1 hour ago. His past medical history is significant for hypertension, diabetes mellitus, hypercholesterolemia, and benign prostatic hypertrophy (BPH). Social history is significant for smoking 1 pack per day for the last 38 years. Current medications include metoprolol 50 mg twice daily, insulin NPH 20 units twice daily, and simvastatin 20 mg daily.

- What signs and symptoms does GR have that are suggestive of stroke?
- What non-modifiable and modifiable risk factors does GR have for acute ischemic stroke?

The short-term goals for the treatment of hemorrhagic stroke include rapid neurointensive care treatment to maintain adequate oxygenation, breathing, and circulation. Management of increased intracranial pressure and blood pressure (BP) are important in the acute setting. Long-term management includes prevention of complications and prevention of a recurrent bleed and delayed cerebral ischemia.

Prevention of long-term disability and death related to the stroke are important regardless of the type of stroke.

TABLE 8–3. Modifiable Risk Factors for Ischemic Stroke

Hypertension (single most important risk factor)
Cardiac disease
Atrial fibrillation (most important and treatable cardiac cause of stroke)
Mitral stenosis
Mitral annular calcification
Left atrial enlargement
Structural abnormalities such as atrial-septal aneurysm
Myocardial infarction
Transient ischemic attacks or prior stroke (major independent risk factor)
Diabetes (independent risk factor)
Hypercholesterolemia
Lifestyle factors
Cigarette smoking
Excessive alcohol use
Physical inactivity
Obesity
Diet
Cocaine and intravenous drug use
Low socioeconomic status
Increased hematocrit
Sickle cell disease
Elevated homocysteine level (still under study, but may be related to stroke risk)
Migraine (risk not clear)
Asymptomatic carotid stenosis
Oral contraceptives (with estrogen content greater than 50 mcg)

GENERAL APPROACH TO TREATMENT

❻ *All patients should have a brain computed tomography (CT) scan or magnetic resonance imaging (MRI) scan to differentiate an ischemic stroke from a hemorrhagic stroke, as the treatment will differ accordingly and thrombolytic (fibrinolytic) therapy must be avoided until a hemorrhagic stroke is ruled out (in other words, until it is determined that it is not a hemorrhagic stroke).* A CT scan is the most important diagnostic test in patients with acute stroke. For those with an ischemic stroke, an evaluation should be done to determine the appropriateness of reperfusion therapy. In hemorrhagic stroke, a surgical evaluation should be completed to assess the need for surgical clipping of an aneurysm or other procedure to control the bleed and prevent re-bleeding and other complications. Figure 8–4 provides an algorithm for the initial management of the acute stroke patient.

TREATMENT OF ACUTE ISCHEMIC STROKE

Acute stroke is considered to be an acute medical emergency. Identification of the time and manner of stroke onset is an important determinant in treatment. The time the patient was last without symptoms is used as the time of stroke onset. Since patients typically do not experience pain, determining the onset time can be difficult. It is also important to document risk factors and previous functional status of the patient to assess current disability due to the stroke.

Supportive Measures

Acute complications of stroke include cerebral edema, increased intracranial pressure, seizures, and **hemorrhagic conversion**. In the acute setting, several supportive interventions and treatments to prevent acute complications should be initiated.

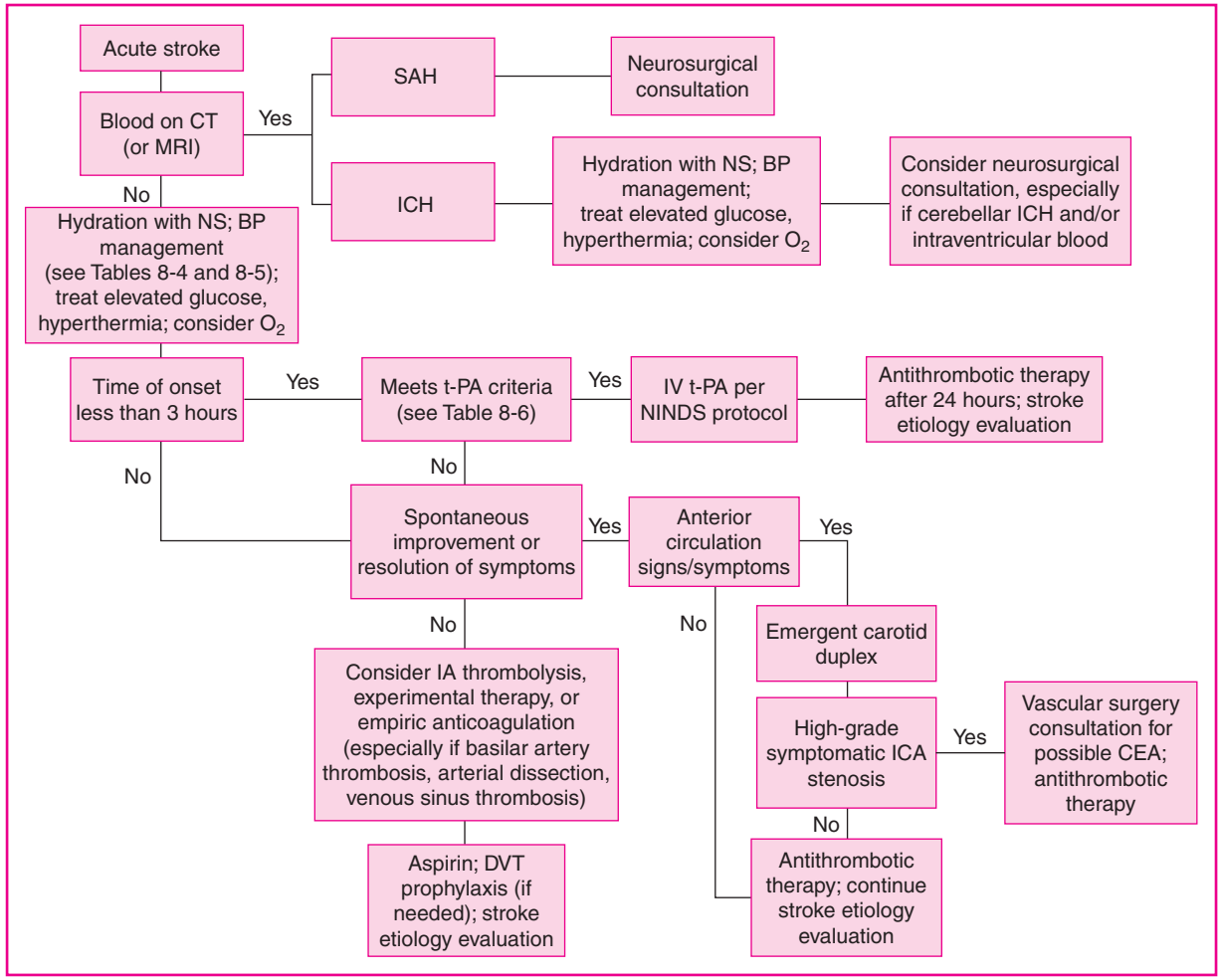


FIGURE 8–4. Acute stroke treatment algorithm. BP, blood pressure; CEA, carotid endarterectomy; CT, computed tomography; DVT, deep vein thrombosis; IA, intra-arterial; ICA, internal carotid artery; ICH, intracerebral hemorrhage; IV, intravenous; MRI, magnetic resonance imaging; NINDS, National Institute of Neurological Disorders and Stroke; NS, normal saline; SAH, subarachnoid hemorrhage; t-PA, tissue plasminogen activator.

Tissue oxygenation should be maintained acutely. Measure the oxygen saturation using pulse oximetry and supplement the patient with oxygen if necessary. The oxygen saturation should be maintained at 95% or greater.[6] Volume status and electrolytes should be corrected. If required, the blood glucose should be corrected, as both hyperglycemia and hypoglycemia may worsen brain ischemia. When hypoglycemia is present, bolus with 50% dextrose immediately. A blood glucose that is severely elevated should be lowered cautiously to less than 300 mg/dL (16.7 mmol/L) using subcutaneous insulin. If the patient is febrile, treat with acetaminophen, as fever is associated with brain ischemia and increased morbidity and mortality after stroke. Alternately, cooling devices can be used.[7] Intravenous (IV) and subcutaneous heparin will significantly decrease the risk of developing deep vein thrombosis (DVT) post-stroke. Heparin 5000 units subcutaneously every 12 hours should be given for DVT prophylaxis in patients who are not candidates for intravenous alteplase. In patients receiving IV alteplase, the administration of subcutaneous heparin should be delayed 24 hours to avoid bleeding complications.

In the setting of acute ischemic stroke, many patients will have an elevated BP in the first 24 to 48 hours.[8] Blood pressure should be optimized; however, hypertension should generally not be treated initially in acute stroke patients, as this may cause decreased blood flow in ischemic areas, potentially increasing the infarction size. The cautious use of antihypertensive medications may be necessary in patients who are otherwise candidates for thrombolytic therapy, including those with severely elevated blood pressure (systolic BP greater than 220 mm Hg or diastolic BP greater than 120 mm Hg), and those with other medical disorders requiring immediate lowering of BP. Tables 8–4 and 8–5 provide recommendations on blood pressure management in those eligible and those not eligible for alteplase. In those not eligible for alteplase, when blood pressure is lowered, aim for a 10% to 15% reduction. Avoid using sublingual calcium channel blockers, as these may lower BP too rapidly. Blood pressure should be checked three times with each reading taken 5 minutes apart.

TABLE 8–4. Blood Pressure Recommendations for Ischemic Stroke (Not Eligible for Alteplase)

Systolic BP less than 220 mm Hg or diastolic BP less than 120 mm Hg	Observe unless other end-organ involvement
Systolic BP greater than 220 mm Hg or diastolic BP 121–140 mm Hg	Labetalol 10–20 mg IV over 1–2 minutes (may repeat or double every 10 minutes); nicardipine infusion 3–5 mg/hour titrated to response
Diastolic BP greater than 140 mm Hg	Nitroprusside 0.25–0.3 mcg/kg/minute titrated to response

BP, blood pressure; IV, intravenous.

TABLE 8–5. Recommendations for Ischemic Stroke (Eligible for Alteplase)

Before treatment, if systolic BP is greater than 185 mm Hg or diastolic BP is greater than 110 mm Hg	Labetalol 10–20 mg IV over 1–2 minutes (may repeat or double every 10 minutes)
During and after treatment, if diastolic BP is greater than 140 mm Hg	Nitroprusside 0.25–0.3 mcg/kg/minute titrated to response
If systolic BP is greater than 230 mm Hg or diastolic BP is 121–140 mm Hg	Labetalol or nicardipine infusion 3–5 mg/hour titrated to response
If systolic BP is 180–230 mm Hg or diastolic BP is 105–120 mm Hg	Labetalol 10–20 mg IV over 1–2 minutes (may repeat or double every 10 minutes)

BP, blood pressure; IV, intravenous.

Nonpharmacologic Therapy

Carotid Endarterectomy and Middle Cerebral Artery Embolectomy

It is unknown whether carotid **endarterectomy** is of value when performed emergently after stroke, meaning within the first 24 hours after symptoms begin.[9] It appears that patients with mild to moderate neurologic deficits, **crescendo** TIAs or stroke-in-evolution can be operated on safely within the first few hours after the onset of symptoms. Patients with more severe neurologic deficits should only be considered for carotid endarterectomy when the procedure can be performed within the first few hours after the onset of symptoms. It is not indicated for patients with permanent deficits from a moderate to severe completed stroke.

Middle cerebral artery embolectomy remains controversial in the acute treatment of stroke. Patients who may benefit from this procedure are those who have good collateral circulation and can be operated on within the first few hours after the onset of symptoms.

Due to the lack of proven efficacy of any of these procedures when performed emergently in acute ischemic stroke, they are not routinely recommended except within a research environment.

Thrombolytic Therapy

Systemic Thrombolytic Therapy

Alteplase

Alteplase (rt-PA; Activase) is an IV thrombolytic (fibrinolytic) that was approved for acute stroke treatment in 1996 based on the results of the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Trial.[10] The current American Stroke Association guidelines include alteplase as the only Food and Drug Administration (FDA) approved acute treatment for ischemic stroke and strongly encourage early diagnosis and treatment of appropriate patients.[11]

Based on several assessment scales, patients treated with alteplase were 30% more likely to have minimal or no disability at 3 months compared with patients given placebo. Alteplase treatment resulted in an 11% to 13% absolute increase in patients with excellent outcomes at 3 months and a benefit was seen regardless of patient age, stroke sub-type, stroke severity, or prior use of aspirin.[12] Intracerebral hemorrhage within 36 hours after stroke onset occurred in 6.4% of those given alteplase versus 0.6% in those given placebo (*p* less than 0.001). There was no significant difference in mortality between the two groups at 3 months. ❼ *In carefully selected patients, alteplase is effective in limiting the infarct size and protecting brain tissue from ischemia and cell death by restoring blood flow. Treatment must be given within 3 hours of the onset of symptoms and offers no benefit if given beyond this time period.* A dose of 0.9 mg/kg (maximum 90 mg) is recommended; the first 10% is given as an IV bolus and the remainder is infused over 1 hour. Table 8–6 details the inclusion and exclusion criteria for the administration of alteplase in acute ischemic stroke.

TABLE 8–6. Inclusion and Exclusion Criteria for Alteplase Use in Acute Ischemic Stroke

Inclusion Criteria
- 18 years of age or older
- Clinical diagnosis of ischemic stroke causing a measurable neurologic deficit
- Time of symptom onset well established to be less than 180 minutes before treatment would begin

Exclusion Criteria
- Evidence of intracranial hemorrhage on CT scan of the brain prior to treatment
- Only minor or rapidly improving stroke symptoms
- Clinical presentation suggestive of subarachnoid hemorrhage even with a normal head CT
- Active internal bleeding
- Known bleeding diathesis, including but not limited to (1) platelet count less than $100 \times 10^3/mm^3$ ($100 \times 10^9/L$); (2) heparin within 48 hours with an elevated aPTT; or (3) current oral anticoagulant use (e.g., warfarin) or recent use with an elevated PT (greater than 15 seconds) or INR (greater than 1.7)
- Intracranial surgery, serious head trauma, or previous stroke within 3 months
- Suspected aortic dissection associated with stroke
- Suspected subacute bacterial endocarditis or vasculitis
- History of gastrointestinal or urinary tract hemorrhage within 21 days
- Major surgery or serious trauma within 14 days
- Recent arterial puncture at a non-compressible site
- Lumbar puncture within 7 days
- History of intracranial hemorrhage
- Known arteriovenous malformation or aneurysm
- Witnessed seizure at the same time as the onset of stroke symptoms occurred
- Recent acute myocardial infarction
- SBP greater than 185 mm Hg or DBP greater than 110 mm Hg at the time of treatment, or patient requires aggressive treatment to reduce blood pressure to within these limits

aPTT, activated partial thromboplastin time; CT, computed tomography; DBP, diastolic blood pressure; INR, International Normalized Ratio; PT, prothrombin time; SBP, systolic blood pressure.

Studies following the NINDS trial protocol have supported alteplase use in acute ischemic stroke and have shown similar rates for both response and intracerebral hemorrhage occurrence. Studies that have varied from this protocol and administered alteplase beyond the 3-hour window have failed to show a benefit to treatment. When the clinical trials are pooled, study results show that the sooner alteplase is given after acute stroke, the greater the benefit seen in neurologic outcome.[13] Current guidelines recommend against using alteplase beyond 3 hours after stroke onset, as beyond this time the risk outweighs the benefit.[12]

Antiplatelet agents, anticoagulants, and invasive procedures such as the insertion of a central line or the placement of a nasogastric tube should be avoided for 24 hours after the infusion of alteplase to prevent bleeding complications. Bladder catheterization should also be avoided for 30 minutes post-infusion.

Efficacy is measured by the elimination of existing neurologic deficits and the long-term improvement in neurologic status and functioning based on neurologic examinations and other outcome measures. Neurologic examinations should be completed every 15 minutes during the infusion of alteplase, every 30 minutes for the first 6 hours after the infusion, and then every 4 hours up to 24 hours after alteplase administration. In the NINDS trial, neurologic function was assessed 24 hours after the administration of alteplase using the National Institutes of Health Stroke Scale (NIHSS). This scale quantifies neurologic deficits in patients who have had a stroke and is easy to perform. At 3 months, four outcome measures were used including the Barthel Index, modified Rankin scale, Glasgow outcome scale, and the NIHSS. The Barthel Index is a measure of the ability to perform activities of daily living, the modified Rankin scale is a simplified overall assessment of functioning, and the Glasgow outcome scale is a global assessment of functioning.

The major adverse effects of thrombolytic therapy are bleeding, including intracerebral hemorrhage and serious systemic bleeding. Mental status changes and a severe headache may indicate an intracerebral hemorrhage. Signs of bleeding include easy bruising; hematemesis; guaiac-positive stools; black, tarry stools; hematoma formation; hematuria; bleeding gums; and nosebleeds.

Streptokinase

Streptokinase is not indicated for use in acute ischemic stroke treatment. Three large randomized controlled trials evaluating streptokinase were stopped early due to a high incidence of hemorrhage in the streptokinase-treated patients.[14–16] At the present time, there is no indication for the use of streptokinase or thrombolytics other than alteplase in the acute treatment of ischemic stroke.

Intra-arterial Thrombolytics

Intra-arterial thrombolytics may improve outcomes in selected patients with acute ischemic stroke due to large-vessel occlusion. Patients in the Prolyse in Acute Cerebral Thromboembolism II (PROACT II) trial were given 9 mg prourokinase (r-pro UK)

plus heparin or heparin alone within 6 hours of symptom onset.[17] In those patients receiving prourokinase plus heparin, 40% had slight or no disability at 90 days. In the heparin-only group, 25% had slight or no disability at 90 days. No difference in mortality was found between the groups, although the incidence of intracranial hemorrhage was greater in the r-pro UK plus heparin group versus heparin alone. Note in particular, the drug used in this trial is not FDA-approved and is not currently available for clinical use. Intra-arterial thrombolytics are typically avoided except at major stroke centers where there is more experience with this route of administration. Alteplase is the only product currently available; therefore, when intra-arterial thombolytics are given, alteplase must be used. Due to the limitations of intra-arterial thrombolysis, current guidelines recommend that treatment with IV alteplase in eligible patients not be delayed by waiting for intra-arterial thrombolytics.

Heparin

Intravenous heparin has been commonly used in acute stroke therapy; however, no adequately designed trials have been done to establish its efficacy and safety. Current acute ischemic stroke treatment guidelines do not recommend routine, urgent anticoagulation with heparin or low-molecular-weight heparins (LMWHs) due to the lack of a proven benefit in improving neurologic function and the risk of intracranial bleeding.[11,18] Heparin may prevent early recurrent stroke in patients with large-vessel atherothrombosis or those thought to be at high risk of recurrent stroke (i.e., cardioembolic stroke); however, more study is required.

The major complications of heparin include evolution of the ischemic stroke into a hemorrhagic stroke, bleeding, and thrombocytopenia. The occurrence of severe headache and mental status changes may indicate an intracerebral hemorrhage. Signs of bleeding include easy bruising; hematemesis; guaiac-positive stools; black, tarry stools; hematoma formation; hematuria; bleeding gums; and nosebleeds. The hemoglobin, hematocrit, and platelet count should be obtained at least every 3 days to detect bleeding and thrombocytopenia.

Low-Molecular-Weight Heparins and Heparinoids

Low-molecular-weight heparins and heparinoids are not recommended in the treatment of acute ischemic stroke.[11] A meta-analysis was performed using data from 10 randomized controlled trials.[19] A non-significant decrease in combined death and disability and a non-significant increase in case fatality and hemorrhage were seen. A reduction in venous thromboembolic events was observed in acute stroke patients; however, there was also an increase in extracranial bleeding.

Aspirin

Aspirin in acute ischemic stroke has been studied in two large, randomized trials, the International Stroke Trial and the Chinese Acute Stroke Trial.[20,21] Patients who received aspirin within 24 to 48 hours of the onset of acute stroke symptoms were less likely to suffer early recurrent stroke, death, and disability. **8** *Early aspirin therapy is recommended in most patients with acute ischemic stroke within the first 24 to 48 hours after stroke onset and should be continued for at least 2 weeks.* The administration of anticoagulants and antiplatelet agents should be delayed for 24 hours in those patients receiving alteplase.

Ancrod

Ancrod is an investigational agent that acts to decrease plasma fibrinogen levels. It may be beneficial in patients with acute ischemic stroke when administered within 3 hours of symptom onset. In a randomized, parallel-group, double-blind, placebo-controlled trial, an improved functional status was observed in more patients receiving ancrod (42.2%) than in patients receiving placebo (34.4%; $p = 0.04$).[22] No difference in mortality was seen between the groups; however, there was a non-significant increase in symptomatic intracranial hemorrhages in the ancrod group (5.2% versus 2.0%; $p = 0.06$). Patients received ancrod or placebo as a 72-hour continuous infusion, followed by 1-hour infusions at 96 and 120 hours. Prior to the completion of this trial, previous trials showed a trend toward an improved outcome, although the number of patients studied was small and a 6-hour treatment window was used. Based upon available clinical trials, ancrod appears to have a potential benefit. However, it is not recommended for clinical use because its efficacy and safety have not been definitively established.[11]

PREVENTION OF ACUTE ISCHEMIC STROKE

Primary Prevention

Aspirin

Randomized trials have been completed assessing the role of antiplatelet therapy with aspirin for primary stroke prevention. The use of aspirin in patients with no history of stroke or ischemic heart disease reduced the incidence of non-fatal myocardial infarction (MI) but not of stroke. A meta-analysis of eight trials found that the risk of stroke was slightly increased with aspirin use, especially hemorrhagic stroke. Major bleeding risk was also increased with aspirin use.[4] Aspirin is beneficial in the primary prevention of MI, but not for primary stroke prevention.

Statin Therapy

Hyperlipidemia has not clearly been established as a risk factor for stroke, although it is a modifiable risk factor for coronary heart disease. Recent studies show that statin use may reduce the incidence of a first stroke in high-risk patients (e.g., hypertension, coronary heart disease, or diabetes) including patients with normal lipid levels. A recent meta-analysis showed a 25% risk reduction for fatal and non-fatal strokes with statin use.[4] Patients with a history of MI, elevated lipid levels, diabetes, and



Patient Encounter, Part 2

In the emergency department an IV line is placed, a physical and neurologic exam is completed, and GR is moved to the stroke unit. The CT scan is negative for hemorrhagic stroke.

- Identify your treatment goals for GR.
- What acute management would be appropriate for GR at this point?

other risk factors may benefit from treatment with a lipid-lowering agent; however, even patients with normal lipid levels may benefit from treatment.

Blood Pressure Management

Lowering blood pressure in patients who are hypertensive has been shown to reduce the relative risk of stroke, both ischemic and hemorrhagic, by 35% to 45%.[23] Also, the more blood pressure is lowered, the greater the reduction in stroke risk.[24] All patients should have their blood pressure monitored and controlled appropriately based on current guidelines for blood pressure management. However, no one agent has been clearly shown to be more beneficial than any other for preventing stroke.

Secondary Prevention

Nonpharmacologic Therapy

Carotid Endarterectomy

The benefit of carotid endarterectomy for prevention of recurrent stroke has been studied previously in major trials.[25,26] A recent meta-analysis has been completed that has combined these clinical trials to evaluate 6,092 patients.[27] Carotid endarterectomy has been shown to be beneficial for preventing **ipsilateral** stroke in patients with symptomatic carotid artery **stenosis** of 70% or greater and is recommended in these patients. In patients with symptomatic stenosis of 50% to 69%, a moderate reduction in risk is seen in clinical trials. In all patients with stenosis of 50% to 69% and a recent stroke, carotid endarterectomy is appropriate. In other patients, surgical risk factors and surgeon skill should be considered prior to surgery. The patient should have, at a minimum, a life expectancy of 5 years, and the surgical risk of stroke and/or death should be less than 6%. Carotid endarterectomy is not beneficial for symptomatic carotid stenosis less than 50% and should not be considered in these patients.

There are data to suggest that patients with asymptomatic carotid artery stenosis of 60% or more benefit from carotid endarterectomy if it is performed by a qualified surgeon with low complication rates (less than 3%). At this time, there is considerable controversy over how this information can be applied to clinical practice. A current review recommends considering carotid endarterectomy in patients with carotid artery stenosis of 60% to 99% who are between 40 and 75 years of age if there is a 5-year life expectancy and the operative risks are low.[28]

Carotid Angioplasty

Carotid angioplasty with or without **stenting** is typically restricted to patients who are refractory to medical therapy and are not surgical candidates. Clinical trials are currently ongoing to further define the role of carotid angioplasty in both symptomatic and asymptomatic patients.

Pharmacologic Therapy

Aspirin

In a recent meta-analysis including 144,051 patients with previous MI, acute MI, previous TIA or stroke, and acute stroke, as well as others at high risk, aspirin was found to decrease the risk of recurrent stroke by approximately 25%.[29] ❾ *Aspirin is typically considered to be the first-line secondary prevention agent for ischemic stroke and decreases the risk of subsequent stroke by approximately 25% in both men and women with previous transient ischemic attacks or stroke.* A wide range of doses have been used (30 to 1500 mg per day); however, enteric-coated aspirin 325 mg orally once daily is the most widely used and recommended regimen. The FDA has approved doses of 50 to 325 mg for secondary ischemic stroke prevention. In those who fail aspirin therapy, increasing the daily dose of aspirin or switching to either clopidogrel or the combination of extended-release dipyridamole plus aspirin are options. Clopidogrel is a reasonable alternative if aspirin is not tolerated, and it may be considered as first-line therapy in patients with peripheral arterial disease. Adverse effects of aspirin include gastrointestinal intolerance, gastrointestinal bleeding, and hypersensitivity reactions.

Warfarin

Warfarin has not been adequately studied in non-cardioembolic stroke, but it is often recommended in patients after antiplatelet agents fail. One small retrospective study suggests that warfarin is better than aspirin.[30] More recent clinical trials have not found oral anticoagulation in those patients without atrial fibrillation or carotid stenosis to be better than antiplatelet therapy. In the majority of patients without atrial fibrillation, antiplatelet therapy is recommended over warfarin. In patients with atrial fibrillation, long-term anticoagulation with warfarin is recommended and is effective in both primary and secondary prevention of stroke.[12] The goal International Normalized Ratio (INR) for this indication is 2 to 3.

Ticlopidine

Ticlopidine is slightly more beneficial in stroke prevention than aspirin in both men and women.[31,32] The usual recommended dosage is 250 mg orally twice daily. Ticlopidine is costly, and side effects include bone marrow suppression, rash, diarrhea, and an increased cholesterol level. Neutropenia is seen in approximately 2% of patients. **Thrombotic thrombocytopenic**

purpura (TTP) occurs in 1 of every 2000 to 4000 patients treated with ticlopidine. For these reasons, monitoring of the complete blood cell count (CBC) is required every 2 weeks for the first 3 months of therapy. Ticlopidine is an alternative in patients who cannot tolerate or who have failed aspirin therapy; however, because of the costly laboratory monitoring required and the adverse effect profile, many clinicians choose an alternative agent such as clopidogrel or aspirin/extended-release dipyridamole.

Clopidogrel

Clopidogrel is slightly more effective than aspirin with a relative-risk reduction of 7.3% more than that provided by aspirin.[33] The usual dose is 75 mg orally taken on a daily basis. Clopidogrel has a significantly lower incidence of diarrhea and neutropenia than ticlopidine, and laboratory monitoring is typically not required. There are 11 case reports of TTP occurring secondary to clopidogrel, with the majority occurring within the first 2 weeks of therapy. Currently, clopidogrel is favored over ticlopidine; however, clinicians need to be aware that there is a potential for the development of TTP. Clopidogrel may be preferred as monotherapy; in the MATCH trial, low-dose aspirin plus clopidogrel combination therapy compared to clopidogrel alone did not show a significant benefit.[34] This trial found that the addition of aspirin increased the risk of major bleeding. However, there is no difference in the bleeding risk between aspirin and clopidogrel as monotherapy, and the cost of clopidogrel is significantly higher than the cost of aspirin.

Extended-Release (ER) Dipyridamole plus Immediate-Release (IR) Aspirin

Combination therapy with extended-release dipyridamole plus immediate-release aspirin was more effective than either treatment alone in the European Stroke Prevention Study 2 (ESPS2).[35] In this study, patients received either placebo, aspirin 25 mg twice daily, ER dipyridamole 200 mg twice daily, or a combination of both agents. The individual agents produced risk reductions of 18.1% with aspirin and 16.3% with ER dipyridamole, whereas the combination produced a 37% risk reduction. Headache and diarrhea were common adverse effects of dipyridamole, while bleeding was more common in the treatment groups receiving aspirin. This is the first study showing that combination antiplatelet therapy has additive effects over each agent alone. The currently available formulation is a combination product containing 25 mg aspirin and 200 mg ER dipyridamole. This agent is not an option for patients who are intolerant to aspirin; however, it may be useful in patients who have failed clopidogrel or aspirin monotherapy. Further trials are underway to compare this combination to each individual component at full doses. Trials comparing this combination to other antiplatelet agents are also necessary.

Recommendations

The most recent CHEST guidelines continue to recommend aspirin therapy for the secondary prevention of stroke.[12] The guidelines also make the recommendation that due to a slight benefit in the absolute risk reduction in ischemic stroke with clopidogrel and the combination of aspirin/ER dipyridamole, these agents may be preferred if cost is factored out.



Patient Encounter, Part 3

GR is ready for discharge after spending 5 days in the hospital.

- What would be an appropriate discharge plan for GR at this time?
- What specific medications would you recommend upon discharge?

Blood Pressure Management

Hypertension is an important risk factor for stroke; however, it had been unclear if lowering BP reduced the incidence of secondary ischemic stroke. In the PROGRESS trial, it was shown that blood pressure reduction using the angiotensin-converting enzyme inhibitor (ACE-I) perindopril alone resulted in a 28% reduction in recurrent stroke compared to placebo. With the addition of the diuretic indapamide to perindopril, a 43% reduction in stroke recurrence was seen.[36] This reduction in stroke incidence occurred even in patients who were not hypertensive. In patients with a previous history of stroke or TIA, the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommends a diuretic and an ACE-I.[37] Table 8–7 provides drug and dosing recommendations for the treatment of ischemic stroke.

TABLE 8–7. Recommendations for Pharmacotherapy of Ischemic Stroke

	Primary Agents	Alternatives
Acute Treatment	t-PA 0.9 mg/kg IV (maximum 90 mg) over 1 hour in selected patients within 3 hours of onset Aspirin 160–325 mg daily started within 48 hours of onset	t-PA (various doses) intra-arterially up to 6 hours after onset in selected patients
Secondary Prevention	Aspirin 50–325 mg daily Clopidogrel 75 mg daily Aspirin 25 mg + extended-release dipyridamole 200 mg twice daily	Ticlopidine 250 mg twice daily
Cardioembolic	Warfarin (INR 2–3)	
All	ACE-I + diuretic or ARB; blood pressure lowering: Peridopril 2–8 mg daily Indapamide 1.25–5 mg daily; Statin therapy	

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; INR, International Normalized Ratio; IV, intravenous; t-PA, tissue plasminogen activator.

TREATMENT OF ACUTE HEMORRHAGIC STROKE

Supportive Measures

Acute hemorrhagic stroke is considered to be an acute medical emergency. Initially, patients experiencing a hemorrhagic stroke should be transported to a neurointensive care unit. ⓫ *There is no proven treatment for intracerebral hemorrhage. Management is based on neurointensive care treatment and prevention of complications.* Treatment should be provided to manage the needs of the critically ill patient including management of increased intracranial pressure, seizures, infections, and prevention of re-bleeding and delayed cerebral ischemia. In those with severely depressed consciousness, rapid endotracheal intubation and mechanical ventilation may be necessary. Blood pressure is often elevated after hemorrhagic stroke and appropriate management is important to prevent re-bleeding and expansion of the hematoma.[8] Blood pressure can be controlled with IV boluses of labetalol 10 to 80 mg every 10 minutes up to a maximum of 300 mg or with IV infusions of labetalol (0.5 to 2 mg/minute) or nicardipine (5 to 15 mg/hour). Deep vein thrombosis prophylaxis with intermittent compression stockings should be implemented early after admission. In those patients with SAH, once the aneurysm has been treated, heparin may be instituted.[2,3]

Nonpharmacologic Therapy

Patients with hemorrhagic stroke are evaluated for surgical treatment of SAH and ICH. In SAH, either clipping of the aneurysm or coil embolization is recommended within 72 hours after the initial event to prevent re-bleeding. Coil embolization, also called coiling, is a minimally invasive procedure in which a platinum coil is threaded into the aneurysm. The flexible coil fills up the space to block blood flow into the aneurysm thereby preventing re-bleeding. Surgical removal of the blood in patients with ICH is controversial, as one large randomized trial did not show a benefit to removal compared with those treated conservatively according to the current guidelines.[38,39]

Calcium Antagonists

⓬ *Oral nimodipine is recommended in subarachnoid hemorrhage to prevent delayed cerebral ischemia.* Delayed cerebral ischemia occurs 4 to 14 days after the initial aneurysm rupture and is a common cause of neurologic deficits and death. A meta-analysis of 12 studies was conducted and concluded that oral nimodipine 60 mg every 4 hours for 21 days following aneurysmal SAH reduced the risk of a poor outcome and delayed cerebral ischemia.[40]

Hemostatic Therapy

Recombinant factor VIIa has been shown to have a benefit in the treatment of ICH. The Recombinant Activated Factor VII Intracerebral Hemorrhage Trial compared three different doses and placebo. Doses were 40, 80, or 160 mcg/kg or placebo given as an IV infusion over 1 to 2 minutes within 4 hours after the onset of symptoms. Hematoma growth was decreased at 24 hours, mortality was decreased at 90 days, and overall functioning was increased at 90 days. Further studies are ongoing to evaluate the role of recombinant factor VIIa in ICH treatment.[41]

OUTCOME EVALUATION

- Stroke outcomes are measured based on the neurologic status and functioning of the patient after the acute event. The National Institutes of Health Stroke Scale (NIHSS) is a measure of daily functioning and is used to assess patient status following a stroke.
- Early rehabilitation can reduce functional impairment after a stroke. Recent stroke rehabilitation guidelines have been endorsed by the American Heart Association and the American Stroke Association. These guidelines recommend that patients receive care in a multidisciplinary setting or stroke unit, receive early assessment using the NIHSS, and recommend that rehabilitation is started as soon as possible after the stroke. Other recommendations include screening for **dysphagia** and aggressive secondary stroke prevention treatments.[42]
- Table 8–8 provides monitoring guidelines for the acute stroke patient.



Patient Care and Monitoring

1. Assess the patient's signs and symptoms including the time of onset of symptoms and the time of arrival in the emergency department.
2. Perform thorough neurological and physical examinations evaluating for a potential cause of the stroke.
3. Perform a CT scan to rule out a hemorrhagic stroke prior to administering any treatment.
4. Evaluate the inclusion and exclusion criteria for thrombolytic therapy to determine if it is appropriate for the patient.
5. Transfer the patient to a stroke center if available and develop a plan for the acute management of the patient.
6. Determine the patient's risk factors for stroke.
7. Develop a plan for the long-term management of risk factors in order to prevent a recurrent stroke.
8. Educate the patient on appropriate lifestyle modifications that will reduce stroke risk.
9. Educate the patient on their medication regimen and stress the importance of compliance.

TABLE 8–8. Monitoring the Stroke Patient

Treatment	Parameter(s)	Monitoring Frequency	Comments
Ischemic Stroke			
t-PA	BP, neurologic function, bleeding	Every 15 minutes × 1 hour, every 0.5 hour × 6 hours, every 1 hour × 17 hours; then every shift	
Aspirin	Bleeding	Daily	
Clopidogrel	Bleeding	Daily	
ASA/extended-release dipyridamole	Headache, bleeding	Daily	
Warfarin	Bleeding, INR, Hb/Hct	INR daily × 3 days; weekly until stable; then monthly	
Hemorrhagic Stroke			
	BP, neurologic function, ICP	Every 2 hours in ICU	May require treatments to lower BP to less than 180 mm Hg systolic
Nimodipine for SAH	BP, neurologic function, fluid status	Every 2 hours in ICU	

ASA, aspirin; BP, blood pressure; Hb, hemoglobin; Hct, hematocrit; ICP, intracranial pressure; ICU, intensive care unit; INR, International Normalized Ratio; SAH, subarachnoid hemorrhage; t-PA, tissue plasminogen activator.

ABBREVIATIONS

ACE-I: angiotensin-converting enzyme inhibitor
ADP: adenosine diphosphate
aPTT: activated partial thromboplastin time
ARB: angiotensin receptor blocker
ASA: aspirin
AVM: arteriovenous malformation
BP: blood pressure
BPH: benign prostatic hypertrophy
CBC: complete blood count
CEA: carotid endarterectomy
CT: computed tomography
CVD: cerebrovascular disease
DBP: diastolic blood pressure
DVT: deep vein thrombosis
ER: extended-release
ESPS2: European Stroke Prevention Study 2
FDA: Food and Drug Administration
Hb: hemoglobin
Hct: hematocrit
IA: intra-arterial
ICA: internal carotid artery
ICH: intracerebral hemorrhage
ICP: intracranial pressure
ICU: intensive care unit
INR: International Normalized Ratio
IR: immediate-release
IV: intravenous
JNC 7: Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
LMWH: low-molecular-weight heparin
MI: myocardial infarction
MRI: magnetic resonance imaging
NIHSS: National Institutes of Health Stroke Scale
NINDS: National Institute of Neurological Disorders and Stroke
NS: normal saline
PROACT II: Prolyse in Acute Cerebral Thromboembolism II
PT: prothrombin time
rt-PA: alteplase
r-pro UK: prourokinase
SAH: subarachnoid hemorrhage
SBP: systolic blood pressure
TIA: transient ischemic attack
t-PA: tissue plasminogen activator
TTP: thrombotic thrombocytopenic purpura

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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9 HYPERLIPIDEMIA

Matthew K. Ito



LEARNING OBJECTIVES

UPON COMPLETION OF THE CHAPTER, THE READER WILL BE ABLE TO:

1. Identify the major components within each lipoprotein and their role in lipoprotein metabolism and the development of atherosclerosis.
2. Identify the common types of lipid disorders.
3. Determine a patient's coronary heart disease risk and corresponding treatment goals according to the National Cholesterol Education Program Adult Treatment Panel III guidelines.
4. Recommend appropriate therapeutic lifestyle changes (TLC) and pharmacotherapy interventions for patients with dyslipidemia.
5. Describe the components of a monitoring plan to assess effectiveness and adverse effects of pharmacotherapy for dyslipidemias.
6. Educate patients about the disease state, appropriate TLC, and drug therapy required for effective treatment.

KEY CONCEPTS

❶ The risk of atherosclerosis is directly related to increasing levels of serum cholesterol.

❷ The National Cholesterol Education Program Adult Treatment Panel III guidelines have set the "optimal" level for low-density lipoprotein (LDL) cholesterol for all adults as less than 100 mg/dL (2.59 mmol/L).

❸ All adults greater than 20 years of age should be screened at least every 5 years using a fasting blood sample.

❹ The benefits of lowering LDL cholesterol to as low as 70 mg/dL (1.81 mmol/L) have been demonstrated in clinical trials; however, the lowest level at which to treat LDL cholesterol has not yet been determined.

❺ An adequate trial of therapeutic lifestyle changes should be employed in all patients, but pharmacotherapy should be instituted concurrently in higher-risk patients.

❻ Typically, statins are the medications of choice to treat high LDL cholesterol because of their ability to substantially reduce LDL cholesterol, ability to reduce morbidity and mortality from atherosclerotic disease, convenient once-daily dosing, and low risk of side effects.

❼ Patients with metabolic syndrome have an additional lipid parameter that needs to be assessed, namely non-high-density lipoprotein (non-HDL) cholesterol (total cholesterol minus HDL cholesterol). The target for non-HDL cholesterol is less than the patient's LDL cholesterol target plus 30 mg/dL (0.78 mmol/L).

❽ After assessment and control of LDL cholesterol, patients with serum triglycerides of 200 to 499 mg/dL (2.26 to 5.64 mmol/L) should be assessed for atherogenic dyslipidemia (low HDL cholesterol and increased small-dense LDL particles) and metabolic syndrome.

❾ Combination drug therapy is an effective means to achieve greater reductions in LDL cholesterol (statin + ezetimibe or bile acid resin, bile acid resin + ezetimibe, or three-drug combinations) as well as raising HDL cholesterol and lowering serum triglycerides (statin + niacin or fibrate).

❿ Reducing LDL cholesterol while substantially raising HDL cholesterol (statin + niacin) appears to reduce the risk of atherosclerotic disease progression to a greater degree than statin monotherapy.

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❶ *The risk of **atherosclerosis** is directly related to increasing levels of serum cholesterol.* Hypercholesterolemia (elevation in serum cholesterol) and other abnormalities in serum lipids play a major role in plaque formation leading to coronary heart disease (CHD) as well as other forms of atherosclerosis, such as **carotid** and peripheral artery disease (atherosclerosis of the peripheral arteries). This predictive relationship has been demonstrated from large epidemiologic,[1] animal, and genetic studies. Coronary heart disease is the leading cause of death in both men and women in the United States and most industrialized nations. It is also the chief cause of premature, permanent disability in the United States workforce. Annually, approximately 700,000 Americans will suffer a new heart attack and 500,000 will have a recurrent event. The average age of a first heart attack is 66 years for American men and 70 years for women. The direct and indirect cost of CHD to the United States economy is almost $140 billion.[2] Clinical trials have consistently demonstrated that lowering serum cholesterol reduces atherosclerotic progression and mortality from CHD.

The development of CHD is a lifelong process. Except in rare cases of severely elevated serum cholesterol levels, years of poor dietary habits, sedentary lifestyle, and life-habit risk factors (e.g., smoking and obesity) contribute to the development of atherosclerosis.[3] Unfortunately, many individuals at risk for CHD do not receive lipid-lowering therapy or are not optimally treated. This chapter will help identify individuals at risk, assess treatment goals based on the level of CHD risk, and implement optimal treatment strategies and monitoring plans.

PATHOPHYSIOLOGY

Lipid and Lipoprotein Metabolism

Cholesterol is an essential substance manufactured by most cells in the body. Cholesterol is used to maintain cell wall integrity and for the biosynthesis of **bile acids** and steroid hormones.[4] Other major lipids in our body are triglycerides and phospholipids. Since cholesterol is a relatively water-insoluble molecule, it is unable to circulate through the blood alone. Cholesterol along with triglycerides and phospholipids are packaged in a large carrier-protein called a lipoprotein (Fig. 9–1). Lipoproteins are water soluble, which allows transportation of the major lipids in the blood. These lipoproteins are spherical and vary in size (~1,000 to 6 nm) and density (less than 0.94 to 1.21 g/mL)[4] (Table 9–1). The amount of cholesterol and triglycerides vary by lipoprotein size. The major lipoproteins in descending size and ascending density are chylomicrons, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). When clinical laboratories measure and report serum total cholesterol, what they are measuring and reporting are total cholesterol molecules in all the major lipoproteins. The estimated value of LDL cholesterol is found using the following equation:

$$\text{LDL cholesterol} = \text{total cholesterol} - (\text{HDL cholesterol} + \text{triglycerides}/5)$$

If serum triglycerides are greater than 400 mg/dL (4.52 mmol/L), this formula becomes inaccurate and LDL cholesterol must be directly measured.[3]

Each lipoprotein has various proteins called apolipoproteins embedded on the surface (Fig. 9-1). These apolipoproteins serve four main purposes, they: (1) are required for assembly and secretion of lipoproteins (such as apolipoproteins B-48 and B-100); (2) serve as major structural components of lipoproteins; (3) act as ligands (apolipoprotein B-100 and apolipoprotein E) for binding to receptors on cell surfaces (LDL receptors); and (4) can be co-factors (such as apolipoprotein C-II) for activation of enzymes (such as lipoprotein lipase [LPL]) involved in the breakdown of triglycerides from chylomicrons and VLDL. Apolipoproteins A-I and A-II are major structural proteins on

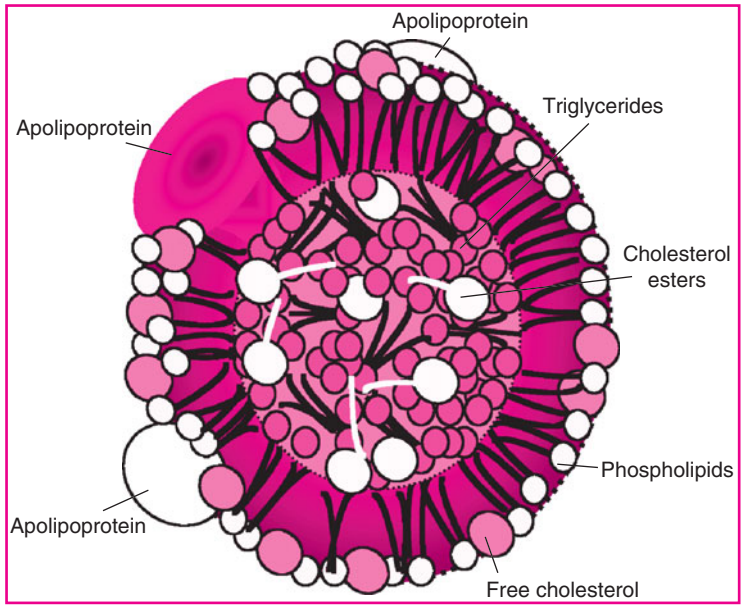


FIGURE 9–1. Lipoprotein structure. Lipoproteins are a diverse group of particles with varying size and density. They contain variable amounts of core cholesterol esters and triglycerides, and have varying numbers and types of surface apolipoproteins. The apolipoproteins function to direct the processing and removal of individual lipoprotein particles. (Reprinted from LipoScience, Inc. with permission.)

TABLE 9–1. Physical Characteristics of Lipoproteins

Lipoprotein	Density Range (g/mL)	Size (nm)	Composition (%)		
			Cholesterol	Triglycerides	Apolipoprotein
Chylomicrons	Less than 0.95	100–1000	3–7	85–95	A-I, A-II, A-IV, B-48, C-I, C-II, E
VLDL	Less than 1.006	40–50	20–30	50–65	B-100, C-I, C-II, C-III, E
IDL	1.006–1.019	25–30	40	20	B-100, E
LDL	1.019–1.063	20–25	51–58	4–8	B-100
HDL	1.063–1.21	6–10	18–25	2–7	A-I, A-II, C-I, C-II, C-III, E

HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

the surface of HDL. Apolipoprotein A-I interacts with adenosine triphosphate (ATP) binding cassette A1 to traffic cholesterol from extra-hepatic tissue (such as the arterial wall) to immature or **nascent** HDL.[4]

Cholesterol from the diet as well as from bile enters the small intestine, where it is emulsified by bile salts into **micelles** (Fig. 9–2). These micelles interact with the duodenal and jejunal enterocyte surfaces, and cholesterol is transported from the micelles into these cells by the Niemann-Pick C1 Like 1 (NPC1L1) transporter.[5] Some cholesterol and most plant sterols, which are structurally similar to cholesterol, are exported back from the enterocyte into the intestinal lumen by the ATP-binding cassette (ABC) G5/G8 transporter. Cholesterol within enterocytes is esterified and packaged into chylomicrons along with triglycerides, phospholipids, and apolipoprotein B-48 as well as apolipoproteins C and E, which are then released into the **lymphatic** circulation. In the circulation, chylomicrons are converted to chylomicron remnants (through loss of triglycerides by the interaction of apolipoprotein C-II and LPL). During this process, chylomicrons also interact with HDL particles (Fig. 9–3) and exchange triglyceride and cholesterol content, and HDL particles acquire apolipoproteins A and C. Chylomicron remnant particles are then taken up by LDL-related protein (LRP).[4]

In the liver, cholesterol and triglycerides are incorporated into VLDL along with phospholipids and apolipoprotein B-100 (Fig. 9–4). Very low-density lipoprotein particles are released into the circulation where they acquire apolipoprotein E and apolipoprotein C-II from HDL. Very-low density lipoprotein loses its triglyceride content through the interaction with LPL to form VLDL remnant and IDL. Intermediate-density lipoprotein can be cleared from the circulation by hepatic LDL receptors or further converted to LDL (by further depletion of triglycerides) through the action of hepatic lipases (HL). Approximately 50% of IDL is converted to LDL. Low-density lipoprotein particles are cleared from the circulation primarily by hepatic LDL receptors by interaction with apolipoprotein B-100. They can also be taken up by extra-hepatic tissues or enter the arterial wall, contributing to atherogenesis.[4,6]

Cholesterol is transported from the arterial wall or other extra-hepatic tissues back to the liver by HDL (Fig. 9–3). Apolipoprotein A-I (derived from the intestine and liver) on nascent HDL interacts with ABCA1 transporter on extra-hepatic tissue. Cholesterol in nascent HDL is esterified by lecithin-cholesterol acyltransferase (LCAT) resulting in mature HDL. The esterified cholesterol can be transferred as noted above to apolipoprotein B-containing particles in exchange for triglycerides. Triglyceride-rich HDL is hydrolyzed by HL, generating fatty acids and nascent HDL particles, or the mature HDL can bind to the scavenger receptors (SR-BI) on hepatocytes and transfer their cholesterol ester content.[4]

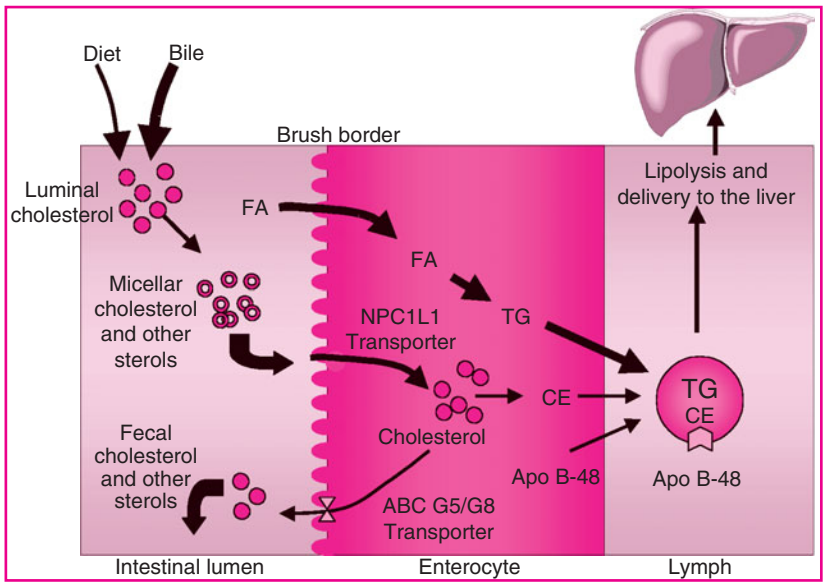


FIGURE 9–2. Intestinal cholesterol absorption and transport. Cholesterol from food and bile enter the gut lumen and are emulsified by bile acids into micelles. Micelles binding to the intestinal enterocytes, and cholesterol and other sterols are transported from the micelles into the enterocytes by a sterol transporter. Triglycerides synthesized by absorbed fatty acids along with cholesterol and apolipoprotein B-48 are incorporated into chylomicrons. Chylomicrons are released into the lymphatic circulation and are converted to chylomicron remnants (through loss of triglyceride), and then taken up by the hepatic LDL receptor-related protein (LRP). ABC G5/G8, ATP-binding cassette G5/G8; Apo, apolipoprotein; CE, cholesterol ester; FA, fatty acid; NPC1L1, Niemann-Pick C1 Like 1; TG, triglyceride.

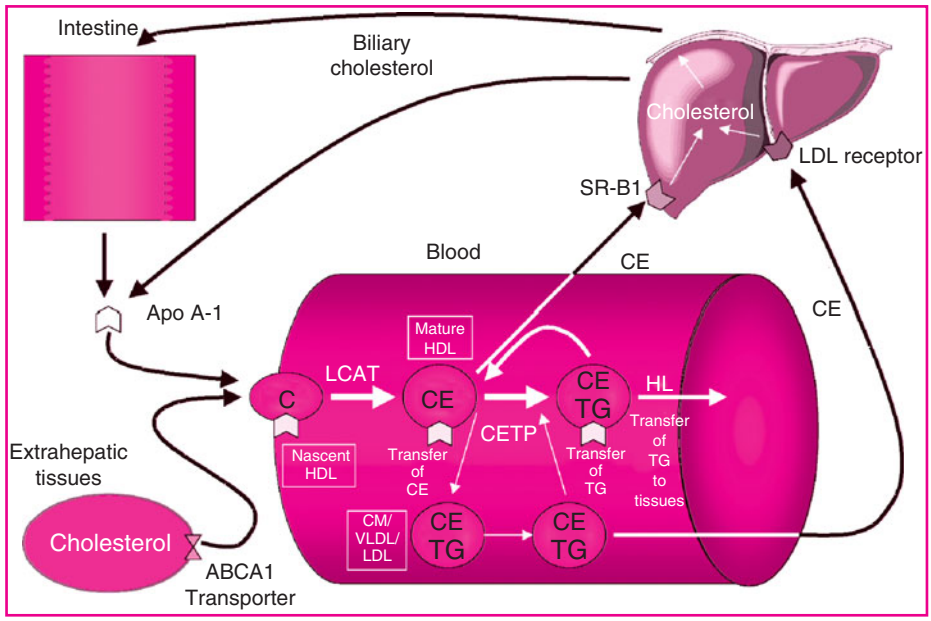


FIGURE 9–3. Reverse cholesterol transport. Cholesterol is transported from the arterial wall or other extra-hepatic tissues back to the liver by HDL. Esterified cholesterol from HDL can be transferred to apolipoprotein B-containing particles in exchange for triglycerides. Cholesterol esters transferred from HDL to VLDL and LDL are taken up by hepatic LDL receptors or delivered back to extra-hepatic tissue. ABCA1, ATP-binding cassette A1; Apo, apolipoprotein; C, cholesterol; CE, cholesterol ester; CETP, cholesterol ester transfer protein; CM, chylomicrons; HDL, high-density lipoprotein; HL, hepatic lipase; LCAT, lecithin cholesterol acyltransferase; LDL, low-density lipoprotein; SR-BI, scavenger receptors; TG, triglyceride; VLDL, very low-density lipoprotein.

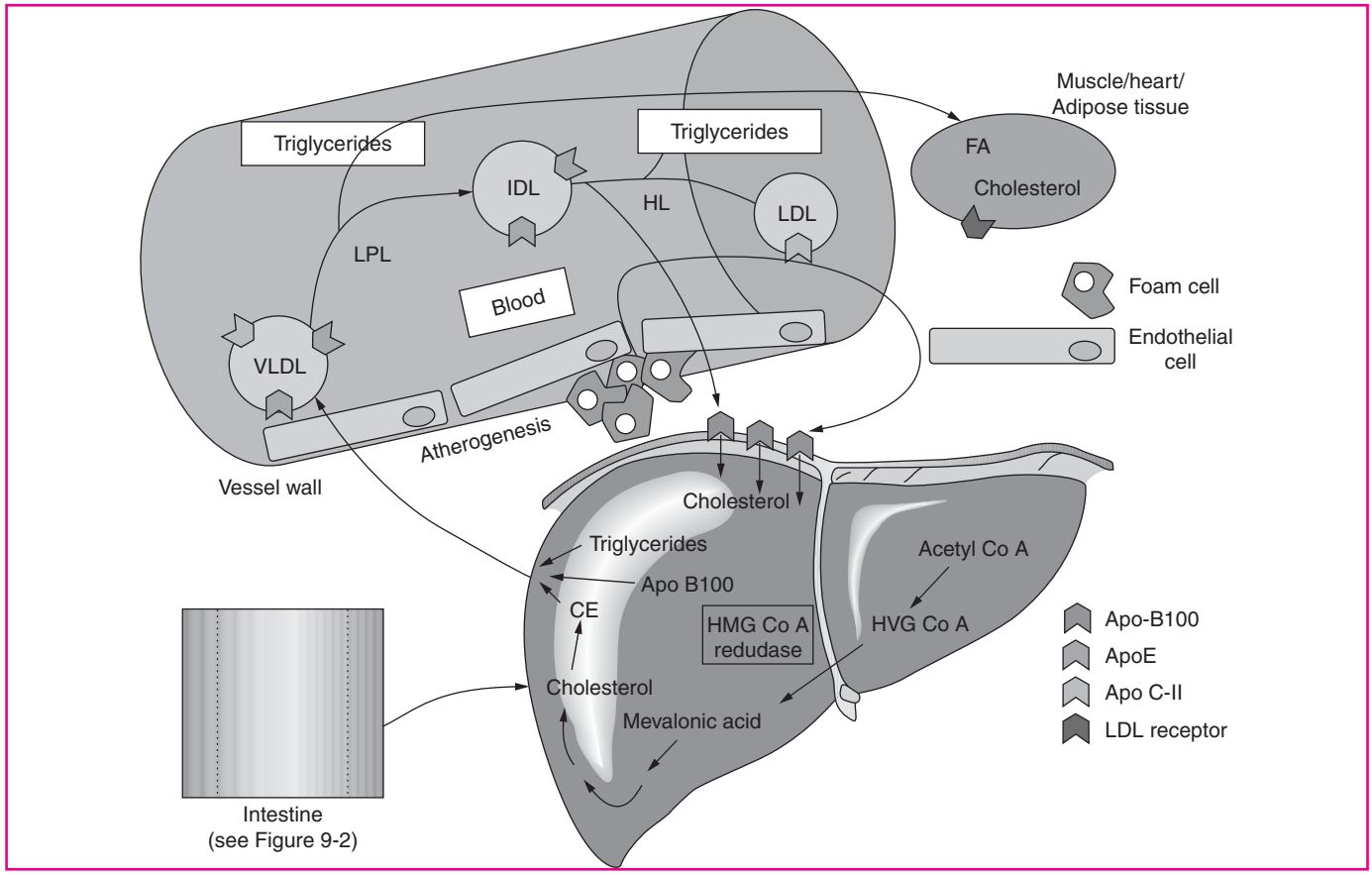


FIGURE 9–4. Endogenous lipoprotein metabolism. In liver cells, cholesterol and triglycerides are packaged into VLDL particles and exported into blood where VLDL is converted to IDL. Intermediate-density lipoprotein can be either cleared by hepatic LDL receptors or further metabolized to LDL. LDL can be cleared by hepatic LDL receptors or can enter the arterial wall, contributing to atherosclerosis. Acetyl CoA, acetyl coenzyme A; Apo, apolipoprotein; C, cholesterol; CE, cholesterol ester; FA, fatty acid; HL, hepatic lipase; HMG CoA, 3-hydroxy-3-methyglutaryl coenzyme A; IDL, intermediate-density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; LPL, lipoprotein lipase; VLDL, very low-density lipoprotein.

A variety of genetic mutations occur in the above steps during lipoprotein synthesis and metabolism that cause lipid disorders. The major genetic disorders and their effect on serum lipids are presented in Table 9–2.[4] Disorders that increase serum cholesterol are generally those that affect the number or affinity of LDL receptors (also known as apolipoprotein B-E receptors) known as familial hypercholesterolemia, or the ability of apolipoprotein B-100 to bind to the receptor known as familial defective apolipoprotein B-100. These patients commonly present with **corneal arcus** of the eye and **xanthomas** of extensor tendons of the hand and Achilles tendon. Elevations in triglycerides are generally associated with overproduction of VLDL, mutations in apolipoprotein E, or lack of LPL. Patients with extremely elevated serum triglycerides can develop **pancreatitis** and **tuberoeruptive xanthomas**. Most individuals have mild to moderate elevations in cholesterol caused by a polygenic disorder. Polygenic hypercholesterolemia is not as well understood as the single-gene disorders discussed above. Polygenic hypercholesterolemia is thought to be caused by various, more subtle genetic defects as well as environmental factors such as diet and lack of physical activity.[3]

Pathophysiology of Coronary Artery Disease

The most widely accepted theory of the process of atherosclerosis is that it is a low-grade inflammatory response due to injury of the vascular endothelium.[6] The process begins when lipoproteins migrate between the **endothelial cells** into the arterial wall (Fig. 9–5). The initial lesion, known as a fatty streak, appears to form after accumulation of lipoproteins within the **intima**. After entering the intima, lipoproteins are then structurally modified by oxidation. Oxidized lipoproteins as well as other cytotoxic agents promote endothelial dysfunction by disturbing the production of vasoactive molecules such as nitric oxide that maintain vasomotor tone. Small, denser LDL particles migrate into the arterial wall more readily and are particularly susceptible to oxidation. The oxidized particles cause an increased expression of cell-adhesion molecules on vascular endothelial cells leading to recruitment of **monocytes** into the intima. The monocytes differentiate into **macrophages** and express scavenger receptors allowing enhanced uptake of apolipoprotein B-containing lipoproteins. The macrophages continue to accumulate lipoproteins and ultimately develop into lipid-laden **foam cells**. Accumulation of foam cells leads to formation of a lipid-rich core, which marks the transition to a more complicated atherosclerotic plaque. Vascular wall remodeling leading to outward growth of the wall occurs to accommodate this lipid-rich core. Thus, the vascular lumen is relatively well preserved and generally the lesion would not be detected using traditional coronary angiographic techniques. Initially, smooth muscle cells migrate and proliferate from the **media** to the intima forming a protective fibrous cap which separates the potentially thrombogenic lipid core from circulating blood. As the plaque matures, inflammatory cells secrete **matrix metalloproteinases** that degrade collagen and fibrin produced by smooth muscle cells that lead to a weakened fibrous cap. Ischemic events result when the fibrous cap of these unstable plaques rupture and produce an occlusive **thrombus**. In contrast, repeated wound healing secondary to less significant plaque disruption that causes no symptoms might produce a more stable plaque as a consequence of smooth muscle cell, collagen, and fibrin accumulation and a resolution of the lipid core.[6] These more stable plaques usually cause luminal encroachment (detected by traditional coronary angiographic techniques) and may produce **angina pectoris**. Unstable lesions usually outnumber the more stable plaques, thus accounting for a majority of **acute coronary syndromes**. Evidence demonstrates that aggressive lipid lowering does stabilize these vulnerable lesions and restores endothelial function.[3,6,7]

TABLE 9–2. Selected Characteristics of Primary Dyslipidemias

Disorder	Estimated Frequency	Metabolic Defect	Main Lipid Parameter
Familial hypercholesterolemia			
Homozygous	1/1 million	LDL-receptor negative	LDL-C greater than 500 mg/dL (12.95 mmol/L)
Heterozygous	1/500	Reduction in LDL receptors	LDL-C 250–500 mg/dL (6.48–12.95 mmol/L)
Familial defective apo B-100	1/1000	Single nucleotide mutation	LDL-C 250–500 mg/L (6.48–12.95 mmol/L)
Polygenic hypercholesterolemia	Common	Metabolic and environmental	LDL-C 160–250 mg/dL (4.14–6.48 mmol/L)
Familial combined dyslipidemia	1/200–300	Overproduction of VLDL and/or LDL	LDL-C 250–350 mg/dL (6.48–9.07 mmol/L) TG 200–800 mg/dL (2.26–9.04 mmol/L)
Familial hyperapobetalipoproteinemia	5%	Increase apo B production	Apo B greater than 125 mg/dL
Familial dysbetalipoproteinemia	0.5%	Apo E2/2 phenotype	LDL-C 300–600 mg/dL (7.77–15.54 mmol/L) TG 400–800 mg/dL (4.52–9.04 mmol/L)
Familial hypertriglyceridemia			
Type IV	1/300	Unknown	TG 200–500 mg/dL (2.26–5.65 mmol/L)
Type V	1/205,000	Unknown	TG greater than 1000 mg/dL (11.3 mmol/L)
Hypoalphalipoproteinemia	3–5%	Defect in HDL catabolism	HDL-C less than 35 mg/dL (0.91 mmol/L)

Apo, apolipoprotein; C, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; VLDL, very low-density lipoprotein.

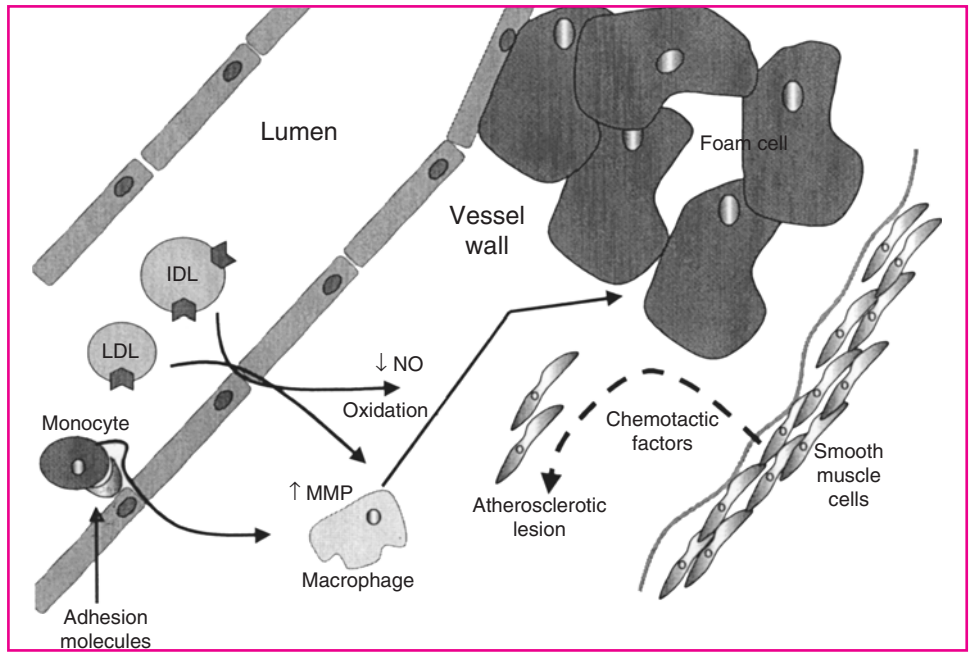


FIGURE 9–5. The process of atherogenesis. Atherosclerosis is initiated by the migration of LDL and remnant lipoprotein particles into the vessel wall. These particles undergo oxidation and are taken up by macrophages in an unregulated fashion. The oxidized particles participate to induce endothelial cell dysfunction leading to a reduced ability of the endothelium to dilate the artery and cause a prothrombotic state. The unregulated uptake of cholesterol by macrophages leads to foam cell formation and the development of a blood clot–favoring fatty lipid core. The enlarging lipid core eventually causes an encroachment of the vessel lumen. Early in the process, smooth muscle cells are activated and recruited from the media to the intima, helping to produce a collagen matrix that covers the growing clot protecting it from circulating blood. Later, macrophages produce and secrete matrix metalloproteinases which degrade the collagen matrix, leading to unstable plaque which may cause a myocardial infarction. IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; MMP, matrix metalloproteinases; NO, nitric oxide.

TREATMENT

In the United States, prevention and treatment of CHD is based primarily on guidelines issued in 2001 by the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]).[3] Low-density lipoprotein cholesterol is the primary diagnostic and therapeutic target. ❷ *The NCEP ATP III guidelines have set the "optimal" level for LDL cholesterol for all adults as less than 100 mg/dL (2.59 mmol/L).* The NCEP panel issued an update in 2004 to the ATP III guidelines based on more recent clinical trial evidence.[8] The update outlines additional treatment options for certain patient populations, mainly those who are at very high risk of recurrent CHD events. These treatment options emphasize the benefits of diet, exercise, and weight control and the use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (or statins) as first-line drugs. If statins or other drugs used to treat hyperlipidemia are prescribed, doses that reduce LDL cholesterol by at least 30% to 40% should be recommended.[8]

Most recently, the American Heart Association and American College of Cardiology issued guidelines for secondary prevention in patients with established CHD or other atherosclerotic vascular disease based on the results of two additional trials published after the 2004 NCEP update.[9] These guidelines suggest it is reasonable to set an LDL cholesterol goal of less than 70 mg/dL (1.81 mmol/L) in all patients with CHD or other forms of atherosclerotic vascular disease. If it is not possible to attain LDL cholesterol less than 70 mg/dL (1.81 mmol/L) due to a high baseline LDL cholesterol, it is generally possible to achieve an LDL cholesterol reduction of greater than 50% with more intensive LDL lowering therapy, including combination drug therapy.

Guidelines for Treatment

Step 1: Patient Assessment

Determine lipoprotein profile after fasting for 9 to 12 hours. ❸ *The NCEP guidelines recommend that all adults greater than 20 years of age should be screened at least every 5 years using a fasting blood sample to obtain a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides).* A fasting lipid profile is preferred so an accurate assessment of LDL cholesterol can be performed. Fasting permits the clearance of triglycerides



Clinical Presentation and Diagnosis

Lipid Panel

- Patients presenting with a total cholesterol level exceeding 200 mg/dL (5.18 mmol/L) or LDL cholesterol exceeding 100 mg/dL (2.59 mmol/L) should be evaluated for high cholesterol.
- Patients with serum triglycerides from 150–500 mg/dL (1.70–5.65 mmol/L) and serum HDL cholesterol less than 40 mg/dL (1.04 mmol/L) may have metabolic syndrome and need to be evaluated.

Physical Findings

- Patients with genetic disorders that cause a marked increase in serum LDL cholesterol (greater than 250 mg/dL [6.48 mmol/L]) may present with corneal arcus of the eye and xanthomas of extensor tendons of the hand and Achilles tendon.
- Patients with extremely elevated serum triglycerides (greater than 1,000 mg/dL [11.3 mmol/L]) can develop pancreatitis and tuberoeruptive xanthomas.

Indications for Lipid Panel

- All adults greater than 20 years of age should be screened at least every 5 years using a fasting blood sample to obtain a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides). A fasting lipid profile is preferred so an accurate assessment of LDL cholesterol can be performed, and fasting will allow the clearance of triglycerides carried by chylomicrons from the circulation, allowing VLDL cholesterol to be determined.
- Children between 2 and 20 years old should be screened for high cholesterol if their parents have premature CHD or if one of their parents has a total cholesterol greater than 240 mg/dL (6.22 mmol/L). Early screening will help to identify children at highest risk of developing CHD in whom early education and dietary intervention is warranted.

Indications for Other Tests

- Conditions that may produce lipid abnormalities (such as those listed in Table 9–3) should be screened for using appropriate tests. If present, these conditions should be properly addressed.

carried by chylomicrons from the circulation thus allowing VLDL cholesterol to be determined. Children between 2 and 20 years old should be screened for high cholesterol if their parents have premature CHD or if one of their parents has a total cholesterol greater than 240 mg/dL (6.22 mmol/L).[3] Early screening will help to identify children at highest risk of developing CHD, in whom early education and dietary intervention is warranted.

Step 2: Rule Out Secondary Causes of Dyslipidemia

Certain drugs and diseases can cause abnormalities in serum lipids and should be evaluated (Table 9–3). Every effort should be made to correct or control underlying diseases such as hypothyroidism and diabetes. Concurrent medications known to induce lipid abnormalities should be evaluated for discontinuation prior to instituting long-term lipid-lowering therapy.[3]

TABLE 9–3. Secondary Conditions and Drugs That May Cause Hyperlipidemias

	↑ LDL cholesterol	↑ Triglycerides	↓ HDL cholesterol
Other Conditions			
Diabetes		√	√
Hypothyroidism	√	√	
Obstructive liver disease/biliary cirrhosis	√		
Renal disease		√	
Nephrotic syndrome	√	√	
Chronic renal failure		√	
Hemodialysis patients		√	
Obesity		√	√
Drugs			
Estrogen		√	
Progestins	√		√
Protease inhibitors		√	√
Anabolic steroids	√		√
Corticosteroids	√	√	
Isotretinoin		√	√
Cyclosporine	√		
Atypical antipsychotics		√	√
Thiazide diuretics	√	√	
β-Blockers		√	√

LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Step 3: Identify the Presence of Clinical Atherosclerotic Disease That Confers High Risk for CHD Events

Individuals with established CHD, other clinical atherosclerotic disease (CAD), or diabetes have a greater than 20% risk over a 10-year period of developing CHD.[3] The ATP III guidelines set the target LDL cholesterol level at less than 100 mg/dL (2.59 mmol/L) for high-risk patients who have a history of one or more of the following:

- Myocardial infarction (MI)
- Unstable angina
- Chronic stable angina
- Coronary interventions (coronary bypass, percutaneous transluminal coronary angioplasty, or stents)
- Peripheral arterial disease (claudication or ankle-brachial index less than 0.9)
- Symptomatic carotid artery disease (stroke or transient ischemic attack)
- Diabetes (types 1 and 2)
- Multiple risk factors with a Framingham calculated risk (Fig. 9–6) greater than 20%

Men
Estimate of 10-year risk for men

(Framingham point scores)

Age	Points
20–34	–9
35–39	–4
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	11
70–74	12
75–79	13

	Points				
Total cholesterol	Age 20–39	Age 40–49	Age 50–59	Age 60–69	Age 70–79
Less than 160	0	0	0	0	0
160–199	4	3	2	1	0
200–239	7	5	3	1	0
240–279	9	6	4	2	1
Greater than or equal to 280	11	8	5	3	1

	Points				
	Age 20–39	Age 40–49	Age 50–59	Age 60–69	Age 70–79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dL)	Points
Greater than or equal to 60	–1
50–59	0
40–49	1
Less than 40	2

Systolic BP (mmHg)	If untreated	If treated
Less than 120	0	0
120–129	0	1
130–139	1	2
140–159	1	2
Greater than or equal to160	2	3

Point total	10-year risk %
Less than 0	Less than 1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
Greater than or equal to 17	Greater than or equal to 30

10-year risk _____%

Women
Estimate of 10-year risk for women

(Framingham point scores)

Age	Points
20–34	–7
35–39	–3
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	12
70–74	14
75–79	15

	Points				
Total cholesterol	Age 20–39	Age 40–49	Age 50–59	Age 60–69	Age 70–79
Less than 160	0	0	0	0	0
160–199	4	3	2	1	1
200–239	8	6	4	2	1
240–279	11	8	5	3	2
Greater than or equal to 280	13	10	7	4	2

	Points				
	Age 20–39	Age 40–49	Age 50–59	Age 60–69	Age 70–79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dL)	Points
Greater than or equal to 60	–1
50–59	0
40–49	1
Less than 40	2

Systolic BP (mmHg)	If untreated	If treated
Less than 120	0	0
120–129	1	3
130–139	2	4
140–159	3	5
Greater than or equal to 160	4	6

Point total	10-year risk %
Less than 9	Less than 1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
Greater than or equal to 25	Greater than or equal to 30

10-year risk _____%

FIGURE 9–6. Framingham point scale for estimating 10-Year CHD risk. The Framingham score is used to determine a patient's CHD risk category when they are found to have two or more CHD risk factors (Table 9–4). This system assigns points to the following risk factors: age, total cholesterol level, smoking status, HDL cholesterol level, and systolic blood pressure. The point total corresponds to the 10-year risk (%) of a CHD event (non-fatal myocardial infarction and coronary death), which serves as a basis for deciding how intensively to treat hypercholesterolemia and other risk factors. To calculate risk factor using the Framingham Point Scale, go to the following website: http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm. The Système International units for the corresponding conventional units in the Framingham Point Scale illustration include: (1) total cholesterol (160 mg/dL = 4.14 mmol/L; 160 to 199 mg/dL = 4.14 to 5.15 mmol/L; 200 to 239 mg/dL = 5.18 to 6.19 mmol/L; 240 to 279 mg/dL = 6.22 to 7.23 mmol/L; 280 mg/dL = 7.25 mmol/L) and (2) HDL (60 mg/dL = 1.55 mmol/L; 50 to 59 mg/dL = 1.3 to 1.53 mmol/L; 40 to 49 mg/dL = 1.04 to 1.27 mmol/L; 40 mg/dL = 1.04 mmol/L). BP, blood pressure; CHD, coronary heart disease; HDL, high-density lipoprotein. (From http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm.)



Patient Encounter 1

MN is a 48-year-old man with a history of hypertension and smoking who presents to the clinic for evaluation of his cholesterol. He denies having chest pain or history of myocardial infarction, stroke, or peripheral artery disease. He has no siblings and both parents are alive with no history of CHD. MN says that he smokes about 1 pack of cigarettes per day. He does not exercise on a regular basis. He has been fasting for approximately 11 hours.

- Can MN be evaluated today for his cholesterol?
- Does he have risk factors for CHD?
- What additional information do you need to know for the evaluation of MN?

❹ *The benefits of lowering LDL cholesterol to as low as 70 mg/dL (1.81 mmol/L) have been demonstrated in clinical trials; however, the lowest level at which to treat LDL cholesterol has not yet been determined.* Thus, in patients considered very high risk and those conferring a CHD risk much greater than 20%, an LDL cholesterol goal of less than 70 mg/dL (1.81 mmol/L) is a therapeutic option.[7] These individuals are those with established CAD plus: multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (especially continued cigarette smoking), multiple risk factors of metabolic syndrome, and acute coronary syndromes.

Step 4: Determine the Presence of Major Risk Factors

In individuals who do not have established CHD or CHD risk equivalent, the next step is to count major risk factors for CHD as presented in Table 9–4. These risk factors are considered independent predictors of CHD. High-density lipoprotein cholesterol of greater than or equal to 60 mg/dL (1.55 mmol/L) is considered a negative risk factor and means 1 risk factor can be subtracted from the total count.[3]

TABLE 9–4. Risk Factors for Coronary Heart Disease

Risk Factor	Definition
Age (years)	Male greater than or equal to 45; female greater than or equal to 55
Family history of premature CHD events	Male first-degree relative at less than 55 years Female first-degree relative at less than 65 years
Hypertension	SBP greater than or equal to 140 mm Hg DBP greater than or equal to 90 mm Hg
HDL cholesterol	Less than 40 mg/dL (1.04 mmol/L)
Cigarette smoking	Within the past month

HDL cholesterol greater than or equal to 60 mg/dL (1.55 mmol/L) is considered a negative risk factor; thus, subtract 1 risk factor from the total from above.
CHD, coronary heart disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.

TABLE 9–5. CHD Risk Factors and Needed Risk Factors for Framingham Score Calculation

Risk Profile	10-Year Risk for CHD	Need for Framingham Calculation
Less than or equal to 1 risk factor	Less than 10%	No
Greater than or equal to 2 risk factors	0–10% 10–20%	Yes Yes
CAD or CAD risk-equivalent	Greater than 20%	No
Very-high risk	Much greater than 20%	No

CAD, clinical atherosclerotic disease; CHD, coronary heart disease.

Step 5: If Two or More Risk Factors are Present Without CHD or CHD Risk Equivalent, Assess 10-Year CHD Risk

Listed in Table 9–5 are the risk groups that require risk calculations using the Framingham scoring system.[3] Since individuals with two or more risk factors may carry a risk equivalent to individuals with established CHD, and therefore should be treated with the same intensity, a scoring system developed from the Framingham Coronary Heart Disease Study is used to estimate this 10-year risk (Fig. 9–6). This system assigns points to the following risk factors: age, total cholesterol level, smoking status, HDL cholesterol level, and systolic blood pressure. The score is used to determine a patient's risk category and the intensity of treatment to lower their LDL cholesterol. To calculate a Framingham score, visit the following website: http://www.nhlbi.nih.gov/guidelines/cholesterol/ index.htm.

Step 6: Determine Treatment Goals and Therapy

Treatment goals for LDL cholesterol and thresholds for the institution of therapeutic lifestyle changes (TLC) and pharmacotherapy is the next step (Table 9–6).

Step 7: Initiate Therapeutic Lifestyle Changes If LDL Is Above Goal

Therapeutic lifestyle changes should be the first approach tried in all patients (Table 9–7).[3] ❺ *An adequate trial of TLC should be employed in all patients, but pharmacotherapy should be instituted concurrently in higher-risk patients.* This includes dietary restrictions of cholesterol and saturated fats as well as regular exercise and weight reduction. In addition, therapeutic options to enhance LDL cholesterol lowering such as consumption of plant stanols/sterols (which competitively inhibit incorporation of cholesterol into micelles) and dietary fiber should be encouraged. These therapeutic options collectively may reduce LDL cholesterol by 20% to 25%.

Step 8: Consider Adding Drug Therapy If LDL Is Above Threshold Level

Patients unable or unlikely to achieve their LDL cholesterol goals following a reasonable trial of TLC (typically 12 weeks for patients without CHD and sooner for those at high risk or

TABLE 9–6. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) Treatment Goals for LDL Cholesterol and Thresholds for Starting Therapeutic Lifestyle Changes and Pharmacotherapy

Risk Category	LDL cholesterol Goal	Initiate Therapeutic Lifestyle Changes (TLC)	Consider Drug Therapy
High Risk CHD or CHD risk equivalents (10-year risk greater than 20%)	Less than 100 mg/dL (2.59 mmol/L)	Greater than or equal to 100 mg/dL (2.59 mmol/L)	Greater than or equal to 100 mg/dL (2.59 mmol/L)
Very-High Risk	Optional goal of less than 70 mg/dL[a] (1.81 mmol/L)		
Moderately-High Risk Greater than or equal to 2 risk factors (10-year risk 10%–20%)	Less than 130 mg/dL (3.37 mmol/L) (Optional goal of less than 100 mg/dL[a] [2.59 mmol/L])	Greater than or equal to 130 mg/dL (3.37 mmol/L)	Greater than or equal to 130 mg/dL (3.37 mmol/L) (consider drug options if LDL cholesterol 100–129 mg/dL [2.59–3.34 mmol/L)
Moderate Risk Greater than or equal to 2 risk factors (10-year risk less than 10%)	Less than 130 mg/dL (3.37 mmol/L)	Greater than or equal to 130 mg/dL (3.37 mmol/L)	Greater than 160 mg/dL (4.14 mmol/L)
Low Risk	Less than 160 mg/dL (4.14 mmol/L)	Greater than or equal to 160 mg/dL (4.14 mmol/L)	Greater than or equal to 190 mg/dL (4.91 mmol/L) (consider drug options if LDL cholesterol 160–189 mg/dL [4.14–4.89 mmol/L])

[a]Optional goals indicated in the NCEP ATP III 2004 update of the guidelines.
CHD, coronary heart disease; LDL, low-density lipoprotein.

with LDL cholesterol greater than 190 mg/dL [4.92 mmol/L] at baseline) are candidates for drug therapy (Table 9–6). ❻ *Typically, statins are the medications of choice to treat high LDL cholesterol because of their ability to substantially reduce LDL cholesterol, ability to reduce morbidity and mortality from atherosclerotic disease, convenient once-daily dosing, and low risk of side effects.*

TABLE 9–7. Essential Components of Therapeutic Lifestyle Changes (TLC)

Component	Recommendation
LDL-raising nutrients	Total fat range should be 25–35% for most cases
Saturated fats	Less than 7% of total calories and reduce intake of trans fatty acids
Dietary cholesterol	Less than 200 mg/day
Therapeutic options for LDL lowering	
Plant stanols/sterols	2 g per day
Increased viscous (soluble) fiber	10–25 g per day
Total calories	Adjust caloric intake to maintain desirable body weight and prevent weight gain
Physical activity	Include enough moderate exercise to expend at least 200 kcal per day

LDL, low-density lipoprotein.

Step 9: Identify Patients with the Metabolic Syndrome

The diagnosis of metabolic syndrome is made when three or more of the following risk factors are present:[3,10]

- Waist circumference greater than 40 inches (101.6 cm) in men (greater than 35 inches in Asian males), or 35 inches (88.9 cm) in women (greater than 31 inches in Asian females)
- Triglycerides greater than or equal to 150 mg/dL (1.70 mmol/L) or on drug treatment for elevated triglycerides
- HDL cholesterol less than 40 mg/dL (1.04 mmol/L) in men or 50 mg/dL (1.3 mmol/L) in women or on drug treatment for reduced HDL cholesterol
- Blood pressure greater than or equal to 130/85 mm Hg or on drug treatment for hypertension
- Fasting blood glucose greater than or equal to 100 mg/dL (5.55 mmol/L) or on drug treatment for elevated glucose

Patients with metabolic syndrome are twice as likely to develop type 2 diabetes and four times more likely to develop CHD.[3,11] These individuals are usually insulin resistant, obese, have hypertension, are in a **prothrombotic state**, and have atherogenic dyslipidemia characterized by low HDL cholesterol and elevated triglycerides, and an increased proportion of their LDL particles are small and dense.[3]

NCEP ATP III identified metabolic syndrome as an important target for further reducing CHD risk. Treatment of metabolic syndrome starts with increased physical activity, weight reduction (which also enhances LDL cholesterol lowering and

insulin sensitivity), and moderation of ethanol use and carbohydrate intake, which effectively reduce many of the associated risk factors. Each of the risk factors should be addressed independently as appropriate, including treatment of hypertension and use of aspirin in CHD patients to reduce the prothrombotic state. ❼ *Patients with metabolic syndrome have an additional lipid parameter that needs to be assessed, namely non-HDL cholesterol (total cholesterol minus HDL cholesterol).*[3] *The target for non-HDL cholesterol is less than the patient's LDL cholesterol target plus 30 mg/dL (0.78 mmol/L).* ❽ *After assessment and control of LDL cholesterol, patients with serum triglycerides between 200 and 499 mg/dL (2.26 and 5.64 mmol/L) should be assessed for atherogenic dyslipidemia (low HDL cholesterol, increased small-dense LDL particles) and metabolic syndrome.* Non-HDL cholesterol estimates the cholesterol carried by all apolipoprotein B-containing lipoprotein particles. Thus, non-HDL cholesterol represents the sum of LDL cholesterol, VLDL cholesterol, and other remnant particles. The non-HDL cholesterol goal is 30 mg/dL (0.78 mmol/L) higher than the LDL cholesterol goal. This is based on the premise that a VLDL cholesterol level less than or equal to 30 mg/dL (0.78 mmol/L) is normal. For example, the LDL cholesterol goal is less than 100 mg/dL (2.59 mmol/L) and the non-HDL cholesterol goal is less than 130 mg/dL (3.37 mmol/L) for a diabetic patient without a history of CHD. Two treatment approaches can be considered for achieving the non-HDL cholesterol goal: titrating existing LDL-lowering therapy or adding niacin or a fibrate to the LDL-lowering therapy.[3]

Step 10: Treatment of Elevated Triglycerides

Patients with serum triglycerides exceeding 500 mg/dL (5.65 mmol/L) are at increased risk of pancreatitis.[3] Reducing triglycerides in these individuals becomes the primary target for intervention. Reduction in ethanol and carbohydrates should be considered and secondary causes (Table 9–3) should be assessed. When pharmacotherapy is instituted, the intensity of therapy should be to reduce triglycerides to less than 150 mg/dL (1.70 mmol/L). Once triglycerides are less than 500 mg/dL (5.65 mmol/L), the primary focus of intervention should once again be on LDL cholesterol. Niacin, fibrates, and fish oils are the most effective agents in patients with hypertriglyceridemia.[3]

Emerging and Life-Habit Risk Factors

In addition to the five major risks, the ATP III guidelines recognize other factors that contribute to CHD risk. These are classified as life-habit risk factors and emerging risk factors. Life-habit risk factors, consisting of obesity, physical inactivity, and an atherogenic diet, require direct intervention. For example, emerging risk factors are lipoprotein(a), homocysteine, prothrombotic/proinflammatory factors, and C-reactive protein (CRP). C-reactive protein is a marker of low-level inflammation and appears to help in predicting CHD risk beyond LDL cholesterol and major CHD risk factors.[11] In some patients, emerging risk factors may be used to guide the intensity of risk-reduction therapy. Deciding when to consider emerging risk factors requires the use of clinical judgment.



Patient Encounter 1, Part 2: Medical History, Physical Exam, and Diagnostic Tests

PMH
Hypertension for 9 years; history of gout

FH
Father and mother both alive with no history of CHD or diabetes.

SH
Works as a computer programmer and sits at his desk most of the day; does not exercise on a regular basis; drinks alcohol (2 to 3 beers) mainly on the weekends while watching sports on TV

Meds
Aspirin 80 mg once daily
Verapamil SR 180 mg once daily

ROS
No chest pain, shortness of breath, or dizziness

PE

VS: BP 142/86 mm Hg, pulse 71 beats per minute, respiratory rate 16 beats per minute, temperature 37°C (98.6°F), waist circumference 38 inches (96.52 cm)
CV: RRR, normal S_1, S_2; no murmurs, rubs, or gallops
Abd: Soft, non-tender, non-distended; positive for bowel sounds, no hepatosplenomegaly or abdominal aortic aneurysm
Exts: Ankle-brachial index 1.1
Neck: No carotid and basilar bruits

Labs
Total cholesterol 256 mg/dL (6.63 mmol/L), triglycerides 235 mg/dL (2.66 mmol/L), HDL cholesterol 27 mg/dL (0.70 mmol/L), glucose 115 mg/dL (6.38 mmol/L), all other labs within normal limits

- Given this additional information, what is your assessment of MN's CHD risk?
- Identify your treatment goals for MN.
- What diagnostic parameters does MN have for the metabolic syndrome?
- What nonpharmacologic and pharmacologic alternatives are available for MN?
- Develop a care plan for MN.

Pharmacotherapy

Statins (HMG-CoA Reductase Inhibitors)

Statins are very effective LDL-lowering medications and are proven to reduce the risk of CHD, stroke, and death. Thus, NCEP ATP III considers statins the preferred LDL-lowering medications. Data concerning the efficacy and safety of the statins now go back nearly 25 years. Statins are effective in reducing MIs, strokes, revascularization procedures, cardiovascular deaths, and in some cases, total mortality. This effectiveness has been demonstrated in both genders, the elderly, patients with diabetes and hypertension, those with and without preexisting CHD, and following an acute coronary syndrome.[12–22] Statins inhibit conversion of HMG-CoA to L-mevalonic acid and subsequently cholesterol. Statins lower LDL cholesterol levels by approximately 25% to 62% (Table 9–8). A substantial reduction in LDL cholesterol occurs at the usual starting dose and each doubling of the daily dose only produces an additional 6% average reduction (known as the "rule of 6"). This is important when considering dose escalation versus adding on an additional LDL-lowering drug. Statins are moderately effective at reducing triglycerides and modestly raise HDL cholesterol (Table 9–8). By inhibiting the synthesis of L-mevalonic acid, statins in turn inhibit other important by-products in the cholesterol biosynthetic pathway that affect intracellular transport, membrane trafficking, and gene transcription.[23] This may explain some of the cholesterol-independent benefits (so-called "pleiotropic" effects) of statins such as reducing lipoprotein oxidation, enhancing endothelial synthesis of nitric oxide, and inhibiting **thrombosis**. These pleiotropic effects are thought to contribute to the rapid/earlier benefits of statins on CHD risk while the decrease in serum lipids accounts for the slower late benefit.

Statins are well tolerated with less than 4% of patients in clinical trials discontinuing therapy due to adverse side effects (Table 9–9). Elevations in liver function tests (LFTs) and **myopathy**, including **rhabdomyolysis**, are important adverse effects associated with the statins. Liver toxicity, defined as LFT elevations greater than three times the upper limit of normal, is reported in less than 2% of patients; however, the incidence is higher at higher doses and the progression to liver failure is thought to be exceedingly rare. Liver function tests should be obtained at baseline and 6 to 12 weeks after starting therapy or any dose escalation. Annual monitoring of LFTs is usually sufficient. Myopathy, defined as muscle symptoms with creatine kinase (CK; or creatine phosphokinase [CPK]) 10 times the upper limit of normal, is reported to range from 0% to less than 0.5% for the currently marketed statins at Food and Drug Administration (FDA)-approved doses. Rhabdomyolysis, defined as muscle symptoms with marked

TABLE 9–8. Effects of Lipid-Lowering Drugs on Serum Lipids at FDA-Approved Doses

Lipid-Lowering Drug	LDL Cholesterol	HDL Cholesterol	Triglycerides	Total Cholesterol
Statins				
Atorvastatin	–26% to –60%	+5% to +13%	–17% to –53%	–25% to –45%
Fluvastatin	–22% to –36%	+3% to +11%	–12% to –25%	–16% to –27%
Fluvastatin ER	–33% to –35%	+7% to +11%	–19% to –25%	–25%
Lovastatin	–21% to –42%	+2% to +10%	–6% to –27%	–16% to –34%
Lovastatin ER	–24% to –41%	+9% to +13%	–10% to –25%	–18% to –29%
Pravastatin	–22% to –34%	+2% to +12%	–15% to –24%	–16% to –25%
Rosuvastatin	–45% to –63%	+8% to +14%	–10% to –35%	–33% to –46%
Simvastatin	–26% to –47%	+8% to +16%	–12% to –34%	–19% to –36%
Bile Acid Sequestrants				
Cholestyramine	–15% to –30%	+3% to +5%	May increase in patients with elevated triglycerides	–10% to –25%
Colesevelam	–8% to –15%	+3% to +5%		–70% to –10%
Colestipol	–15% to –30%	+3% to +5%		–10% to 25%
Cholesterol Absorption Inhibitor				
Ezetimibe	–18%	+1% to +2%	–7% to –9%	–12% to –13%
Nicotinic Acid				
Niacin ER	–5% to –17%	+14% to +26%	–11% to –38%	–3% to –12%
Niacin IR	–5% to –25%	+15% to +39%	–20% to –60%	–3% to –25%
Fibric Acid Derivatives				
Fenofibrate	–31% to +45%	+9% to +23%	–23% to –54%	–9% to –22%
Gemfibrozil	–30% to +30%	+10% to +30%	–20% to –60%	–2% to –16%
Combination Products				
Niacin ER and lovastatin	–30% to –42%	+20% to +30%	–32 to –44%	Not stated
Simvastatin and ezetimibe	–46% to –59%	+8% to +12%	–26% to –25%	–34% to –43%

ER, extended-release; FDA, Food and Drug Administration; HDL, high-density lipoprotein; IR, immediate-release; LDL, low-density lipoprotein; SR, sustained-release.

TABLE 9–9. Formulation, Dosing, and Common Adverse Effects of Lipid-Lowering Drugs

Lipid-Lowering Drug	Dosage Forms	Usual Adult Maintenance Dose Range	Adverse Effects
Statins			
Atorvastatin	10, 20, 40, 80 mg tablets	10 to 80 mg once daily (at any time of day)	Most frequent side effects are constipation, abdominal pain, diarrhea, dyspepsia, and nausea. Statins should be discontinued promptly if serum transaminase levels (liver function tests) rise to 3 times upper limit of normal, or if patient develops signs or symptoms of myopathy. Approximate equivalent doses of HMG-CoA reductase inhibitors are: atorvastatin 10 mg, fluvastatin 80 mg, lovastatin 40 mg, pravastatin 40 mg, simvastatin 20 mg, and rosuvastatin 5 mg.
Fluvastatin	20, 40 mg capsules; 80 mg extended-release tablets	20–40 mg/day as a single dose (evening) or 40 mg twice daily; 80 mg once daily (evening)	
Lovastatin	10, 20, 40 mg tablets	10 to 80 mg/day as a single dose (with evening meal) or divided twice daily with food	
Lovastatin ER	20, 30, 60 mg tablets	20 to 60 mg/day as a single dose	
Pravastatin	10, 20, 40, 80 mg tablets	10 to 80 mg/day as a single dose at bedtime	
Rosuvastatin	5, 10, 20, 40 mg tablets	5–40 mg/day (at any time of day). 40 mg reserved for those who don't achieve LDL cholesterol goal on 20 mg	
Simvastatin	5, 10, 20, 40, 80 mg tablets	5–80 mg/day as a single dose in the evening, or divided	
Bile Acid Sequestrants			
Cholestyramine	4 g packets	4–24 g/day in two or more divided doses	Main side effects are nausea, constipation, bloating, and flatulence, although these may be less with colesevelam. Increasing fluid and dietary fiber intake may relieve constipation and bloating. Impair absorption of fat-soluble vitamins.
Colesevelam	625 mg tablets	3750–4375 mg/day as a single dose or divided twice daily, with meals	
Colestipol	5 g packets	5–30 g/day as a single dose or divided	
	1 g tablets	2–16 g/day as a single dose or divided	
Cholesterol Absorption Inhibitors			
Ezetimibe	10 mg tablet	10 mg once daily	The overall incidence of adverse events reported with ezetimibe alone was similar to that reported with placebo and generally similar between ezetimibe with a statin and statin alone. The frequency of increased transaminases was slightly higher in patients receiving ezetimibe plus a statin compared with those receiving statin monotherapy (1.3% versus 0.4%).
Nicotinic Acid			
Niacin ER	500, 750, 1000 mg extended-release tablets	1000–2000 mg once daily at bedtime	Side effects include flushing, itching, gastric distress, headache, hepatotoxicity, hyperglycemia, and hyperuricemia.
Niacin	50 to 750 mg tabs or caps, immediate-release	1–5 g/day in three or more divided doses	
	250 to 750 mg sustained-release	1–2 g/day (never exceed 2 g/day due to increased risk of hepatotoxicity)	
Fibric Acid Derivatives			
Fenofibrate	54, 160 mg tablets	54–160 mg/day	Most common side effects are nausea, diarrhea, abdominal pain, and rash. Increased risk of rhabdomyolysis when given with a statin. Fibric acids are associated with gallstones, myositis, and hepatitis.
Gemfibrozil	600 mg tablets	1200 mg/day in two doses, 30 minutes before meals	

(*Continued*)

TABLE 9–9. Formulation, Dosing, and Common Adverse Effects of Lipid-Lowering Drugs (*Continued*)

Lipid-Lowering Drug	Dosage Forms	Usual Adult Maintenance Dose Range	Adverse Effects
Combination Products			
Niacin ER and lovastatin	500 mg/20 mg, 750 mg/20 mg, 1000 mg/20 mg tablets	500 mg/20 mg to 2000 mg/40 mg daily, at bedtime	See entries on prior page for each drug (niacin ER and lovastatin)
Ezetimibe and simvastatin	10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg	The dosage range is 10/10 mg/day through 10/80 mg/day. The recommended usual starting dose is 10/20 mg/day. Initiation of therapy with 10/10 mg/day may be considered for patients requiring less aggressive LDL cholesterol reductions.	See entries on prior page for each drug (ezetimibe and simvastatin)

ER, extended release; HMG-CoA, 3-hydroxy-3-methyglutaryl coenzyme A; LDL, low-density lipoprotein.

elevation in CK 10 times the upper limit of normal with creatinine elevation usually associated with **myoglobinuria** and brown urine, is very rare.[24] The concern of statin-associated myopathy has increased since the voluntary removal of cerivastatin from the world market in 2001 because the reported rate of fatal rhabdomyolysis was 16 to 80 times higher than the rate for any other statins, and many of these cases were reported in patients treated with concomitant gemfibrozil.[25] The American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute published a clinical advisory with a focus on myopathy.[24] Listed below are the risks associated with statin-induced myopathy published in this report:

- Small body frame and frailty
- Multisystem disease (e.g., chronic renal insufficiency, especially due to diabetes)
- Multiple medications
- Perioperative periods
- Specific concomitant medications or consumptions (check specific statin package insert for warnings): fibrates (especially gemfibrozil, but other fibrates too), nicotinic acid (rarely), cyclosporine, azole antifungals such as itraconazole and ketoconazole, macrolide antibiotics such as erythromycin and clarithromycin, protease inhibitors used to treat Acquired Immune Deficiency Syndrome, nefazodone (antidepressant), verapamil, amiodarone, large quantities of grapefruit juice (usually more than 1 quart per day), and alcohol abuse (independently predisposes to myopathy)

Baseline CK should be obtained in all patients prior to starting statin therapy. Follow-up CK should only be obtained in patients complaining of muscle pain, weakness, tenderness, or brown urine. Routine monitoring of CK is of little value in the absence of clinical signs or symptoms. Patient assessment for symptoms of myopathy should be done 6 to 12 weeks after starting therapy and at each visit. More frequent monitoring should be done in higher-risk individuals such as those identified above.

With the exception of pravastatin which is mainly metabolized by isomerization in the gut to a relatively inactive metabolite, the other statins undergo biotransformation by the cytochrome P-450 system. Therefore, drugs known to inhibit statin metabolism should be used cautiously. The time until maximum effect on lipids for statins is generally 4 to 6 weeks.

Cholesterol Absorption Inhibitors

Ezetimibe is the first drug in a new class of agents referred to as cholesterol absorption inhibitors. Ezetimibe blocks biliary and dietary cholesterol as well as phytosterol (plant sterol)



Patient Encounter 2

LC is a 51-year-old female with a history of CHD (stent placement in the left anterior descending coronary artery 3 years prior) and type 2 diabetes who is referred to you for follow-up of her cholesterol. She is taking simvastatin 20 mg once daily in the evening for her cholesterol, and metformin 2000 mg once daily in the evening and pioglitizone 15 mg once daily for diabetes. Her diabetes is well controlled. Her laboratory test results are within normal limits, except for her fasting lipid profile: total cholesterol 215 mg/dL (5.57 mmol/L), triglycerides 135 mg/dL (1.53 mmol/L), HDL cholesterol 51 mg/dL (1.32 mmol/L), and LDL cholesterol 137 mg/dL (3.55 mmol/L).

- What is your assessment of LC's cholesterol results?
- Identify treatment goals for LC.
- Assess LC's risk for statin-induced side effects.
- Design a treatment plan for LC.

absorption by interacting with the NPC1L1 transporter located in the brush border membrane of enterocytes[5] (Fig. 9–2). Ezetimibe inhibits 54% of all intestinal cholesterol absorption on average. By reducing the cholesterol content within chylomicrons delivered to the liver, ezetimibe reduces liver cholesterol stores, inducing an up-regulation of LDL receptors resulting in a decrease in serum cholesterol. As a result, ezetimibe also induces a compensatory increase in cholesterol biosynthesis. Since statins inhibit cholesterol biosynthesis, the compensatory increase in cholesterol biosynthesis by ezetimibe can be blocked by combining ezetimibe with a statin.

Ezetimibe reduces LDL cholesterol by an average of 18% (Table 9–8). However, larger reductions can be seen in some individuals, presumably due to higher absorption of cholesterol. These individuals appear to have a blunted response to statin therapy. Ezetimibe lowers triglycerides by 7% to 9% and modestly increases HDL cholesterol.

Once absorbed, ezetimibe undergoes extensive glucuronidation in the intestinal wall to the active metabolite (ezetimibe glucuronide). Ezetimibe and the active metabolite are enterohepatically recirculated back to the site of action, which limits systemic exposure and may explain the low incidence of adverse effects (Table 9–9). Ezetimibe alone or with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in LFTs. Currently, clinical trials designed to determine ezetimibe's effects on CHD morbidity and mortality have not been completed. The time until maximum effect on lipids for ezetemibe is generally 2 weeks.

Bile Acid Sequestrants

Cholestyramine, colestipol, and colesevelam are the bile acid-binding resins or sequestrants (BAS) currently available in the United States. Resins are highly charged molecules that bind to bile acids (which are produced from cholesterol) in the gut. The resin-bile acid complex is then excreted in the feces. The loss of bile causes a compensatory conversion of hepatic cholesterol to bile, reducing hepatocellular stores of cholesterol resulting in an up-regulation of LDL receptors to replenish hepatocellular stores which then result in a decrease in serum cholesterol. Resins have been shown to reduce CHD events in patients without CHD.[26]

Resins are moderately effective in lowering LDL cholesterol but do not lower triglycerides (Table 9–8). Moreover, in patients with elevated triglycerides, the use of a resin may worsen the condition. This may be due to a compensatory increase in HMG-CoA reductase activity and results in an increase in assembly and secretion of VLDL. The increase in HMG-CoA reductase activity can be blocked with a statin, resulting in enhanced reductions in serum lipids (see section on combination therapy). Resins reduce LDL cholesterol from 15% to 30%, with a modest increase in HDL cholesterol (3% to 5%) (Table 9–8). Resins are most often used as adjuncts to statins in patients who require additional lowering of LDL cholesterol. Since these drugs are not absorbed, adverse effects are limited to the gastrointestinal tract (Table 9–9). About 20% of patients taking cholestyramine or colestipol report constipation and symptoms such as flatulence and bloating. A large number of patients stop therapy because of this. Resins should be started at the lowest dose and escalated slowly over weeks to months as tolerated until the desired response is obtained. Patients should be instructed to prepare the powder formulations in 6 to 8 ounces (approximately 180–240 mL) of noncarbonated fluids, usually juice (enhances palatability) or water. Fluid intake should be increased to minimize constipation. Colesevelam is better tolerated with fewer gastrointestinal side effects, although it is more expensive. All resins have the potential to prevent the absorption of other drugs such as digoxin, warfarin, thyroxine, thiazides, β-blockers, fat-soluble vitamins, and folic acid. Potential drug interactions can be avoided by taking a resin either 1 hour before or 4 hours after these other agents. Colesevelam appears less likely than the older agents to reduce drug absorption, and the manufacturer does not state that colesevelam has to be dosed hours apart from other medications.[27] The time until maximum effect on lipids for resins is generally 2 to 4 weeks.

Niacin

Niacin (vitamin B_3) has broad applications in the treatment of lipid disorders when used at higher doses than those used as a nutritional supplement. Niacin inhibits fatty acid release from adipose tissue and inhibits fatty acid and triglyceride production in liver cells. This results in an increased intracellular degradation of apolipoprotein B, and in turn, a reduction in the number of VLDL particles secreted (Fig. 9–4). The lower VLDL levels and the lower triglyceride content in these particles leads to an overall reduction in LDL cholesterol as well as a decrease in the number of small, dense LDL particles. Niacin also reduces the uptake of HDL-apolipoprotein A1 particles and increases uptake of cholesterol esters by the liver, thus improving the efficiency of reverse cholesterol transport between HDL particles and vascular tissue (Fig. 9–4). Niacin is indicated for patients with elevated triglycerides, low HDL cholesterol, and elevated LDL cholesterol.[3]

Several different niacin formulations are available: niacin immediate-release (IR), niacin sustained-release (SR), and niacin extended-release (ER).[28,29] These formulations differ in terms of dissolution and absorption rates, metabolism, efficacy, and side effects. Limitations of niacin IR and SR are flushing and **hepatotoxicity**, respectively. These differences appear related to the dissolution and absorption rates of niacin formulations and its subsequent metabolism. Niacin IR is available by prescription (Niacor®) as well as a dietary supplement which is not regulated by the FDA.[28] Currently, there are no FDA-approved niacin SR products, thus, all SR products are available only as dietary supplements.

Niacin IR is usually completely absorbed within 1 to 2 hours; thus, it quickly saturates a high-affinity, low-capacity metabolic pathway, and the majority of the drug is metabolized by a

second low-affinity, high-capacity system with metabolites associated with flushing.[30] Conversely, absorption of niacin SR may exceed 12 hours. Because niacin SR is absorbed over 12 or more hours, the high-affinity pathway metabolizes the majority of the drug, resulting in the production of metabolites associated with hepatotoxicity. Niacin ER was developed as a once-daily formulation to be taken at bedtime, with the goal of reducing the incidence of flushing without increasing the risk of hepatotoxicity. Niacin ER (Niaspan®) is the only long-acting niacin product approved by the FDA for dyslipidemia. Niacin ER has an absorption rate of 8 to 12 hours, intermediate to niacin IR and SR, and therefore balances metabolism more evenly over the high-affinity, low-capacity pathway and the low-affinity, high-capacity pathway. Furthermore, taking niacin ER at bedtime can minimize the impact of flushing.

Niacin use is limited by cutaneous reactions such as flushing and pruritus of the face and body. The use of aspirin or a non-steroidal anti-inflammatory drug 30 minutes prior to taking niacin can help alleviate these reactions, as they are mediated by an increase in prostaglandin D_2.[3] In addition, taking niacin with food and avoiding hot liquids at the time niacin is taken is helpful in minimizing flushing and pruritus.

In general, niacin reduces LDL cholesterol from 5% to 25%, reduces triglycerides by 20% to 50%, and increases HDL cholesterol by 15% to 35% (Table 9–8). Niacin has been shown to reduce CHD events and total mortality[31] as well as the progression of atherosclerosis when combined with a statin.[31]

Niacin can raise uric acid levels, and in diabetics can raise blood glucose levels. However, several clinical trials have shown that niacin can be used safely and effectively in patients with diabetes.[33] Due to the high cardiovascular risk of patients with diabetes, the benefits of improving the lipid profile appear to outweigh any adjustment in diabetic medication(s) that is needed.[33]

Niacin should be instituted at the lowest dose and gradually titrated to a maximum dose of 2 grams daily for ER and SR products and no more than 5 grams daily for IR products. FDA-approved niacin products are preferred because of product consistency. Moreover, niacin products labeled as "no flush" don't contain nicotinic acid and therefore have no therapeutic role in the treatment of lipid disorders.[28] The time until maximum effect on lipids for niacins is generally 3 to 5 weeks.

Fibrates

The predominant effects of fibrates are a decrease in triglyceride levels by 20% to 50% and an increase in HDL cholesterol levels by 9% to 30% (Table 9–8). The effect on LDL cholesterol is less predictable. In patients with high triglycerides, however, LDL cholesterol may increase. Fibrates increase the size and reduce the density of LDL particles much like niacin. Fibrates are the most effective triglyceride-lowering drugs and are used primarily in patients with elevated triglycerides and low HDL cholesterol.

Fibrates work by reducing apolipoproteins B, C-III (an inhibitor of LPL), and E, and increasing apolipoproteins A-I and A-II through activation of peroxisome proliferator-activated receptors-alpha (PPAR-α), a nuclear receptor involved in cellular function. The changes in these apolipoproteins result in a reduction in triglyceride-rich lipoproteins (VLDL and IDL) and an increase in HDL.

Clinical trials of fibrate therapy in patients with elevated cholesterol and no history of CHD demonstrated a reduction in CHD incidence, although less than the reduction attained with statin therapy.[35] In addition, a large study of men with CHD, low HDL cholesterol, low LDL cholesterol, and elevated triglycerides demonstrated a 24% reduction in the risk of death from CHD, non-fatal MI, and stroke with gemfibrozil.[36] Fibrates may be appropriate in the prevention of CHD events for patients with established CHD, low HDL cholesterol, and triglycerides below 200 mg/dL (2.26 mmol/L). However, LDL-lowering therapy should be the primary target if LDL cholesterol is elevated. Evidence of a reduction in CHD risk among patients with established CHD has not been demonstrated with fenofibrate.

The fibric acid derivatives are generally well tolerated. The most common adverse effects include dyspepsia, abdominal pain, diarrhea, flatulence, rash, muscle pain, and fatigue (Table 9–9). Myopathy and rhabdomyolysis can occur, and the risk appears to increase with renal insufficiency or concurrent statin therapy. If a fibrate is used with a statin, fenofibrate is preferred because it appears to inhibit the glucuronidation of the statin hydroxy and moiety less than gemfibrozil, allowing greater renal clearance of the statins.[24,37] A CK level should be checked before therapy is started and if symptoms occur. Liver dysfunction has been reported, and LFTs should be monitored. Fibrates increase cholesterol in the bile and have caused gallbladder and bile duct disorders, such as **cholelithiasis** and **cholecystitis**. Unlike niacin, these agents do not increase glucose or uric acid levels. Fibrates are contraindicated in patients with gallbladder disease, liver dysfunction, or severe kidney dysfunction. The risk of bleeding is increased in patients taking both a fibrate and warfarin. The time until maximum effect on lipids is generally 2 weeks for fenofibrate and 3 to 4 weeks for gemfibrozil.

Fish Oils

Omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid), the predominant fatty acids in the oil of cold-water fish, lower triglycerides by as much as 35% when taken in large amounts. Fish oil supplements may be useful for patients with high triglycerides despite diet, alcohol restriction, and fibrate therapy. This effect may be modulated thru PPAR-α and a reduction in apolipoprotein B-100 secretion. Omega-3 fatty acids reduce platelet aggregation and have

anti-arrhythmic properties, and therefore their use has been associated with a reduction in MI and sudden cardiac death, respectively.[38]

Omega-3 fatty acids are usually started at 1 gram daily, and the FDA recommends not exceeding 4 grams daily for the treatment of elevated triglycerides. Use of high-quality omega-3 fatty acids free of contaminants such as mercury and organic pollutants should be encouraged when using these agents. Common side effects associated with omega-3 fatty acids are diarrhea and excess bleeding. Patients taking anticoagulant or antiplatelet agents should be monitored more closely when consuming these products because excessive amounts of omega-3 fatty acids (for example, greater than 3 grams daily) may lead to bleeding and may increase the risk of hemorrhagic stroke.

Combination Therapy

A large proportion of the United States population won't achieve their NCEP cholesterol targets for a variety of reasons.[39] These include inadequate patient adherence, adverse events, inadequate starting doses, lack of dose escalation, and lower treatment targets.[28,40] Moreover, patients with concomitant elevations in triglycerides and/or low levels of HDL cholesterol may need combination drug therapy to normalize their lipid profile. ❾ *Combination drug therapy is an effective means to achieve greater reductions in LDL cholesterol (statin + ezetimibe or bile acid resin, bile acid resin + ezetimibe, or three-drug combinations) as well as raising HDL cholesterol and lowering serum triglycerides (statin + niacin or fibrate).*

Combination Therapy for Elevated LDL Cholesterol

For patients who don't achieve their LDL or non-HDL cholesterol goals with statin monotherapy and lifestyle modifications including those unable to tolerate high doses due to adverse effects, combination therapy may be appropriate. Resins or ezetimibe combine effectively with statins to augment LDL cholesterol reduction. When added to a statin, ezetimibe can reduce LDL cholesterol levels by an additional 18% to 21% or up to 65% total reduction with maximum doses of the more potent statins. Ezetimibe and simvastatin are available as a combination tablet (Vytorin®) and indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL cholesterol, apolipoprotein B, triglycerides, and non-HDL cholesterol, and to increase HDL cholesterol. The usual starting dose is 10 mg/20 mg, and the maximum dose is 10 mg/80 mg (Table 9–9). Adverse events are similar to those of each product taken separately; however, the percentage of patients with LFT elevations greater than 3 times normal is slightly higher than with a statin alone, and there appears to be a slightly higher risk of myopathy and rhabdomyolysis when statins and ezetimibe are combined. The time until maximum effect on lipids for this combination is generally 2 to 6 weeks.

A statin combined with a resin results in similar reductions in LDL cholesterol as those seen with ezetimibe. However, the magnitude of triglyceride reduction is less with a resin compared to ezetimibe, and this should be considered in patients with higher baseline triglyceride levels. In addition, gastrointestinal adverse events and potential drug interactions limit the utility of this combination.

Ezetimibe and a resin can also be combined. A study which assessed the effects of adding ezetimibe to ongoing resin therapy showed an additional 19% reduction in LDL cholesterol and an additional 14% reduction in triglycerides. This combination was well tolerated.[41]

Some patients, in particular those with genetic forms of hypercholesterolemia (Table 9–2), will require three or more drugs to manage their disorder. Regimens using a statin, resin, and niacin were found to reduce LDL cholesterol up to 75%.[42] These early studies were conducted with lovastatin, so larger reductions would be expected with the more potent statins available today.

Combination Therapy for Elevated Cholesterol and Triglyceridemia with or without Low HDL Cholesterol

Fibrates are the most effective triglyceride-lowering agents and also raise HDL cholesterol levels. Combination therapy with a fibrate, particularly gemfibrozil, and a statin has been found to increase the risk for myopathy. Of the 31 rhabdomyolysis deaths reported with cerivastatin use, 12 involved concomitant gemfibrozil.[25] Therefore, more frequent monitoring, thorough patient education, and consideration of factors that increase the risk as reviewed previously should be considered.

❿ *Reducing LDL cholesterol while substantially raising HDL cholesterol (statin + niacin) appears to reduce the risk of atherosclerotic disease progression to a greater degree than statin monotherapy.* Combining niacin with a statin augments the LDL cholesterol–lowering potential of niacin while enhancing both the HDL cholesterol–raising effects and triglyceride–lowering effects of the statin. A statin combined with niacin appears to offer greater benefits for reducing atherosclerosis progression compared to a statin alone.[32] A formulation combining ER niacin and lovastatin (Advicor™) is available and is indicated for treatment of primary hypercholesterolemia and mixed dyslipidemia in patients treated with lovastatin who require further triglyceride lowering or HDL cholesterol raising and may benefit from having niacin added to their regimen. The combination is also indicated for patients treated with niacin who require further LDL cholesterol lowering and may benefit from having lovastatin added to their regimen. The time until maximum effect on lipids for this combination is generally 3 to 6 weeks.

Niacin can be combined with a fibrate in patients with high elevations in serum triglycerides. The combination may increase the risk of myopathy compared to either agent alone.

Compared with monotherapy, combination therapy is relatively unstudied in terms of the effects on CHD event reduction and may reduce patient compliance through increased side effects and increased costs. When used appropriately and with proper precautions, however, they are effective in normalizing lipid abnormalities, particularly in patients who cannot tolerate adequate doses of statin therapy for more severe forms of dyslipidemia.

Investigational Agents

There are numerous investigational drugs in development for the treatment of lipid disorders and prevention of atherosclerosis. Many of these will likely be used in combination with currently available lipid-modulating drugs. The most promising are the cholesterol ester transfer protein (CETP) inhibitors, which have the potential to significantly raise HDL cholesterol.[43] Other agents in development include newer statins; bile acid transport inhibitors; phytostanol analogues; acyl coenzyme A: cholesterol acyltransferase (ACAT) inhibitors; squalene synthase inhibitors; and newer PPAR-α, -γ, and -δ agonists, as well as dual PPAR-α/γ agonists. In addition, weekly infusions of genetically engineered HDL (Apolipoprotein A1 Milano) in patients with atherosclerosis has been shown to cause significant reduction in atheroma volume compared to placebo after just 5 weeks of therapy.[44]

These novel therapies will provide opportunities for developing different combination strategies to further reduce the risk of CHD even after adequate treatment with existing agents. Well-designed studies using non-invasive imaging technology and long-term follow-up periods are needed to ensure that there is a favorable risk:benefit ratio.

OUTCOME EVALUATION

- The successful outcome in cholesterol management is to reduce cholesterol and triglycerides below the NCEP ATP III goals in an effort to alter the natural course of atherosclerosis and decrease future cardiovascular events.
- ❺ *Employ an adequate trial of TLC in all patients, but institute pharmacotherapy concurrently in higher-risk patients.*
- When indicated, initiate drug therapy at a dose that will reduce LDL cholesterol in the range of 30% to 40%.
- ❻ *Typically, statins are the medications of choice to treat high LDL cholesterol because of their ability to substantially reduce LDL cholesterol, ability to reduce morbidity and mortality from atherosclerotic disease, convenient once-daily dosing, and low risk of side effects.*
- Employ an individualized patient monitoring plan in an effort to minimize side effects and maintain treatment adherence and lipid goals.



Patient Care and Monitoring

1. Assess the patient for the presence of CHD or other atherosclerosis disorders.
2. Assess major risk factors for CHD.
3. For patients without CHD or CHD risk equivalent, but two or more major CHD risk factors, perform Framingham risk assessment.
4. Obtain fasting cholesterol profile and assess any abnormal lipid levels.
5. Obtain a thorough history of prescription, nonprescription, and natural drug product use. Determine what treatments for cholesterol the patient has used in the past (if any). Assess if the patient is taking any medications that may contribute to his or her abnormal lipid levels.
6. Assess concomitant diseases that may contribute to the patient's abnormal lipid levels.
7. Assess risk factors for metabolic syndrome.
8. Determine the treatment goal for LDL cholesterol based on the patient's CHD risk and non-HDL cholesterol goal if patient meets criteria for metabolic syndrome.
9. Educate all patients on therapeutic lifestyle changes (TLC) and the importance of regular physical activity.
10. For patients exceeding their LDL cholesterol goal, initiate TLC. Consider starting concurrent pharmacotherapy in patients in the high-risk or moderately-high-risk categories. Pharmacotherapy should be initiated at a dose to reduce LDL cholesterol by 30% to 40% at a minimum.
11. Therapeutic lifestyle changes should be continued and intensified (consider adding plant sterols/stanols and increase fiber) after 6 weeks if not below LDL cholesterol target. For those patients above their LDL cholesterol target after adequate trial of TLC (12 to 18 weeks), pharmacotherapy should be strongly considered.
12. Institute appropriate pharmacotherapy based on lipid abnormality. Obtain appropriate baseline labs to monitor for adverse drug effects. Assess potential disease and drug interactions that may affect choice or intensity of pharmacotherapy.
13. Monitor response, safety, and adherence after a minimum of 4 to 6 weeks. Titrate therapy or add a second drug as needed.
14. Once the LDL cholesterol goal is achieved, assess non-HDL cholesterol in those with metabolic syndrome and intensify LDL-lowering therapy further or consider adding niacin or fibrate.
15. Provide patient education in regard to CHD, hyperlipidemia, therapeutic lifestyle modifications, drug therapy, and therapy adherence.

ABBREVIATIONS

ABC:	ATP-binding cassette
ABCA1:	ATP-binding cassette A1
ACAT:	acyl coenzyme A: cholesterol acyltransferase
Acetyl:	CoA acetyl coenzyme A
Apo:	apolipoprotein
ATP:	adenosine triphosphate
ATP III:	Adult Treatment Panel III edition
BAS:	bile acid sequestrant
BP:	blood pressure
Bpm:	beats per minute
C:	cholesterol
CAD:	clinical atherosclerotic disease
CE:	cholesterol ester
CETP:	cholesterol ester transfer protein
CHD:	coronary heart disease
CK:	creatine kinase
CM:	chylomicrons
CPK:	creatine phosphokinase
CRP:	C-reactive protein
DBP:	diastolic blood pressure
ER:	extended-release
FA:	fatty acid
FDA:	Food and Drug Administration
HDL:	high-density lipoprotein
HMG-CoA:	3-hydroxy-3-methyglutaryl coenzyme A
HL:	hepatic lipase
IDL:	intermediate-density lipoprotein
IR:	immediate-release
LCAT:	lecithin-cholesterol acyltransferase
LDL:	low-density lipoprotein
LFT:	liver function test
LPL:	lipoprotein lipase
LRP:	LDL-related protein
MI:	myocardial infarction
MMP:	matrix metalloproteinase
NCEP:	National Cholesterol Education Program
NO:	nitric oxide
NPC1L1:	Niemann-Pick C1 Like 1
PPAR-α:	peroxisome proliferator-activated receptor-alpha
SBP:	systolic blood pressure
SR:	sustained-release
SR-BI:	scavenger receptors
TG:	triglyceride
TLC:	therapeutic lifestyle changes
VLDL:	very low-density lipoprotein

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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10 Hypovolemic Shock

Bradley A. Boucher and G. Christopher Wood



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. List the most common etiologies of decreased intravascular volume in hypovolemic shock patients.
2. Describe the major hemodynamic and metabolic abnormalities that occur in patients with hypovolemic shock.
3. Describe the clinical presentation, including signs, symptoms, and laboratory test measurements, for the typical hypovolemic shock patient.
4. Prepare a treatment plan with clearly defined outcome criteria for a hypovolemic shock patient that includes both fluid management and other pharmacologic therapy.
5. Compare and contrast the relative advantages and disadvantages of crystalloids, colloids, and blood products in the treatment of hypovolemic shock.
6. Formulate a stepwise monitoring strategy for a hypovolemic shock patient.

Key Concepts

❶ Hypovolemic shock occurs as a consequence of inadequate intravascular volume to meet the oxygen and metabolic needs of the body.

❷ Protracted tissue hypoxia sets in motion a downward spiral of events secondary to organ dysfunction and eventual failure if untreated.

❸ The overarching goals in treating hypovolemic shock are to restore effective circulating blood volume, as well as managing its underlying cause, thereby reversing organ dysfunction and returning to homeostasis.

❹ Three major therapeutic options are available to clinicians for restoring circulating blood volume: crystalloids (electrolyte-based solutions), colloids (large-molecular-weight solutions), and blood products.

❺ In the absence of ongoing blood loss, administration of 2000 to 4000 mL of isotonic crystalloid will normally re-establish baseline vital signs in adult hypovolemic shock patients.

❻ The volume of colloid administered is primarily confined to the intravascular space, in contrast to isotonic crystalloid solutions that distribute throughout the extracellular fluid space.

❼ Blood products are indicated in adult hypovolemic shock patients who have sustained blood loss from hemorrhage exceeding 1500 mL.

❽ Vasopressors may be warranted as a temporary measure in patients with profound hypotension or evidence of organ dysfunction in the early stages of shock.

❾ Major treatment goals in hypovolemic shock following fluid resuscitation are as follows: arterial systolic blood pressure greater than 90 mm Hg within 1 hour, organ dysfunction reversal, and normalization of laboratory measurements as rapidly as possible (less than 24 hours).

The principal function of the circulatory system is to supply oxygen and vital metabolic substrates to cells throughout the body, as well as removal of metabolic waste products. **Circulatory shock** is a life-threatening condition whereby this principal function is compromised. When circulatory shock is caused by a severe loss of blood volume or body water it is called **hypovolemic shock,** the focus of this chapter. Regardless of etiology, the most distinctive manifestations of hypovolemic shock are **arterial hypotension** and **metabolic acidosis.** Metabolic acidosis is a consequence of an accumulation of lactic acid resulting from tissue hypoxia and anaerobic

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metabolism. If the decrease in arterial blood pressure is severe and protracted, such hypotension will inevitably lead to severe hypoperfusion and organ dysfunction. Rapid and effective restoration of circulatory homeostasis through the use of blood products, fluids, and/or pharmacologic agents is imperative to prevent complications of untreated shock and ultimately death.

ETIOLOGY AND EPIDEMIOLOGY

Practitioners must have a good understanding of cardiovascular physiology to diagnose, treat, and monitor circulatory problems in critically ill patients. Eugene Braunwald, a renowned cardiologist, described the interrelationships between the major hemodynamic variables (Fig. 10–1).[1] These variables include: arterial blood pressure, **cardiac output** (CO), **systemic vascular resistance** (SVR), heart rate (HR), **stroke volume** (SV), left ventricular size, **afterload, myocardial contractility,** and **preload.** While an oversimplification, Fig. 10–1 is beneficial in conceptualizing where the major abnormalities occur in patients with circulatory shock as well as predicting the body's compensatory responses.

Shock can be effectively categorized by etiology into four major types: hypovolemic, obstructive, cardiogenic, and distributive (Table 10–1).[2] As noted, all patients with shock have profound decreases in arterial blood pressure. Understanding the primary cause of the circulatory abnormality in these respective shock states is invaluable to their management. Hypovolemic shock is caused by a loss of intravascular volume. Obstructive shock is caused by an obstruction that directly compromises inflow or outflow of blood from the heart. Cardiogenic shock is caused by diminished myocardial contractility resulting in decreased CO. Lastly, distributive shock is caused by a major decrease in SVR. In all shock types, one would expect a compensatory increase in HR to bolster the fallen arterial blood pressure. The exception is relative bradycardia seen in **spinal shock** resulting from spinal cord injury. Differentiating between the underlying abnormality and the

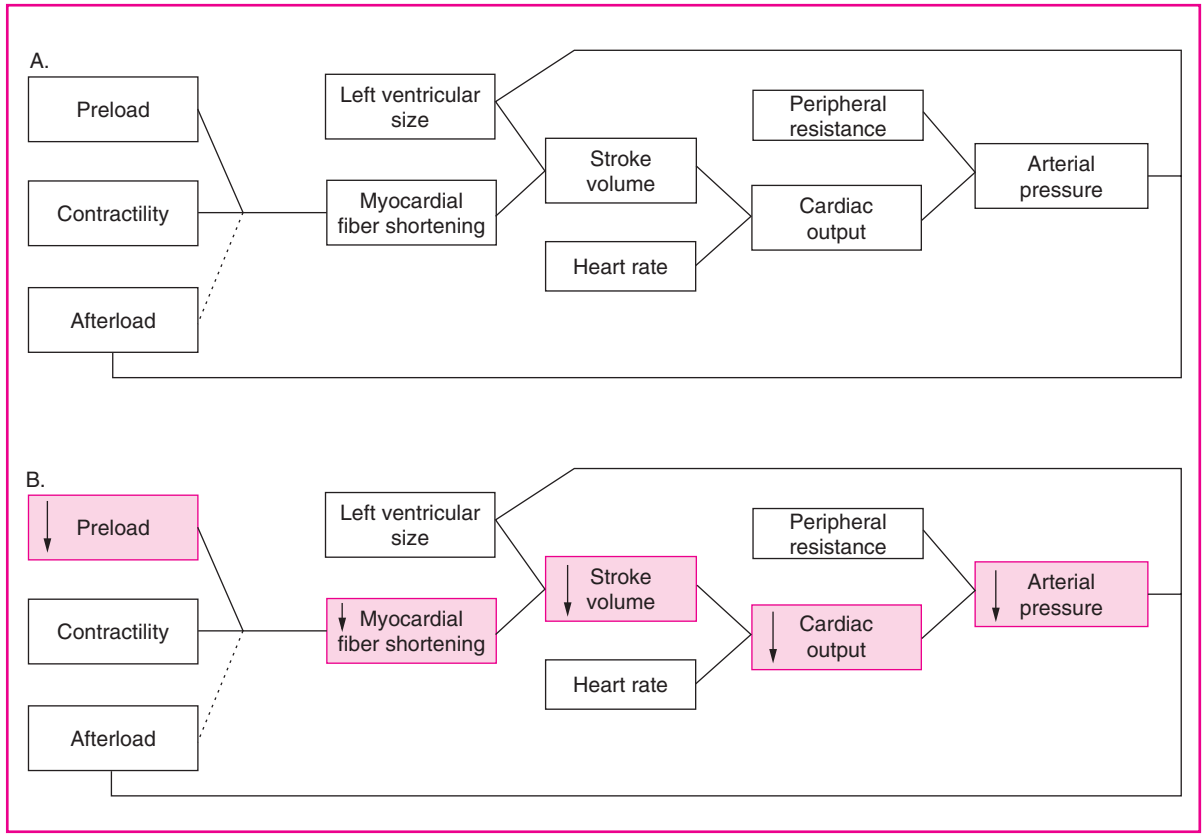


FIGURE 10–1. Hemodynamic relationships between key cardiovascular parameters (panel *A*). Solid lines represent a direct relationship; the broken line represents an inverse relationship. In panel *B*, the perturbations typically observed in hypovolemic shock are highlighted in blue with arrows depicting the likely direction of the pertubation. (Reprinted from Braunwald E. Regulation of the circulation. I. N Engl J Med 1974;290:1129, with permission.)

TABLE 10–1. Major Shock Classifications and Etiologies[2,49]

I. Hypovolemic
- *Hemorrhagic*
  - Trauma
  - Gastrointestinal
- *Non-hemorrhagic (dehydration)*
  - Vomiting
  - Diarrhea

II. Cardiogenic
- Myocardial infarction
- Septal wall rupture
- Acute mitral valve regurgitation
- Myocarditis
- Pericardial tamponade
- Arrhythmias

III. Obstructive
- Pulmonary embolism
- Amniotic fluid embolism
- Tumor embolism

IV. Distributive
- Sepsis
- Anaphylactic
- Neurogenic (spinal trauma)

associated compensatory response is also essential in terms of treatment and monitoring. Hypovolemic shock is considered to be essentially a profound deficit in preload. Preload is defined as the volume in the left ventricle at the end of diastole. Decreased preload results in subsequent decreases in SV, CO, and eventually, **mean arterial pressure** (MAP). As such, restoration of preload becomes an overriding goal in the management of hypovolemic shock.

The prognosis of shock patients depends on several variables including severity, duration, underlying etiology, preexisting organ dysfunction, and reversibility.[2] Data are not readily available as to the incidence of hypovolemic shock, although mortality rates have been reported as high as 30% to 40% in trauma patients.[3]

PATHOPHYSIOLOGY

The total amount of water in a typical 70 kg (154 lb) adult is approximately 42 liters (Fig. 10–2).[4] About 28 of the 42 liters are inside the cells of the body (intracellular fluid) while the remaining 14 liters are in the extracellular fluid space (fluid outside of cells: interstitial fluid and plasma). Circulating blood volume for a normal adult is roughly 5 liters (70 mL/kg) and is comprised of 2 liters of red blood cell fluid (intracellular) and 3 liters of plasma (extracellular).❶ *By definition, hypovolemic shock occurs as a consequence of inadequate intravascular volume to meet the oxygen and metabolic needs of the body.* Diminished intravascular volume can result from severe external or internal bleeding, profound fluid losses from gastrointestinal sources such as diarrhea or vomiting, or urinary losses such as diuretic use, diabetic ketoacidosis, or diabetes insipidus (Table 10–1).[2] Other sources of intravascular fluid loss can occur through damaged skin, as

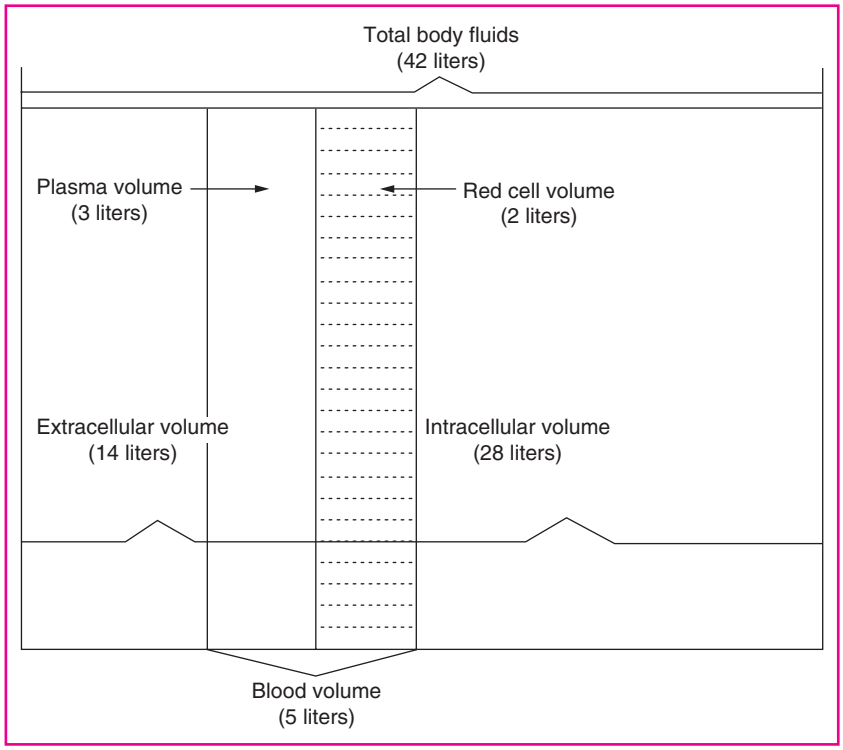


FIGURE 10–2. Distribution of body fluids showing the extracellular fluid volume, intracellular body fluid volume, and total body fluids in a 70 kg adult. Extracellular volume (ECV) comprises 14 liters of total body fluid (42 liters). Plasma volume makes up approximately 3 liters of the 14 liters of ECV. Intracellular volume accounts for the remaining 28 liters of total body fluids with roughly 2 liters being located within the red blood cells. Blood volume (approximately 5 liters) is also depicted and is made up of primarily red blood cells and plasma. (Reprinted from Guyton AC, Hall JE. *Textbook of Medical Physiology*. 8th ed. Philadelphia: Saunders, 1991: 275, with permission.)

seen with burns, or via "**capillary leak**" into the interstitial space or peritoneal cavity, as seen with edema or ascites. This latter phenomenon is often referred to as "third spacing" since fluid accumulates in the interstitial space disproportionately to the intracellular and extracellular fluid spaces. Regional ischemia may also develop as blood flow is naturally shunted from organs such as the gastrointestinal tract or the kidneys to more immediately vital organs such as the heart and brain.

Hypovolemic shock symptoms begin to occur with decreases in intravascular volume in excess of 750 mL or 15% of the circulating blood volume (20 mL/kg in pediatric patients).[5] As previously outlined, decreases in preload or left ventricular end-diastolic volumes result in decreases in SV. Initially, CO may be partially maintained by compensatory tachycardia. Similarly, reflex increases in SVR and myocardial contractility may attenuate arterial hypotension. This neurohumoral response to hypovolemia is mediated by the sympathetic nervous system in an attempt to preserve perfusion to vital organs such as the heart and brain (Fig. 10–3). Two major endpoints of this response are to conserve water to maximize intravascular volume and to improve tissue perfusion by increasing blood pressure and CO (oxygen delivery). The body attempts to maximize its fluid status by decreasing water and sodium excretion through release of antidiuretic hormone, aldosterone, and cortisol. Blood pressure is maintained by peripheral vasoconstriction mediated by catecholamine release and the renin-angiotensin system. Cardiac output is augmented by catecholamine release and fluid retention.[6] However, when intravascular volume losses exceed 1500 mL, the compensatory mechanisms are inadequate, typically resulting in a fall in CO and arterial blood pressure, while acute losses greater than 2000 mL are life-threatening (35 mL/kg in pediatric patients).[6] The decrease in CO results in a diminished delivery of oxygen to tissues within the body. Oxygen delivery can be further compromised by inadequate blood hemoglobin levels due to hemorrhage and/or diminished hemoglobin saturation due to impaired ventilation. Decreased delivery of oxygen and other vital nutrients results in diminished production of the energy substrate, adenosine triphosphate (ATP). Lactic acid is then produced as a by-product of anaerobic metabolism within tissues throughout the body.[7] Hyperglycemia produced during the stress response from cortisol release is also a contributing factor in the development of **lactic acidosis**. Lactic acidosis indicates that inadequate tissue perfusion has occurred.[7] Intracellularly, organelles such as endoplasmic reticulum and mitochondria begin to swell. Eventually, lysosomal rupture that releases degradative enzymes into the cell and abnormal calcium deposition contribute to cellular damage. Reactive oxygen species may also have a role in facilitating cellular damage, especially when organs are reperfused with blood and fluids after the initial hemorrhage.[2] The degree to which irreparable cellular damage has occurred will largely determine the reversibility of the shock event.

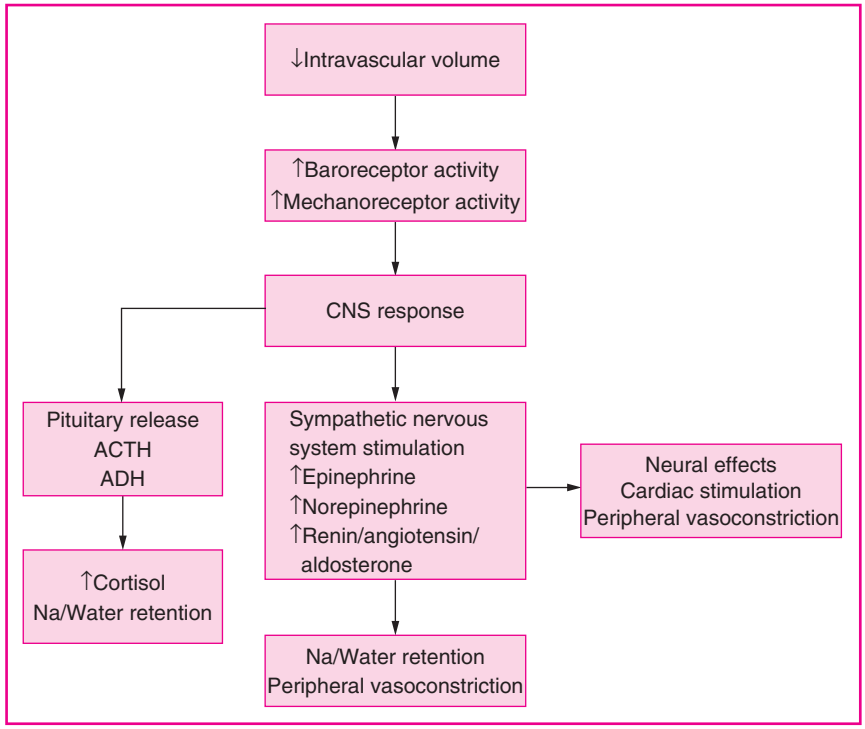


FIGURE 10–3. Expected neurohumoral response to hypovolemia. ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; CNS, central nervous system; Na, sodium. (Reprinted from Jimenez EJ. Shock. In: Civetta JM, Taylor RW, Kirby RR, eds. Critical Care. New York: Lippincott-Raven; 1997: 369, with permission.)

❷ *Protracted tissue hypoxia sets in motion a downward spiral of events secondary to organ dysfunction and eventual failure if untreated.*[5] Table 10–2 describes the effects of shock on the body's major organs. Relative failure of more than one organ, regardless of etiology, is referred to as the **multiple organ dysfunction syndrome** (MODS). Involvement of the heart is particularly devastating considering the central role it plays in oxygen delivery and the potential for myocardial dysfunction to perpetuate the shock state. Preexisting organ dysfunction can also exacerbate the effects of hypovolemic shock and its complications. For example, acute or chronic heart failure can lead to pulmonary edema, further aggravating gas exchange in the lungs and, ultimately, tissue hypoxia. MODS develops in approximately 20% of trauma patients who require fluid resuscitation. Only about one-third of early-onset MODS is quickly reversible (within 48 hours) with proper fluid resuscitation. Thus, it is imperative that hypovolemic shock be treated quickly to avoid MODS.[8]



Clinical Presentation and Diagnosis

General

Patients will be in acute distress although symptoms and signs will vary depending on the severity of the hypovolemia and whether the etiology is hemorrhagic versus non-hemorrhagic.

Symptoms

- Thirst
- Weakness
- Lightheadedness

Signs

- Hypotension, arterial SBP (systolic blood pressure) less than 90 mm Hg or fall in SBP greater than 40 mm Hg
- Tachycardia
- Tachypnea
- Hypothermia
- **Oliguria**
- Dark, yellow-colored urine
- Skin color: pale to ashen; may be cyanotic in severe cases
- Skin temperature: cool to cold
- Mental status: confusion to coma
- **Pulmonary artery catheter** measurements: decreased CO, decreased SV, increased SVR, low PAOP (pulmonary artery occlusion pressure)

Laboratory Tests

- Hypernatremia
- Elevated serum creatinine
- Elevated blood urea nitrogen
- Decreased hemoglobin/hematocrit (hemorrhagic hypovolemic shock)
- Hyperglycemia
- Increased serum lactate
- Decreased arterial pH

TABLE 10–2. Shock Manifestations on Major Organs

Heart	
	• Myocardial ischemia
	• Dysrhythmias
Brain	
	• Restlessness, confusion, obtundation
	• Global cerebral ischemia
Liver	
	• Release of liver enzymes
	• Biliary stasis
Lungs	
	• Pulmonary edema
	• Acute respiratory distress syndrome (ARDS)
Kidneys	
	• Oliguria
	• Decreased glomerular filtration
	• Acute renal failure
Gastrointestinal tract	
	• Stress-related mucosal disease
	• Bacterial translocation

TREATMENT

Desired Outcomes

❸ *The overarching goals in treating hypovolemic shock are to restore effective circulating blood volume, as well as manage its underlying cause. In achieving this goal, the downward spiral of events that can perpetuate severe or protracted hypovolemic shock is interrupted.*[2] *This is accomplished through the delivery of adequate oxygen and metabolic substrates such as glucose and electrolytes to the tissues throughout the body that will optimally bring about a restoration of organ function and return to homeostasis.* Evidence of the latter is a return to the patient's baseline **vital signs,** relative normalization of laboratory test results, and alleviation of the other signs and symptoms of hypovolemic shock previously discussed.[9] Concurrent supportive therapy is also warranted to avoid exacerbation of organ dysfunction associated with the hypovolemic shock event.

General Approach to Therapy

Securing an adequate airway and ventilation is imperative in hypovolemic shock patients consistent with the "ABCs" (airway, breathing, and circulation) of life support. Any compromise in ventilation will only accentuate the tissue hypoxia occurring secondary to inadequate perfusion. Thus, tracheal intubation and mechanical ventilation may be needed (Fig. 10–4). Intravenous access is also essential for administration of intravenous fluids and medications. Intravenous access can be accomplished through the placement of peripheral intravenous lines or catheterization with central venous lines if rapid or large volumes of resuscitative fluids are indicated. While primarily facilitating fluid administration, the intravenous lines provide access for blood samples for obtaining

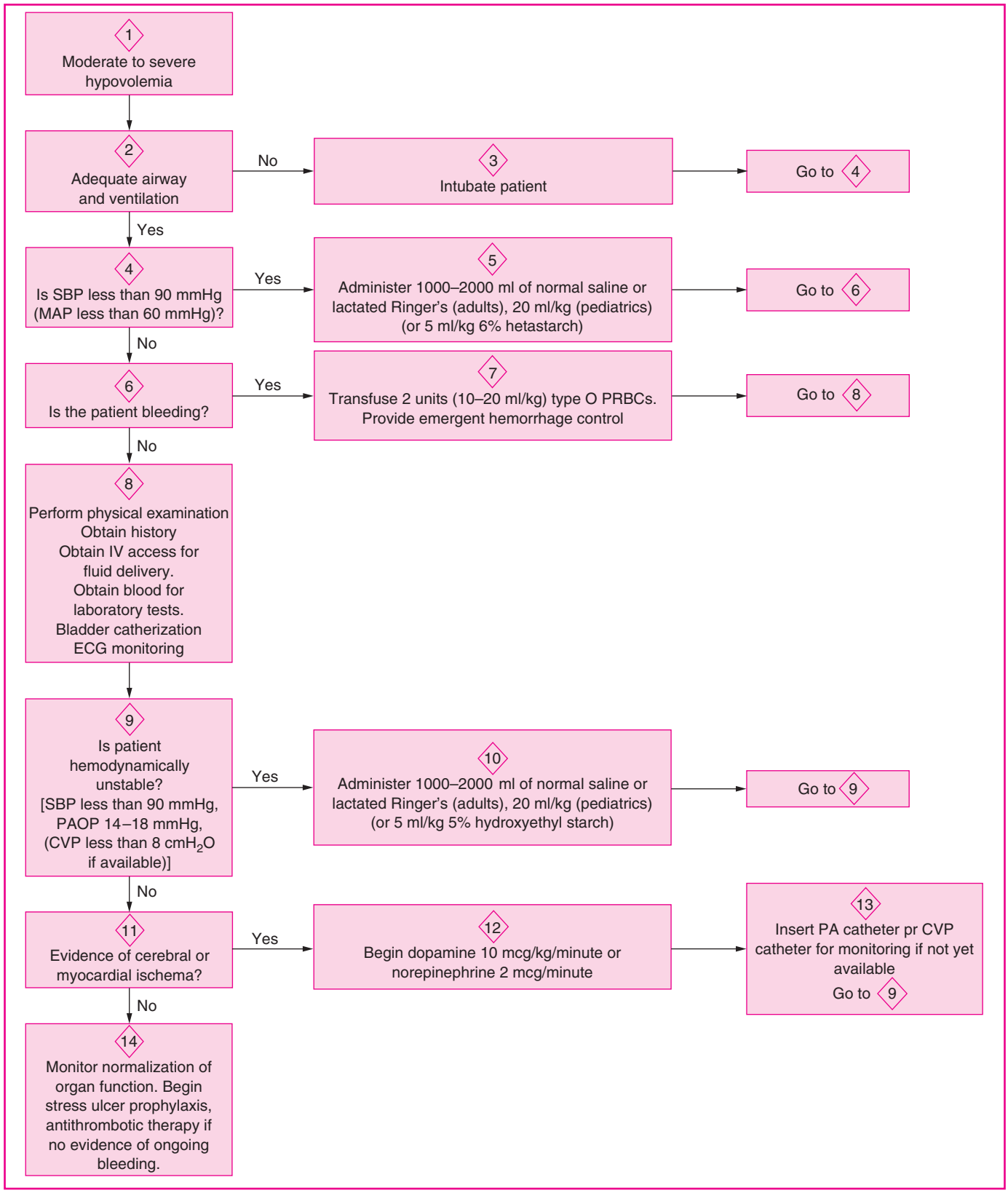


FIGURE 10–4. Treatment algorithm for the management of moderate to severe hypovolemia. BP, blood pressure; CVP, central venous pressure; ECG, electrocardiogram; MAP, mean arterial pressure; PA, pulmonary artery; PAOP, pulmonary artery occlusion pressure; PRBCs, packed red blood cells; SBP, systolic blood pressure.

appropriate laboratory tests. Placement of an arterial catheter is advantageous to allow for accurate and continual monitoring of blood pressure, as well as arterial blood gas (ABG) sampling. A bladder catheter should be inserted for ongoing monitoring of urine output. Baseline laboratory tests that should be done immediately include: complete blood cell counts with differentials, platelet count, serum chemistry profile, liver enzymes, prothrombin and partial thromboplastin times, and serum lactate. A urinalysis and an ABG should also be obtained and ongoing electrocardiogram (ECG) monitoring should be performed. In addition to restoring circulating blood volume, it is necessary to prevent further losses from the vascular space. This is especially true with hemorrhagic hypovolemic shock where identifying the bleeding site and achievement of hemostasis are critical in the successful resuscitation of the patient. This frequently involves surgical treatment of hemorrhages. Similarly, other types of shock may also require interventions that treat the underlying cause of hypovolemia, such as epinephrine to treat anaphylactic shock.

Upon stabilization, placement of a pulmonary artery (PA) catheter may be indicated based on the need for more extensive cardiovascular monitoring than is available from noninvasive measurements such as vital signs, cardiac rhythm, and urine output.[9,10] Key measured parameters that can be obtained from a PA catheter are the pulmonary artery occlusion pressure, which is a measure of preload, and CO. From these values and simultaneous measurement of HR and blood pressure (BP), one can calculate the left ventricular SV and SVR.[10] Placement of a PA catheter should be reserved for patients at high risk of death due to the severity of shock or preexisting medical conditions such as heart failure.[11] Use of PA catheters in broad populations of critically ill patients is somewhat controversial because clinical trials have not shown consistent benefits with their use.[12–14] However, critically ill patients with a high severity of illness may have improved outcomes from PA catheter placement. It is not clear why this was seen, but it could be that more severely ill patients have less physiologic reserve and less "room for error" and benefit from the therapeutic decisions that come from detailed PA catheter data.[15] The goal of resuscitating patients to supra-normal hemodynamic values (e.g., cardiac index [CI] greater than 4.5 L/minute per square meter) has also been controversial, but does not appear to be beneficial for most patients.[16] An alternative to the PA catheter is placement of a central venous catheter that typically resides in the superior vena cava to monitor central venous pressure (CVP). While central venous catheters are less expensive and more readily placed, they are not particularly accurate in monitoring effective fluid resuscitation.



Patient Encounter, Part 1

TJ is a 21-year-old male who is admitted to the emergency department (ED) after being stabbed in the leg during an assault. The paramedics report a large amount of blood loss at the scene from a probable blood vessel injury. The acute bleeding has been partially stabilized with pressure but the patient has just lost consciousness. The initial diagnosis by the ED team is hypovolemic shock. A physical exam is being performed and blood samples are being sent to the laboratory.

- What type of hypovolemic shock does TJ have?
- What signs and symptoms of hypovolemic shock would you expect to see in TJ?
- What laboratory abnormalities might be expected in TJ?

Fluid Therapy

❹ *Three major therapeutic options are available to clinicians for restoring circulating blood volume: blood products,* ***crystalloids*** *(electrolyte-based solutions), and colloids (large-molecular-weight solutions).* Blood products are used only in instances involving hemorrhage (or severe preexisting anemia), thus leaving crystalloids and colloids as the mainstay of therapy in all types of hypovolemic shock, along with adjunctive **vasopressor** support. The aggressiveness of fluid resuscitation (rate and volume) will be dictated by the severity of the hypovolemic shock and the underlying cause. Warming of all fluids to 37°C (98.6°F) prior to administration is an important consideration to prevent hypothermia, since hypothermia will have a negative impact on the success of the resuscitation effort.[17]

Crystalloids

Conventional, "balanced" crystalloids are fluids with (1) electrolyte composition that approximates plasma, such as lactated Ringer's (LR), or (2) a total calculated osmolality similar to that of plasma (280 to 295 mOsm/kg), such as 0.9% sodium chloride (also known as normal saline [NS] or 0.9% NaCl) (Table 10–3).[18] Thus, conventional crystalloids will distribute in normal proportions throughout the extracellular fluid space upon administration. In other words, expansion of the intravascular space will only increase by roughly 200 to 250 mL for every liter of isotonic crystalloid fluid administered.[18] Hypertonic crystalloid solutions such as 3% NaCl or 7.5% NaCl have osmolalities substantially higher than plasma. The effect observed with these fluids is a relatively larger volume expansion of the intravascular space. By comparison to conventional crystalloids, administration of 1 liter of 3% sodium chloride will result in an intravascular space increase of 1000 mL.[18] This increase is a result of the fluid administered as well as osmotic drawing of intracellular fluid into the intravascular and interstitial spaces. This occurs because the hypertonic saline increases the osmolality of the intravascular and interstitial fluid compared to the intracellular fluid. Hypertonic saline also has the potential for decreasing the inflammatory response.[19] Despite these theoretical advantages, data are lacking demonstrating

TABLE 10–3. Composition of Common Resuscitation Fluids[18]

Fluid	Na mEq/L[a]	Cl mEq/L[a]	K mEq/L[a]	Mg mEq/L[b]	Ca mEq/L[b]	Lactate mEq/L[a]	Other	pH	Osmolality mOsm/kg[c]
0.9 NaCl	154	154						5.0	308
3% NaCl	513	513						5.0	1027
7.5% NaCl	1283	1283						5.0	2567
Lactated Ringer's	130	109	4		3	28			
Hextend	143	124	3	0.9	5	28	Hetastarch 6 g/dL	5.9	307
Hetastarch	154	154					Hetastarch 6 g/dL	5.5	310
Pentastarch	154	154					Pentastarch 10 g/dL	5.0	326
5% Albumin	130–160	130–160					Albumin 5 g/dL (50 g/dL)	6.9	
25% Albumin	130–160	130–160					Albumin 25 g/dL (250 g/L)	6.9	
5% Plasma protein fraction (PPF)	130–160	130–160	0.25				Plasma Proteins 5 g/dL (50 g/L) (88% albumin)	7.0	
Dextran 40	154	154					Dextran 10 g/dL (avg. molecular weight 40 kDa)		
Dextran 70	154	154					Dextran 6 gm/dL (avg. molecular weight 70 kDa)	5.5	308
Dextran 75	154	154					Dextran 6 gm/dL (avg. molecular weight 75 kDa)	5.5	308

[a]For these values, mEq/L = mmol/L; e.g., 154 mEq/L Na = 154 mmol/L.
[b]For these values, mEq/L × 0.5 = mmol/L; e.g., 0.9 mEq/L Mg = 0.45 mmol/L Mg.
[c]For this value, mOsm/kg = mmol/kg; e.g., 308 mOsm/kg = 308 mmol/kg.
avg., average; Ca, calcium; Cl, chloride; K, potassium; kDa, kilodalton; Mg, magnesium; Na, sodium.

superiority of hypertonic crystalloid solutions compared with isotonic solutions.[20] Crystalloids are generally advocated as the initial resuscitation fluid in hypovolemic shock because of their availability, low cost, and equivalent outcomes compared with colloids.[9] A reasonable initial volume of an isotonic crystalloid (0.9% NaCl or LR) in adult patients is 1000 to 2000 mL administered over the first hour of therapy. Ongoing external or internal bleeding will require more aggressive fluid resuscitation. ❺ *In the absence of ongoing blood loss, administration of 2000 to 4000 mL of isotonic crystalloid will normally re-establish baseline vital signs in adult hypovolemic shock patients.*[2] Selected populations, such as burn patients, may require more aggressive fluid resuscitation, while other patient subsets such as those with cardiogenic shock or heart failure may warrant less aggressive fluid administration to avoid over-resuscitation.[21] In hemorrhagic shock patients, approximately three to four times the shed blood volume of isotonic crystalloids is needed for effective resuscitation.[21,22]

Side effects from crystalloids primarily involve fluid overload and electrolyte disturbances of sodium, potassium, and chloride.[23] Dilution of coagulation factors can also occur resulting in a dilutional coagulopathy.[24] Two clinically significant reasons LR is different from NS is that LR contains potassium and has a lower sodium content (130 versus 154 mEq/L or mmol/L). Thus, LR has a greater potential than NS to cause hyponatremia and/or hyperkalemia. Alternatively, NS can cause hypernatremia and hypokalemia. While LR does contain lactate, it does not result in increases in serum lactate when used for fluid replacement.[25] This is likely because the exogenous lactate is used as a metabolic substrate. Overall, there is no clear cut advantage when comparing NS and LR. Clinician preference and the patient's serum electrolyte concentrations will usually guide selection.

Colloids

Understanding the effects of colloid administration on circulating blood volume necessitates a review of those physiologic forces that determine fluid movement between capillaries and the interstitial space throughout the circulation (Fig. 10–5).[4] Relative hydrostatic pressure between the capillary lumen and the interstitial space is one of the major determinants of net fluid flow into or out of the circulation. The other major determinant is the relative colloid osmotic pressure between the two spaces. Administration of exogenous colloids results in an increase in the intravascular colloid osmotic pressure. In the case of isosomotic colloids (5% albumin, 6% hetastarch, and dextran products), initial expansion of the intravascular space is essentially that of the volume of colloid administered. In the case of hyperoncotic solutions such as 25% albumin, fluid is pulled from the interstitial space into the vasculature

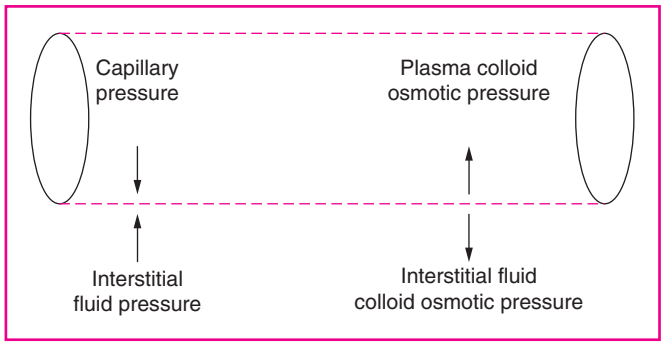


FIGURE 10–5. Operative forces at the capillary membrane tending to move fluid either outward or inward through the capillary membrane. In hypovolemic shock, one therapeutic strategy is the administration of colloids that can sustain and/or draw fluid from the interstitial space by increasing the plasma colloid osmotic pressure. (Reprinted from Guyton AC, Hall JE. *Textbook of Medical Physiology*. 8th ed. Philadelphia: Saunders, 1991: 174, with permission.)

resulting in an increase in the intravascular volume that is much greater than the original volume of the 25% albumin that was administered. While theoretically attractive, hyperoncotic solutions should not be used for hypovolemic shock since the expansion of the intravascular space is at the expense of depletion of the interstitial space. The effects of colloids on intravascular volume are a consequence of their relatively large molecular size (greater than 30 kilodaltons [kDa]), limiting their passage across the capillary membrane in large amounts except under conditions in which capillary permeability may be increased such as during a "capillary leak." Examples of the latter, situations in which colloids may be less effective as intravascular volume expanders, include any condition involving the systemic inflammatory response syndrome (SIRS) such as trauma, sepsis, and pancreatitis.[2] Nonetheless, under circumstances in which capillary permeability is normal, colloids can be thought of as "sponges" drawing fluid into the intravascular space from the interstitial space. ❻ *Thus, the volume of colloid administered remains primarily confined to the intravascular space, in contrast to isotonic crystalloid solutions that distribute throughout the extracellular fluid space.* Eventually, the exogenous colloids will migrate to the interstitial space diminishing the expansion in intravascular volume. Exogenous colloids available in the United States include 5% albumin, 25% albumin, 5% plasma protein fraction (PPF), 6% hetastarch, 10% pentastarch, 10% dextran 40, 6% dextran 70, and 6% dextran 75 (Table 10–3). The first three products are derived from pooled human plasma. Hetastarch and pentastarch are semisynthetic hydroxyethyl starches derived from amylopectin. The dextran products are semisynthetic glucose polymers that vary in terms of the average molecular weight of the polymers. Superiority of one colloid solution over another has not been clearly established.[26]

For years within the critical care literature a controversy known as the "colloid versus crystalloid debate" raged over the relative merits of the two types of resuscitation fluids. At the center of the debate was what the goal of fluid resuscitation in shock should be: immediate expansion of the intravascular space with colloids versus expansion of the entire extracellular fluid space with crystalloids. A meta-analysis showed no difference in outcomes between crystalloids and albumin.[27] However, the balance was tipped in favor of those advocating crystalloids after a meta-analysis performed by the Cochrane group revealed a relative increase in mortality in all shock patients receiving albumin versus crystalloids.[28] This increased risk was not statistically significant when only comparing studies of hypovolemic shock patients.[28] A more recent randomized controlled study involving 6997 critically ill patients [Saline versus Albumin Fluid Evaluation (SAFE) Study] challenged the overall Cochrane findings by demonstrating no difference in mortality between patients receiving saline versus albumin.[28,29] Largely in response to the SAFE trial, the Food and Drug Administration (FDA) issued a revised notice to health care providers in May 2005 declaring albumin safe for use in most critically ill patients. Burn, traumatic brain injury, and septic shock patients were excluded from the SAFE trial; however, based on previous data there does not appear to be a clear-cut overall advantage for either crystalloids or colloids in these patient groups.[30] Thus, while the debate is not fully resolved, most clinicians today prefer using crystalloids based on their availability and inexpensive cost compared with colloids.[21,31]

Generally, the major adverse effects associated with colloids are fluid overload, dilutional coagulopathy, and anaphylactoid/anaphylactic reactions.[24,32] Although derived from pooled human plasma, there is no risk of disease transmission from commercially available albumin or PPF products since they are heated and sterilized by ultrafiltration prior to distribution.[24] Because of direct effects on the coagulation system with the hydroxyethyl starch and dextran products, they should be used cautiously in hemorrhagic shock patients. This is another reason why crystalloids may be preferred in hemorrhagic shock. Furthermore, hetastarch can result in an increase in amylase not associated with pancreatitis. As such, the adverse-effect profiles of the various fluid types should also be considered when selecting a resuscitation fluid.

Blood Products

❼ *Blood products are indicated in hypovolemic shock patients who have sustained blood losses from hemorrhage exceeding 1500 mL (30 to 35 mL/kg).* This, in fact, is the only setting in which freshly procured whole blood is administered. In virtually all other settings, blood products are given as the individual components of whole blood units, such as packed red blood cells (PRBCs), fresh frozen plasma (FFP), platelets, cryoprecipitate, and concentrated coagulation factors.[33,34] This includes ongoing resuscitation of hemorrhagic shock, when PRBCs can be transfused to increase oxygen-carrying

capacity in concert with crystalloid solutions to increase blood volume. In patients with documented coagulopathies, FFP for global replacement of lost or diluted clotting factors, or platelets for patients with severe thrombocytopenia (less than 20,000 cells/m^3 [$20 \times 10^3/\mu L$ or $20 \times 10^9/L$]) should be administered.[34] Type O blood or "universal donor blood" is given in emergent cases of hemorrhagic shock. Thereafter, blood that has been typed and cross-matched with the recipient's blood is given. The traditional threshold for PRBC transfusion in hypovolemic shock has been a serum hemoglobin of less than 10 g/dL (100 g/L or 6.2 mmol/L) and hematocrit less than 30%.[35] However, a more restrictive transfusion threshold of 7 g/dL (70 g/L or 4.34 mmol/L) appears to be safe for critically ill patients after they have received appropriate fluid resuscitation and have no signs of ongoing bleeding. Traditional risks from allogenic blood product administration include hemolytic and non-hemolytic transfusion reactions and transmission of blood-borne infections in contaminated blood. However, recent large studies have also shown that transfusions are associated with higher mortality, possibly because of adverse immune and inflammatory effects.[36,37] Based on limitations of homologous blood donations, intraoperative salvage techniques can be employed in patients with massive hemorrhage in an effort to conserve blood.[5,38]

Due to blood shortages and associated risks with transfusions, there are ongoing research efforts concerning the development of red blood cell substitutes as a possible therapy alternative. Products that have reached clinical trials include perfluorocarbon emulsions and hemoglobin-based oxygen carriers (HBOCs).[39,40] These blood products have several advantages over PRBCs including greater availability (because donors aren't needed), increased shelf-life, absence of infectious risks, and no need for cross-matching. As such, red blood cell substitutes have the potential to serve as temporizing measures in hypovolemic shock patients until conventional red blood cell transfusions can be administered or in instances in which availability of donated PRBCs is extremely limited. Nonetheless, lack of adequate efficacy data and additional side effects associated with each of the respective red blood cell substitutes have precluded their approval in the United States at present.

Research also continues into the use of recombinant activated factor VII (rFVIIa) as an adjunctive agent to treat uncontrolled hemorrhage. Initial experiences with rFVIIa show that it can decrease transfusions, though large studies have not been performed.[41] Ultimately, pharmacoeconomic analyses of rFVIIa will be needed because of the very high acquisition costs of the drug.

Pharmacologic Therapy

Vasopressor Therapy

Vasopressor is the term used to describe any pharmacologic agent that can induce arterial vasoconstriction through stimulation of the α_1-adrenergic receptors. 8 *While replenishment of intravascular volume is undoubtedly the cornerstone of hypovolemic shock therapy, use of vasopressors may be warranted as a temporary measure in patients with profound hypotension or evidence of organ dysfunction in the early stages of shock.*[2,9,42] Often vasopressors are used concurrently with fluid administration. Table 10–4 is a list of those vasopressors used in the management of hypovolemic shock. Dopamine or norepinephrine may be preferred over epinephrine because epinephrine has an increased potential for causing cardiac arrhythmias and impaired abdominal organ (splanchnic) circulation.[43] In cases involving concurrent heart failure, an inotropic agent such as dobutamine may be needed, in addition to the use of a vasopressor. Patients with spinal shock may require some level of vasopressor and/or inotropic support even after adequate fluid resuscitation.

Vasopressors are almost exclusively administered as continuous infusions because of their very short half-lives and the need for close titration of their dose-related effects. Starting doses should be at the lower end of the dosing range followed by rapid titration upward if needed to maintain adequate blood pressure. Monitoring of end-organ function such as adequate urine output can also be used to monitor therapy. Once blood pressure is restored, vasopressors should be weaned and discontinued as soon as possible to avoid any untoward events. The most significant systemic adverse events associated with vasopressors are excessive vasoconstriction resulting in decreased organ perfusion and potential to induce arrhythmias (Table 10–4). Central venous catheters should be used to minimize the risk of local tissue necrosis that can occur with extravasation of peripheral intravenous catheters.[42]

Treatment of Lactic Acidosis

Lactic acidosis, which typically accompanies hypovolemic shock as a consequence of tissue hypoxia, is best treated by reversal of the underlying cause. Administration of alkalizing agents such as sodium bicarbonate has not been demonstrated to have any

TABLE 10–4. Vasopressor Drugs

Drug	Usual IV Dose	Adrenergic Effects			Potential to Cause Arrhythmias
		α_1	β_1	Dopaminergic	
Dopamine	10–20 mcg/kg per minute[a]	+++	++	+++	+++
Norepinephrine	0.5–80 mcg/minute	+++	++	0	++
Epinephrine	1–200 mcg/minute	++	+++	0	+++
Phenylephrine	0.5–9 mcg/kg per minute	+++	0	0	0

IV, intravenous.
[a]Note: Lower dosages of dopamine may not produce desired α_1-adrenergic (vasopressor) effects.

beneficial effects[44] and may actually worsen intracellular acidosis.[45] Nonetheless, administration of sodium bicarbonate, 100 to 150 mEq intravenously, can be considered when the pH is below 7.1.[2] An alternative to sodium bicarbonate is the proton acceptor tromethamine (i.e., tris-hydroxymethyl aminomethane, or THAM). THAM has the advantage over sodium bicarbonate in buffering lactic acidosis without increasing sodium concentrations or fostering the production of additional carbon dioxide.[46,47] This could be particularly advantageous in hypovolemic shock patients with respiratory failure who may have a difficult time clearing carbon dioxide from their lungs. However, there are no large studies evaluating THAM for treating metabolic acidosis. If used, the initial dose of THAM can be determined by the following equation: amount (in milliliters) of 0.3 mol/L THAM = lean body weight (kg) × base deficit (mmol/L).[47] THAM should not be used in patients with renal failure.



Patient Encounter, Part 2: Physical Exam, Diagnostic Tests, and Initial Treatment

PMH
Non-contributory

Meds
None

SH
Occasional alcohol use (per family)

FH
Non-contributory

PE
Ht 5′10″ (178 cm), Wt 85 kg (187 lb)

VS: BP 80/40 mm Hg, pulse 130/minute, respiratory rate 22 beats per minute, temperature 35°C (95°F), urine output: none since catheterization 10 minutes ago.
Neurologic: Recent loss of consciousness, had been conscious but confused during transport to the ED, pupils equal and reactive
Pulmonary: Normal breath sounds, undergoing tracheal intubation for mechanical ventilation
CV: ECG shows sinus tachycardia, otherwise normal
Abd: Within normal limits
Exts: Stab wound to left thigh with some ongoing bleeding

Pertinent labs
pH 7.18, P_{CO_2} 45 mm Hg (5.985 kPa), Pa_{O_2} 70 mm Hg (9.31 kPa), HCO_3 18 mEq/L (18 mmol/L), lactate 7.0 mg/dL (0.777 mmol/L), SCr 1.7 mg/dL (150 μmol/L), Hgb 7 g/dL (70 g/L or 4.34 mmol/L), Hct 21%

- What are the first nonpharmacologic steps in treating TJ?
- Identify treatment goals for TJ in the next 24 hours.
- What initial pharmacologic/fluid therapy is required at this time?

Supportive Care Measures

Since gastrointestinal ischemia is a common complication of hypovolemic shock, prevention of stress-related mucosal disease should be instituted as soon as the patient is stabilized. The most common agents used for stress ulcer prophylaxis are the histamine$_2$-receptor antagonists and proton pump inhibitors. Prevention of thromboembolic events is another secondary consideration in hypovolemic shock patients. This can be accomplished with the use of external devices such as sequential compression devices and/or antithrombotic therapy such as the low-molecular-weight heparin products or unfractionated heparin. Patients with adrenal insufficiency due to preexisting disease, glucocorticoid use, or critical illness may have refractory hypotension despite resuscitation. Such patients should receive appropriate glucocorticoid replacement therapy.

OUTCOME EVALUATION

❾ *Successful treatment of hypovolemic shock is measured by the restoration of blood pressure to baseline values and reversal of associated organ dysfunction. The likelihood of a successful fluid resuscitation will be directly related to the expediency of treatment. Therapy goals include:*

- *Arterial systolic blood pressure greater than 90 mm Hg (MAP greater than 60 mm Hg) within 1 hour;*
- *Organ dysfunction reversal evident by increased urine output to greater than 0.5 mL/kg per hour (1.0 mL/kg per hour in pediatrics), return of mental status to baseline, and normalization of skin color and temperature over the first 24 hours;*
- *Heart rate should begin to decrease reciprocally to increases in the intravascular volume within minutes to hours;*
- *Normalization of laboratory measurements expected within hours to days following fluid resuscitation. Specifically, normalization of base deficit and serum lactate is recommended within 24 hours to potentially decrease mortality;[48] and*
- *Achievement of PAOP to a goal pressure of 14 to 18 mm Hg occurs (alternatively CVP 8 to 15 mm Hg).*



Patient Encounter, Part 3: Care Plan/Ongoing Therapy

One hour after the initial fluid bolus and transfusion TJ's vital signs are:
BP 85/50 mm Hg, HR 120 beats per minute, RR 20/minute, urine output: 5 mL in the past hour. Pertinent new labs: pH 7.2, lactate 3.8 mg/dL (0.422 mmol/L). The bleeding has stopped.

- What is your assessment of TJ's condition compared to 1 hour ago?
- What therapy is required at this time?
- Describe monitoring over the next 24 hours for TJ.



Patient Care and Monitoring

1. Does the patient have an adequate airway and ventilation (hemoglobin saturation greater than 92%)? If not, trained emergency personnel should consider performing tracheal intubation with initiation of mechanical ventilation.
2. Is there a detectable blood pressure? If yes, obtain history, perform physical examination, obtain blood for baseline laboratory tests, and monitor ECG. If not, begin isotonic crystalloid fluid resuscitation immediately (see step 4 below).
3. Monitor the following serial laboratories for comparison to baseline values every 6 hours in the first 24 hours and daily thereafter until normalized: sodium, serum creatinine, blood urea nitrogen, serum lactate, glucose, bilirubin, hemoglobin, hematocrit, platelets, prothrombin time, partial thromboplastin time, arterial blood gases, and pH.
4. Is the systolic blood pressure less than 90 mm Hg (MAP less than 60 mm Hg)? If yes, start aggressive fluid therapy beginning with 1000 to 2000 mL lactated Ringer's over 1 hour in adults (20 mL/kg in pediatrics). Monitor blood pressure at least every 15 minutes (or continuously via an arterial catheter).
5. Is the patient bleeding? If yes, transfuse 5 to 10 mL/kg PRBCs (note: 1 unit PRBCs will provide approximately 3% increase in hematocrit or 1 g/dL [10 g/L or 0.62 mmol/L] increase in hemoglobin). Do not allow hemoglobin concentrations to fall below 7 g/dL (70 g/L or 4.34 mmol/L) (hematocrit 20%). Conventional goal hemoglobin concentration is 10 g/dL (100 g/L or 6.2 mmol/L) (alternatively hematocrit greater than or equal to 30%). Provide emergent control of ongoing hemorrhaging.
6. Is there evidence of cerebral or myocardial ischemia? If yes, begin vasopressor therapy of dopamine 10 mcg/kg per minute or norepineprhine 2 mcg/minute. Titrate dosage every 5 minutes as needed. Wean and discontinue vasopressor as soon as the goal arterial blood pressure has been achieved.
7. Has the goal arterial blood pressure been achieved? If not, give additional fluid therapy hourly blending crystalloids and isooncotic colloids based on inadequate blood pressure response.
8. Is the patient hemodynamically stable? If not, admit to the intensive care unit for ongoing treatment and monitoring. A PA catheter (or CVP catheter) should be inserted by trained medical personnel. Monitor PAOP to a goal pressure of 14 to 18 mm Hg and minimum cardiac index of 2.2 L/minute per square meter (alternatively CVP 8 to 15 cm H_2O).
9. Is the arterial pH less than 7.1? If yes, consider administration of sodium bicarbonate 100 to 150 mEq intravenously as slow infusion. Alternatively, consider use of tromethamine intravenously.
10. Monitor normalization of organ function to baseline state including mental status, urine output to greater than 0.5 mL/kg per hour (1 mL/kg per hour in pediatric patients), normal skin color and temperature, and normalization of base deficit and/or lactate. Begin supportive care measures including stress ulcer prophylaxis and antithrombotic therapy if there is no evidence of ongoing bleeding.
11. Has the underlying cause of the hypovolemic shock been addressed to prevent its recurrence? If not, treat as necessary.
12. Is there any evidence of adverse events from the resuscitation therapies employed such as fluid overload, electrolyte disturbances, transfusion reactions, and/or alterations in coagulation? If yes, manage the particular adverse event accordingly.

ABBREVIATIONS

ABCs: airway, breathing, and circulation
ABG: arterial blood gas
ACTH: adrenocorticotropic hormone
ADH: antidiuretic hormone
ARDS: acute respiratory distress syndrome
ATP: adenosine triphosphate
BP: blood pressure
bpm: beats per minute
Ca: calcium
CI: cardiac index
Cl: chloride
CNS: central nervous system
CO: cardiac output
CVP: central venous pressure
ECG: electrocardiogram
ECV: extracellular volume
ED: emergency department
FDA: Food and Drug Administration
FFP: fresh frozen plasma
HBOC: hemoglobin-based oxygen carrier
HCO_3: bicarbonate
Hct: hematocrit
Hgb: hemoglobin
HR: heart rate
IV: intravenous
K: potassium
kDa: kilodalton
LR: lactated Ringer's
MAP: mean arterial pressure
Mg: magnesium
MODS: multiple organ dysfunction syndrome
Na: sodium

NaCl: sodium chloride
NS: normal saline
PA: pulmonary artery
Pa_{O_2}: partial pressure of arterial oxygen
PAOP: pulmonary artery occlusion pressure
P_{CO_2}: partial pressure of carbon dioxide
PPF: plasma protein fraction
PRBCs: packed red blood cells
rFVIIa: recombinant activated factor VII
RR: respiratory rate
SAFE: Saline versus Albumin Fluid Evaluation Study
SBP: systolic blood pressure
SCr: serum creatinine
SIRS: systemic inflammatory response syndrome
SV: stroke volume
SVR: systemic vascular resistance
THAM: tris-hydroxymethyl aminomethane (tromethamine)

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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11 Asthma

W. Greg Leader



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Explain the pathophysiology of asthma.
2. Identify the goals of asthma management.
3. Classify asthma severity based on asthma symptoms.
4. Recommend environmental control strategies for patients with identified allergies.
5. Educate patients on the use of inhaled drug delivery devices, peak flow monitors, and asthma education plans.
6. Develop a therapeutic plan for patients with chronic asthma that maximizes patient response while minimizing adverse drug events and other drug-related problems.
7. Evaluate current asthma therapy and make changes when necessary.
8. Develop a therapeutic plan for treating patients with acute asthma.

Key Concepts

❶ Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role.
❷ Therapy for chronic asthma is directed at suppressing the underlying inflammatory response and normalizing pulmonary function.
❸ Classification of asthma severity is based on daytime and nighttime symptoms, physical activity, lung function, variability in peak expiratory flow (PEF), and use of reliever medications.
❹ Direct airway administration of asthma medications through inhalation is the most efficient route and minimizes systemic adverse effects.
❺ Inhaled short-acting β_2-agonists are the most effective agents for reversing acute airway obstruction caused by bronchoconstriction.
❻ In persistent asthma, inhaled corticosteroids provide the most comprehensive control of the inflammatory process.
❼ Intensity of pharmacologic therapy is based on the severity of the disease.
❽ Adding a long-acting inhaled β_2-agonist to low-dose inhaled corticosteroids is equally or more effective than doubling the inhaled corticosteroid dose or adding other long-term control medications and decreases the potential for adverse effects.
❾ Excessive use of inhaled short-acting β_2-agonists is an indicator of inadequately controlled asthma.

❶ "*Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role*, in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of **wheezing**, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible spontaneously or with treatment. The inflammation also causes an associated increase in existing airway hyperresponsiveness to a variety of stimuli."[1] Additionally, it is now recognized that airway remodeling may occur, resulting in a fixed or irreversible airway defect.[2,3]

Asthma is a diverse disease that presents in a heterogeneous manner. Severity of chronic disease ranges from mild with intermittent symptoms to severe and disabling if left untreated. Despite variances in the underlying severity of chronic asthma, all asthmatics are at risk of severe acute disease when exposed to the appropriate trigger or if inadequately treated. The National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 2[1] and its subsequent update[2] provide guidelines for the diagnosis and management of asthma. These guidelines emphasize the importance of treating underlying

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airway inflammation as a means of controlling persistent asthma and preventing acute exacerbations of the disease.

EPIDEMIOLOGY AND ETIOLOGY

Asthma is the most common chronic disease of childhood, and it causes significant morbidity and mortality in both adults and children. Approximately 20 million people in the United States carried the diagnosis of asthma in 2002, with Puerto Ricans, non-Hispanic blacks, and Native Americans having a significantly higher prevalence than non-Hispanic whites.[4] Approximately 12 million workdays and 15 million schooldays are missed yearly due to asthma. In 2002, there were 1.9 million emergency department visits and 484,000 hospitalizations for asthma. Children younger than 4 years of age have the highest rate of emergency department visits and hospitalizations. There were approximately 4600 asthma-related deaths in 2002, but the annual mortality rate appears to be decreasing.[4]

Asthma is also a significant economic burden in the United States, costing $12.7 billion in 1998 with direct medical expenditures accounting for 58% of the cost or approximately $7.4 billion.[5] Hospital and emergency department care accounted for 45.1% of the direct medical expenditures, with prescription drugs and physician office visits accounting for 43.3% and 11.6%, respectively. Costs appear to increase with disease severity, and it has been suggested that fewer than 20% of asthma patients account for more than 80% of direct medical expenditures.[5]

Asthma results from a complex interaction of genetic and environmental factors; however, the underlying cause is not well understood. There appears to be an inheritable component, as the presence of asthma in a parent is a strong risk factor for the development of asthma in a child. This risk increases when a family history of **atopy** is also present.[1,3] Approximately 50% of asthma can be attributed to atopy, and atopic asthma is more common in children than adults.[3] Furthermore, atopy in childhood asthma is the strongest prognostic factor for continued asthma as an adult.[1,3]

Genetic factors cannot explain the recent rapid rise in asthma prevalence. Asthma appears to require both genetic predisposition and environmental exposure. Many patients with occupational asthma develop the disease late in life upon exposure to specific allergens in the workplace. Environmental influences in utero or in infancy may contribute to the development of asthma. Maternal smoking during pregnancy or exposure to secondhand smoke after birth increases the risk of childhood asthma.[3] Adult-onset asthma is not uncommon and may be related to atopy, nasal polyps, aspirin sensitivity, occupational exposure, or a recurrence of childhood asthma.

PATHOPHYSIOLOGY

Asthma is characterized by inflammation, airway hyperresponsiveness (AHR), and airway obstruction. Inhaled antigens induce a type 2 T-helper CD4+ (T_H2) response. Antigens are taken up by antigen-presenting cells,[6] and presentation of antigens to T lymphocytes causes activation of the T_H2 type response, leading to B-cell production of antigen-specific immunoglobulin E (IgE) and proinflammatory cytokines and chemokines that recruit and activate eosinophils, neutrophils, and alveolar macrophages.[6,7] Further exposure to the antigen results in cross-linking of cell-bound IgE in mast cells and basophils, causing the release or generation of inflammatory mediators such as histamine, cysteinyl leukotrienes (C_4, D_4, and E_4), and prostaglandins. Activation and degranulation of mast cells and basophils results in an early phase response that involves an acute bronchoconstriction that usually lasts approximately 1 hour after allergen exposure.[6] This early phase response can be blocked by pretreatment with an inhaled β_2-agonist or cromolyn.

In the late phase response, activated airway cells release inflammatory cytokines and chemokines, recruiting inflammatory cells into the lungs. The late phase response occurs 4 to 6 hours after the initial allergen challenge and results in a less intense bronchoconstriction as well as increased airway hyperresponsiveness and airway inflammation.[6]

Airway Inflammation and Hyperresponsiveness

T_H2 lymphocytes are one of the primary factors initiating and perpetuating the inflammatory response.[7] In addition, proinflammatory mediators such as the leukotrienes generated during mast cell degranulation can increase vascular permeability, leading to airway edema and increased mucus production.[8] Eosinophilic infiltration of the airways is a hallmark of asthma, and activated eosinophils can cause bronchoconstriction and AHR.[9]

Airway hyperresponsiveness is defined as the exaggerated ability of the airways to narrow in response to a variety of stimuli. Although AHR exists in patients without asthma, it is a characteristic feature of asthma and appears to be directly related to airway inflammation and the severity of asthma.[1,3] Treatment of airway inflammation with inhaled corticosteroids attenuates AHR in asthma but does not eliminate it.[1] Clinically, AHR manifests as increased variability of airway function. Although not commonly used to diagnose asthma, AHR can be evaluated clinically using a methacholine or histamine bronchoprovocation test.

Airway Obstruction

Airway obstruction manifests itself as symptoms such as chest tightness, cough, and wheezing. Airway obstruction can be caused by multiple factors including airway smooth muscle constriction, airway edema, mucus hypersecretion, and airway remodeling. Airway smooth muscle tone is maintained by an interaction between sympathetic, parasympathetic, and nonadrenergic mechanisms. Acute bronchoconstriction usually

results from preformed or generated mediators such as histamine and cysteinyl leukotrienes released during mast cell and basophil degranulation that act directly on the airways.[3] Inflammatory mediators such as histamine, leukotrienes, and bradykinin increase microvascular permeability leading to mucosal edema, which causes the airway to become more rigid and limits airflow.[10] These changes exaggerate the consequences of acute bronchoconstriction. In asthmatics, there is an increased number and volume of mucous glands with increased mucus secretion.[11] Extensive mucus plugging has been demonstrated in patients who have died from acute asthma and is likely a cause of persistent airway obstruction in severe acute attacks.

Although airway obstruction in asthma has generally been considered reversible, some asthmatics have an irreversible or fixed obstruction. The process that produces the structural airway changes leading to this fixed obstruction has been termed airway remodeling and is characterized by airway epithelial damage, subepithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, increased mucus production, and increased vascularity of the airways.[3,11] Airway remodeling may be caused by repetitive injury to the airways, by an abnormal injury-repair cycle of dysfunctional epithelial cells, or in response to the chronic inflammatory process. Structural airway changes can be demonstrated early in asthma, may be present in newly diagnosed asthmatics, and has been seen prior to the onset of asthma.[11]

CLINICAL PRESENTATION AND DIAGNOSIS

Factors Affecting Asthma Severity

Major factors that may contribute to the severity of asthma include allergens typically associated with atopy; chemical exposures in occupational environments; and exposure to tobacco smoke, irritants, and indoor and outdoor pollution. Other factors include concurrent disease states or medications that may worsen asthma severity.

Up to 80% of asthmatics have symptoms of rhinitis, and inflammation of the upper airways may increase AHR.[1,3] Treatment of rhinitis with intranasal corticosteroids may improve asthma symptoms and is recommended for asthma patients with rhinitis.

Acute and chronic sinusitis can also aggravate asthma, and antibiotic therapy of sinusitis may improve asthma symptoms.[3] Nasal polyps are associated with aspirin-sensitive asthma, and adult patients with nasal polyps should be counseled against using non-steroidal anti-inflammatory medications.[1,3]

Gastroesophageal reflux has been associated with increased asthma symptoms, especially nighttime symptoms.

Non-selective β-blockers, including those in ophthalmic preparations, may cause asthma symptoms, and these agents should be avoided in asthmatics unless the benefits of therapy outweigh the risks.[1] In asthmatic patients requiring β-blocker therapy, a β_1-selective agent should be chosen. Because selectivity is dose related, the lowest effective dose should be used. β-Blockers may inhibit β-agonist reversal of bronchospasm, and a larger dose of β-agonist or the use of an anticholinergic agent may be necessary to reverse bronchospasm.



Clinical Presentation of Chronic Asthma

General

Asthma severity ranges from normal pulmonary function and symptoms only with acute exacerbations to significantly decreased pulmonary function with continuous symptoms.

Symptoms

- Symptoms may include **dyspnea**, cough, wheezing, and chest tightness. These symptoms may be continual, episodic, seasonal, or occur in association with known triggers.
- Symptoms may occur more often at night, early in the morning, or with exercise.
- Patients with mild intermittent asthma may be symptom-free and have normal pulmonary function between exacerbations.

Signs

- Patients may have end-expiratory wheezing and dry cough.

Laboratory Tests

- Increased serum concentrations of IgE or eosinophils may help confirm the diagnosis of asthma but are not diagnostic for asthma.

Other Diagnostic Tests

- **Spirometry**, an objective measure of pulmonary function, can be used to assist in confirming the diagnosis of asthma. The primary pulmonary function tests used to assist in the diagnosis of asthma are the forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and **peak expiratory flow** (PEF). Values used to support a diagnosis of asthma include:

- Decreased FEV_1/FVC (less than 80%, but may be normal between exacerbations) demonstrates airway obstruction.
- A greater than or equal to 12% (at least 200 mL) improvement in FEV_1 after an inhaled bronchodilator demonstrates a reversible obstruction. A 2- to 3-week course of oral corticosteroids may be necessary to demonstrate reversibility in airway obstruction.
- A greater than or equal to 15% decrease in FEV_1 after an exercise test is diagnostic for exercise-induced asthma.

Assessment of diurnal variation of PEF may be useful in patients who have asthma symptoms and normal spirometry. When spirometry is equivocal, a 20% or greater decrease in FEV_1 after the administration of methacholine is diagnostic for asthma. A negative bronchoprovocation test with methacholine may help rule out asthma.

A positive allergen test may help guide nonpharmacologic therapy but is not diagnostic for asthma.



Clinical Presentation of Acute Asthma

General

Acute asthma can present rapidly (within 3 to 6 hours) but more commonly, deterioration occurs over several hours, days, or even weeks. Typically there is gradual deterioration over several days followed by a more rapid deterioration over 2 to 3 days. Acute asthma can be a life-threatening event, and severity does not correspond to severity of the chronic disease.

Symptoms

- The patient usually presents with complaints of dyspnea, cough, shortness of breath, and chest tightness.
- Because of their inability to breathe, patients are generally anxious and may be agitated. In severe acute asthma, patients may be unable to communicate in complete sentences.
- Mental status changes may indicate impending respiratory failure.

Signs

- The patient usually has **tachypnea** and may have tachycardia.
- Wheezing may vary from end-expiratory wheezing in mild exacerbations to wheezing throughout inspiration and expiration in severe exacerbations.
- Bradycardia and absence of wheezing may indicate impending respiratory failure.
- Patients may also present with hyperinflation, use of accessory muscles to breathe, **pulsus paradoxus**, diaphoresis, and **cyanosis**.

Laboratory Tests

- Arterial blood gases for evaluating partial arterial pressure of carbon dioxide (P_{CO_2}) should be considered for patients in severe distress, suspected hypoventilation, or when PEF or FEV_1 is less than or equal to 30% after initial treatment.
- A complete blood count with differential should be obtained in patients with fever or purulent sputum.
- Serum electrolytes should be obtained, because frequent β_2-agonist administration may decrease serum potassium, magnesium, and phosphate.

Other Diagnostic Tests

- Patients may present with PEF rates greater than 80% and oxygen saturation greater than 95% in mild exacerbations to PEF rates less than 50%, oxygen saturations less than 91%, partial arterial oxygen pressures (Pa_{O_2}) less than 50 mm Hg (less than 6.65 kPa), and P_{CO_2} greater than 42 mm Hg (greater than 5.59 kPa) in a severe exacerbation.
- A chest x-ray should be performed when pneumonia is suspected.

The ingestion of sulfites can also worsen asthma. These agents are often found in processed potatoes, shrimp, dried foods, beer, and wines. Patients sensitive to sulfites should be warned not to ingest these products, as they have been known to cause severe exacerbations, particularly in severe asthmatics.



Patient Encounter, Part 1

RB is a 13-year-old African-American female who presents with complaints of shortness of breath when she exercises. She has joined the cross-country team, and she is having trouble keeping up with the other girls on the team because she gets extremely short of breath 5 or 10 minutes into her run; her chest begins to feel tight, and she coughs. The symptoms usually go away 30 minutes to an hour after she stops running. She also wakes up at night approximately once a week because she is having trouble catching her breath.

- What information is suggestive of asthma?
- How would you classify this patient's asthma severity?
- What additional information do you need to know before creating a treatment plan for this patient?

There is little evidence for other food allergies as a routine cause of worsening asthma symptoms.[1,3]

Viral infections are the most common cause of increased asthma symptoms and asthma exacerbations.

TREATMENT OF ASTHMA

Desired Outcomes

Chronic Asthma

❷ *Therapy for chronic asthma is directed at suppressing the underlying inflammatory response and normalizing pulmonary function*. The goals of treatment for chronic asthma are to: (1) prevent chronic and troublesome symptoms; (2) maintain normal or near normal pulmonary function; (3) maintain normal activity levels, including exercise and other physical activities; (4) prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalizations; (5) provide optimal pharmacotherapy with minimal or no adverse effects; and (6) meet patients' and families' expectations of and satisfaction with asthma care.[1]

Because of the varying presentation of asthma, treatment guidelines for asthma therapy should serve as a guide for therapy with the therapeutic plan individualized for each patient to achieve these goals.

Acute Severe Asthma

Worsening or acute asthma can be a life-threatening situation, and appropriate outcomes require rapid assessment and appropriate intensification of therapy. Mortality associated with asthma exacerbations is usually related to an inappropriate assessment of the severity of the exacerbation resulting in insufficient treatment or referral for medical care.[12] The goals

of therapy are to: (1) correct significant **hypoxemia**; (2) rapidly reverse airflow obstruction; and (3) reduce the likelihood of recurrent severe airflow obstruction.[1]

Because of the significance of the event, patients may be more open to education about asthma after resolution of the exacerbation. Health care professionals should use this opportunity to provide information to help prevent future episodes, including recognition of early indicators of an exacerbation and a process to appropriately intensify pharmacotherapy during the early stages of future exacerbations, including an individualized written asthma action plan.

General Approach to Treatment

❸ In chronic asthma, *classification of asthma severity is based on daytime and nighttime symptoms, physical activity, lung function (PEF or FEV_1), PEF variability, and reliever medication use.* Because lung function is difficult to measure in preschool children (children 5 years of age or younger), it cannot be used to classify disease severity in this age group. Chronic asthma is classified as mild intermittent asthma, or mild, moderate or severe persistent asthma (Table 11–1).

Treatment of asthma involves avoidance of triggers known to precipitate or worsen asthma and the use of long-term control and quick relief medications. Long-term control medications include inhaled corticosteroids, inhaled long-acting β_2-adrenergic agonists, oral theophylline, and oral leukotriene modifying agents. In patients with severe asthma, systemic corticosteroids may be used as a long-term control medication. Quick relief medications include short-acting β_2-agonists, anticholinergics, and systemic corticosteroids. A stepwise approach to therapy is recommended to achieve the treatment goals[2] (Table 11–1).

In acute severe asthma, the severity of an exacerbation is not dependent upon the classification of the patient's chronic asthma, as even patients with mild intermittent asthma can have life-threatening acute exacerbations. Treatment of acute or worsening asthma primarily involves pharmacologic treatment. Early and aggressive treatment is necessary for quick resolution.[1,3] Important elements of an early treatment plan include: (1) a written action plan; (2) recognition of early indicators of an acute exacerbation, including asthma symptoms as well as worsening PEF or FEV_1; (3) appropriate intensification of pharmacotherapy, which may include a short course of oral corticosteroids; and (4) removal of triggers or irritants that may be contributing to the acute exacerbation.

Treatment of severe acute asthma includes the use of oxygen for the rapid reversal of hypoxemia, a short-acting β_2-agonist to reverse airway constriction, and a systemic corticosteroid to attenuate the inflammatory response.[1] Close monitoring of objective measures such as FEV_1 or PEF is important to quantify the response to therapy. Because recovery from exacerbations is often gradual, intensified therapy should be continued for several days.

Nonpharmacologic Therapy

Patients should play an active role in their therapy. The development of a health care provider–patient partnership is vital to the success of any treatment plan. Goals for asthma treatment should be shared with the patient and family, and the patient and health care provider should jointly agree on the patient's personal treatment goals.

Nonpharmacologic therapy should be incorporated into each step of therapy. Patient education should occur early in the disease process, include all members of the health care team, and be tailored to meet individual patient needs.[1] Patients should be taught basic facts about asthma, including the difference between the asthmatic and normal lung, what happens to the lung during an asthma attack, how medications work, environmental control measures, and self-management of asthma, including skills for self-monitoring of pulmonary function, symptoms of asthma deterioration, and when and how to take rescue actions.

Patients must understand the role of long-term control and quick relief medications in their asthma treatment plan. The importance of understanding asthma as a chronic disease and the need for daily treatment with long-term control medications should be stressed. Additionally, the importance of proper use of medication delivery devices should be continually reinforced. Basic education should be provided over several visits with the health care provider.

Risk Factor Avoidance

Patients who smoke should be strongly encouraged to quit; cigarette smoking decreases the efficacy of inhaled corticosteroids and can trigger an acute asthmatic response.[3] All patients should also avoid secondhand smoke. Parents of children with asthma should be instructed not to smoke in the home and not to allow others to smoke in the home. Patients should also avoid outdoor activities when air quality is poor and avoid exposure to other irritants such as hairspray, paint, exhaust fumes, and smoke from any fire.

Patients sensitive to specific allergens should be educated on ways to avoid them. Environmental controls to reduce the allergen load in the patient's home may reduce asthma symptoms, school absences because of asthma, and unscheduled clinic and emergency visits for asthma.[13] Patients allergic to warm-blooded pets should remove them from the home if possible or at least keep them out of the bedroom. However, allergens may remain in the home for months after the pet is removed.[1]

Patients allergic to cockroach antigens should ensure that food and garbage are not left exposed and cockroach populations are controlled. For patients with house dust mite allergies, essential measures to reduce the allergen load include encasing the mattress and pillow in allergen-impermeable covers and washing the patient's bed sheets and covers in hot water [130°F (54°C)] weekly. Dust mite exposure may also be minimized by removing carpets from the bedroom, removing

TABLE 11–1. Classification of Severity and Stepwise Approach For Managing Asthma

Severity Classification (Prior to Treatment)	Clinical Features Before Treatment or Adequate Control[a,b,c]	Medication Required to Maintain Long-Term Control: Adults and Children Older Than 5 Years of Age	Medication Required to Maintain Long-Term Control: Children 5 Years of Age and Younger
Step 4: Severe persistent	**Daytime Symptoms** • Continual symptoms • Limited physical activity **Nighttime Symptoms** • Frequent **Exacerbations** • Frequent **Lung Function** • FEV_1 or PEF less than or equal to 60% predicted; PEF variability greater than 30%	**Preferred Treatment** • High-dose inhaled corticosteroids *AND* • Long-acting inhaled β_2-agonists *AND* if needed • Corticosteroid tablets or syrup long term (2 mg/kg per day; generally do not exceed 60 mg/day); make repeated attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids	**Preferred Treatment** • High-dose inhaled corticosteroids *AND* • Long-acting inhaled β_2-agonists *AND* if needed • Corticosteroid tablets or syrup long term (2 mg/kg per day; generally do not exceed 60 mg/day); make repeated attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids
Step 3: Moderate persistent	**Daytime Symptoms** • Daily symptoms • Daily use of inhaled short-acting β_2-adrenergic agonists **Nighttime Symptoms** • Greater than 1 time per week **Exacerbations** • Affect activity; occur greater than or equal to 2 times per week; exacerbations may last days **Lung Function** • FEV_1 or PEF greater than 60% but less than 80% predicted; PEF variability greater than 30%	**Preferred Treatment** • Low- to medium-dose inhaled corticosteroids and long-acting inhaled β_2-agonists **Alternate Treatment** • Increase inhaled corticosteroid dose into the medium-dose range *OR* • Low- to medium-dose inhaled corticosteroids and either leukotriene modifier or theophylline If needed (particularly in patients with recurring severe exacerbation): **Preferred Treatment** • Increase inhaled corticosteroids within medium-dose range and add long-acting β_2 agonist **Alternative Treatment** • Increase inhaled corticosteroids within medium-dose range and add either leukotriene modifier or theophylline	**Preferred Treatment** • Low-dose inhaled corticosteroids and long-acting inhaled β_2-agonists *OR* • Medium-dose inhaled corticosteroids **Alternate Treatment** • Low-dose inhaled corticosteroids and either leukotriene receptor antagonist or theophylline If needed (particularly in patients with recurring severe exacerbations): **Preferred Treatment** • Medium-dose inhaled corticosteroids and long-acting β_2-agonists **Alternative Treatment** • Medium-dose inhaled corticosteroids and either a leukotriene receptor antagonist or theophylline
Step 2: Mild persistent	**Daytime Symptoms** • Symptoms greater than 2 times per week but less than 1 time per day **Nighttime Symptoms** • Greater than 2 times per month **Exacerbations** • May affect activity **Lung Function** • FEV_1 or PEF greater than or equal to 80%; PEF variability 20–30%	**Preferred Treatment** • Low-dose inhaled corticosteroids **Alternative Treatment** • Cromolyn, leukotriene modifiers, nedocromil *OR* sustained-release theophylline adjusted to a serum concentration of 5–15 mcg/mL (28–83 µmol/L)	**Preferred Treatment** • Low-dose inhaled corticosteroids (with nebulizer or MDI with holding chamber with or without facemask or DPI) **Alternative Treatment** • Cromolyn (nebulizer is preferred or MDI with holding chamber) *OR* leukotriene receptor antagonists

Step 1: Mild intermittent	**Daytime Symptoms** • Symptoms less than or equal to 2 times per week • Asymptomatic or normal PEF between exacerbations **Nighttime Symptoms** • Less than or equal to 2 times per month **Exacerbations** • Brief (from a few hours to a few days); intensity may vary **Lung Function** • FEV_1 or PEF greater than or equal to 80% PEF variability less than 20%	• No daily medications needed • Severe exacerbations may occur, separated by long periods of normal lung function; a course of systemic corticosteroids is recommended	• No daily medications needed
Quick Relief for All Patients[c]		• Short-acting bronchodilator: 2–4 puffs short-acting inhaled β_2-agonist as needed for symptoms • Intensity of treatment depends on severity of exacerbation: up to 3 treatments at 20-minute intervals or a single nebulizer treatment as needed; a course of systemic corticosteroids may be needed • Use of short-acting β_2-agonist greater than 2 times a week in intermittent asthma (daily or increasing use in persistent asthma) may indicate the need to initiate or increase long-term-control therapy	• Bronchodilators as needed for symptoms; intensity of treatment depends on the severity of the exacerbation • **Preferred Treatment** Short-acting inhaled β_2-agonist by nebulizer or facemask and spacer/holding chamber • **Alternative Treatment** Oral β_2-agonist • With viral respiratory infection: • Bronchodilator every 4–6 hours up to 24 hour (longer with physician consult); in general, repeat no more than once every 6 weeks • Consider systemic corticosteroid if exacerbation is severe or patient has a history of previous severe exacerbations • Use of short-acting β_2-agonist greater than 2 times a week in intermittent asthma (daily or increasing use in persistent asthma) may indicate the need to initiate or increase long-term-control therapy

Notes:

- The stepwise approach is intended to assist, not replace, the clinical decision making required to meet individual patient needs.
- There are very few studies on asthma therapy for infants.
- Gain control as quickly as possible (a short course of systemic corticosteroids may be required.); then step down to the least medication necessary to maintain control.
- Minimize use of short-acting inhaled β_2-agonists. Overreliance on short-acting inhaled β_2-agonists (e.g., use of short-acting inhaled β_2-agonists every day, increasing use or lack of expected effect, or use of approximately one canister a month even if not using it every day) indicates inadequate control of asthma therapy and the need to initiate or intensify long-term control therapy.
- Provide education on self-management or parent education on asthma management and controlling environmental factors that make asthma worse (e.g., allergens and irritants).
- Consultation with an asthma specialist is recommended for patients with moderate or severe persistent asthma. Consider consultation for patients with mild, persistent asthma.

[a]The presence of one of the features of severity is sufficient to place a patient in that category. An individual should be assigned the most severe grade to which any feature occurs. The characteristics noted in this table are general and may overlap because asthma is highly variable. Furthermore, an individual's classification may change over time.
[b]Accurate assessment of FEV_1 or PEF may not be possible in children less than 5 years of age.
[c]Patients at any level can have mild, moderate, or severe exacerbations. Some patients with intermittent asthma experience severe and life-threatening exacerbations separated by long periods of normal lung function and no symptoms.
FEV_1, forced expiratory volume in 1 second; PEF, peak expiratory flow; MDI, metered-dose inhaler; DPI, dry powder inhaler.
Adapted from NHLBI. National Asthma Education and Prevention Program, Expert Panel Report 2. Guidelines for the Diagnosis and Management of Asthma. NIH Publication No. 97-4051. Bethesda, MD: United States Department of Health and Human Services, 1997, and National Institutes of Health. National Heart, Lung and Blood Institute. National Asthma Education and Prevention Program. Expert Panel Report. Guidelines for the Diagnosis and Management of Asthma. Update on Selected Topics 2002. http://www.nhlbi.nih.gov/guidelines/astham/asthmafullrpt.pdf; accessed August 2005; with permission.

carpets laid over concrete slabs, and avoiding sleeping or lying on upholstered furniture. Reducing indoor humidity to less than 50% helps control dust mite populations and decreases exposure to indoor mold. Patients allergic to outdoor allergens should stay indoors during times of peak allergen levels.

Asthma patients should receive the influenza vaccine every year.[1] Although the pneumococcal vaccine may decrease the risk of invasive pneumococcal disease in asthmatics, current guidelines do not include the routine administration of this vaccine to asthma patients.[1,14]

Drug Delivery Devices

❹ *Direct airway administration of asthma medications through inhalation is most efficient and minimizes systemic adverse effects.* Poor inhaler technique can result in increased oropharyngeal deposition of the drug with decreased efficacy and increased adverse effects. Figure 11–1 provides steps for the appropriate use of inhaled delivery devices. Inhaled asthma medications are available in metered-dose inhalers (MDIs), dry powder inhalers (DPIs), and nebulized solutions.

Patients switched from an MDI to a DPI should be counseled that the DPI requires a rapid and forceful inhalation as compared to the slow inhalation used for an MDI. Patients using a DPI should also be counseled not to exhale into the device, as it will cause a loss of dose or decreased drug delivery. Because delivery technique with inhalers deteriorates over time, the health care provider should take every opportunity to reinforce appropriate inhaler technique.

Patients should also be educated to keep track of inhaler use. Many DPIs have a built-in counter or device to notify the patient of how many doses are remaining (e.g., Diskus® and Twisthaler®) or that the inhaler is approaching empty (e.g., Turbuhaler®).

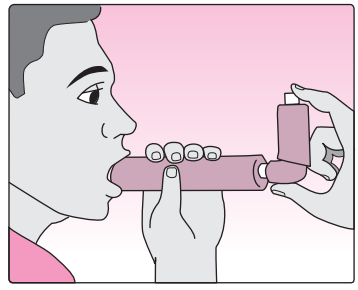
Steps for Using Your Inhaler

Please demonstrate your inhaler technique at every visit.

1. Remove the cap and hold inhaler upright.
2. Shake the inhaler.
3. Tilt your head back slightly and breathe out slowly.
4. Position the inhaler in one of the following ways (A or B is optimal, but C is acceptable for those who have difficulty with A or B. C is required for breath-activated inhalers):



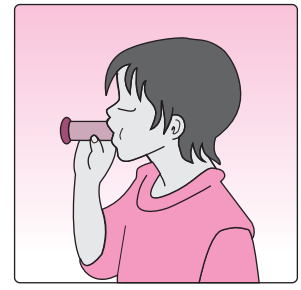
A Open mouth with inhaler 1 to 2 inches away.



B Use spacer/holding chamber (that is recommended especially for young children and for people using corticosteroids).



C In the mouth. Do not use for corticosteroids.



D NOTE: Inhaled dry powder capsules require a different inhalation technique. To use a dry powder inhaler, it is important to close the mouth tightly around the mouthpiece of the inhaler and to inhale rapidly.

5. Press down on the inhaler to release medication as you start to breathe in slowly.
6. Breathe in slowly (3 to 5 seconds).
7. Hold your breath for 10 seconds to allow the medicine to reach deeply into your lungs.
8. Repeat puff as directed. Waiting 1 minute between puffs may permit second puff to penetrate your lungs better.
9. Spacers/holding chambers are useful for all patients. They are particularly recommended for young children and older adults and for use with corticosteroids.

Avoid common inhaler mistakes. Follow these inhaler tips:

- Breathe out *before* pressing your inhaler.
- Inhale *slowly*.
- Breathe in through your mouth, not your nose.
- Press down on your inhaler at the *start* of inhalation (or within the first second of inhalation).
- Keep inhaling as you press down on inhaler.
- Press your inhaler only *once* while you are inhaling (one breath for each puff).
- Make sure you breathe in evenly and deeply.

NOTE: Other inhalers are becoming available in addition to those illustrated above. Different types of inhalers require different techniques.

FIGURE 11–1. Steps for using your inhaler. (From Kelly HW, Sorkness CA. Asthma. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 515, with permission.)

Spacers or holding chambers decrease the need for coordination of actuation of MDI devices with inhalation, decrease oropharyngeal deposition of drug, and increase pulmonary drug delivery.[15,16] These devices are equipped with a mouthpiece or a facemask allowing the use of an MDI in children less than 5 years of age. Patients using a spacer or holding chamber should be counseled to place only one puff of the drug into the chamber at a time, because actuating the MDI more than once into the chamber before inhalation decreases drug delivery.[15] Additionally, patients should be instructed not to delay inhalation after actuation of the MDI, as a 10- to 20-second delay in inhalation may also significantly decrease drug delivery. Taking multiple breaths after a single actuation is appropriate and does not decrease drug efficacy.[15]

Although nebulizers have often been used for drug delivery in children, their use is expensive and time consuming. Nebulizers may atomize drug using compressed air or oxygen (jet nebulizers) or by high-frequency vibration (ultrasonic nebulizers). Ultrasonic nebulizers should not be used for drugs in suspension, as they are ineffective in delivering the suspended particles.[16]

Asthma Self-Management

Asthma self-management plans give patients the freedom to adjust therapy based on personal assessment of disease severity and a pre-agreed upon action plan. Furthermore, because most asthma exacerbations occur at home or in the community, these plans allow for the rapid initiation of patient-specific therapy. Asthma self-management plans reduce morbidity and the need for medical services.[17] For self-management plans to be effective, patients should be given a written action plan that is part of a global educational program.[3]

Patients should be educated to assess asthma severity by evaluating key asthma symptoms and monitoring PEF. Early signs of asthma deterioration include increasing nocturnal symptoms, increasing use of short-acting inhaled β_2-agonists, or symptoms that do not respond to increased use of short-acting inhaled β_2-agonists. Patients with moderate to severe persistent asthma should monitor PEF every day.[1] Measurement of PEF may be particularly important for the patient who is a poor judge of symptoms or whose perceptions of decreased airflow do not correlate with objective measures of airflow.[3]

Measurement of PEF is highly dependent upon patient effort and technique; therefore, the health care provider should educate the patient on the proper technique for measuring PEF and review this technique on a regular basis. To use the peak flow meter properly, the patient should be instructed to move the indicator to the bottom of the numerical scale; stand up; take a deep breath completely filling their lungs; place the mouthpiece in the mouth being careful to close their lips around it and not to obstruct the hole with their tongue; and blow out as hard and fast as they can in a single blow.[1] This effort should be repeated three times, with the highest value of the three recorded in the patient's PEF diary. The NAEPP recommends PEF be measured daily in the morning on waking, prior to taking a bronchodilator.[1]

Because PEF values in patients do not always correlate well with predicted PEF values, daily PEF values should be compared to the patient's personal best PEF. Personal best PEF should be established over a 2- to 3-week period when the patient is receiving optimal treatment.[1,3] During this time, the patient should measure PEF at least twice a day, in the morning and early afternoon, and before and after a dose of bronchodilator if the patient is taking one. At each time period, the patient should record the best of three attempts. The highest PEF recorded during this 2- to 3-week period is the patient's personal best. If the patient's personal best is less than 80% of predicted values or if peak flow variability is greater than 20%, more aggressive therapy (including a short course of oral corticosteroids) may be required to adequately assess the patient's personal best.[3]

Subsequent evaluation of PEF is done in relation to its variability from the patient's best. Consistent PEF measurements less than 80% of personal best indicate the need for intensifying therapy and a PEF measurement less than 50% indicates a severe exacerbation. The NAEPP recommends that these zones be associated with a "traffic light" system to assist the patient in their use.[1] PEF measurements in the range of 80% to 100% of personal best are in the green zone and indicate that current therapy is acceptable. A PEF in the range of 50% to 79% of personal best is in the yellow zone and indicates caution. PEF measurements in the yellow zone may indicate an impending exacerbation and based on his or her self-management plan, the patient should increase the use of relief medication, intensify inhaled corticosteroid therapy, or begin a short course of oral corticosteroids. A PEF less than 50% is in the red zone and signals a medical alert. Patients should use their short-acting β_2-agonist immediately and consult their asthma action plan.

Pharmacologic Therapy

Beta$_2$-Adrenergic Agonists

β_2-Agonists relax airway smooth muscle by directly stimulating β_2-adrenergic receptors.[18] They also increase mucociliary clearance and stabilize mast cell membranes. Inhalation, oral, and injectable dosage forms are available, and the inhalation dosage forms are most commonly used. Oral β_2-agonists should not be used in acute asthma because of a delayed onset of action compared to the inhaled route.[1] Inhaled β_2-agonists are classified as either short- or long-acting based on their duration of action.

Short-Acting Inhaled Beta$_2$-Agonists

❺ *Inhaled short-acting β_2-agonists are the most effective agents for reversing acute airway obstruction caused by bronchoconstriction* and are the drugs of choice for treating acute severe asthma and symptoms of chronic asthma.[1] Short-acting inhaled β_2-agonists have an onset of action of less than 5 minutes and a duration of action of 4 to 6 hours. β_2-Agonists have

significantly better bronchodilating activity in acute asthma than theophylline or anticholinergic agents.

Adverse effects of the inhaled β_2-agonists include tachycardia, tremor, and hypokalemia, which are usually not problematic. Because of increased adverse effects, oral β_2-agonists should be avoided in patients who are able to use inhaled medications.

Albuterol (also known as salbutamol outside the United States), the most commonly used inhaled short-acting β_2-agonist, is a racemic mixture (50:50) of albuterol enantiomers. The R-enantiomer is the active component whereas the S-enantiomer is inactive or may be associated with unwanted effects. Levalbuterol, the pure R-enantiomer of albuterol, is available as a solution for nebulization and as an MDI dosage form. Comparative studies show similar efficacy and safety between levalbuterol and albuterol, but the acquisition cost of levalbuterol is substantially higher.

Other commonly used short-acting inhaled β_2-agonists include pirbuterol and terbutaline. Non-selective β_2-agonists such as metaproterenol are no longer commonly used due to the potential for increased adverse effects. Although not equivalent on a milligram basis, the inhaled short-acting β_2-agonists are equally potent when given in equivalent doses. Doses for use as quick relief drugs in chronic asthma are provided in Table 11–2. Usual rescue doses may be doubled for mild exacerbations. Because of previous β-agonist use by the patient and the underlying inflammatory process in acute severe asthma, the dose-response curve for β_2-agonists is shifted to the right, and the duration of action is decreased; therefore, larger doses of short-acting inhaled β_2-agonists may need to be administered more often.[18]

Inhaled short-acting β_2-agonists may be administered through a nebulizer or an MDI. Compared to nebulization, administration through an MDI with a spacer is quicker and at least as effective with fewer adverse effects. In infants and young children, short-acting β_2-agonists administered by MDI should be administered through a spacer with a facemask, and in older children and adults through a spacer with a mouthpiece. In the case of crying infants and patients unwilling to use an MDI with a spacer, short-acting β_2-agonists may be administered via nebulization connected to oxygen. Infants should receive nebulization via a facemask that fits over the nose and mouth. Continuous nebulization is as effective as intermittent nebulization with fewer adverse effects.[19]

In patients hospitalized because of asthma, patient-initiated (on-demand) therapy may result in decreased nebulized doses, decreased adverse effects, and shorter hospital stays than therapy given regularly at 4-hour intervals.[20] In patients admitted to the intensive care unit and placed on mechanical ventilation, β_2-agonists can be delivered via an MDI or nebulization through the ventilatory circuit.

Long-Acting Inhaled Beta$_2$-Agonists

Salmeterol and formoterol are long-acting inhaled β_2-agonists that provide up to 12 hours of bronchodilation after a single dose. Both agents are approved for the chronic prevention of asthma symptoms. Salmeterol is a partial agonist with an onset of action of approximately 30 minutes. Because of this delayed onset of action, patients should be cautioned not to use salmeterol as a quick relief medication. Formoterol is a full agonist that has an onset of action similar to that of albuterol, but it is not currently indicated for the treatment of acute bronchospasm.

Inhaled long-acting β_2-agonists are indicated for add-on therapy for asthma not controlled on low to medium doses of inhaled corticosteroids. Adding a long-acting inhaled β_2-agonist is at least as effective as doubling the dose of an inhaled corticosteroid with respect to improving lung function and symptom scores and decreasing nocturnal symptoms, reliever medication use, and asthma exacerbations.[2] Addition of a long-acting inhaled β_2-agonist to inhaled corticosteroid therapy also reduces the amount of inhaled corticosteroids necessary for asthma control.[2,21] Combined therapy with a long-acting inhaled β_2-agonist and an inhaled corticosteroid is also superior to the combination of a leukotriene modifier or theophylline with an inhaled corticosteroid.[2,22–24]

Although both formoterol and salmeterol are effective as add-on therapy for moderate persistent asthma, neither agent should be used as monotherapy for chronic asthma. Patients treated with salmeterol alone are at greater risk of worsening asthma than those treated with inhaled corticosteroids.[25,26]

Salmeterol is also available in a fixed ratio combination product containing fluticasone, and a new drug application has been filed for a fixed combination product containing budesonide and formoterol. Combination products have the potential advantage of increasing patient adherence due to the decreased number of inhalers and inhalations; however, these products offer less flexibility with respect to dosage adjustments when necessary.

Corticosteroids

Corticosteroids are the most potent anti-inflammatory agents available for the treatment of asthma. The efficacy of corticosteroids is due to their ability to affect multiple inflammatory pathways, resulting in the suppression of inflammatory cell activation and function, prevention of microvascular leakage, decreased mucus production, and upregulation of β_2-adrenergic receptors.[10,18] Clinically, corticosteroids decrease airway inflammation, decrease AHR, decrease mucus production and secretion, and improve the response to β_2-agonists.[18] Corticosteroids for the treatment of asthma are available in inhaled, oral, and injectable dosage forms.

Inhaled Corticosteroids

❻ *In persistent asthma, inhaled corticosteroids provide the most comprehensive control of the inflammatory process* and are the cornerstone of therapy.[2] Inhaled corticosteroids are more effective than cromolyn, leukotriene modifiers, nedocromil, and theophylline in reducing markers of inflammation and AHR, improving lung function, and preventing emergency department visits and hospitalizations due to asthma exacerbations.[2,25] The primary

TABLE 11–2. Usual Dosages for Selected Quick-Relief Medications

Medication	Dosage Form	Adult Dose	Child Dose[a]
Short-Acting Inhaled β_2-Agonists			
Albuterol	MDI: 90 mcg/puff 200 puffs	2 puffs 5 minutes before exercise 2 puffs 3–4 times a day as needed	1–2 puffs 5 minutes before exercise 2 puffs 3–4 times a day as needed
Albuterol HFA	MDI: 90 mcg/puff 200 puffs		
Levalbuterol HFA	MDI: 45 mcg/puff 200 puffs	2 puffs every 4–6 hours (1 puff every 4 hours may be sufficient in some patients)	2 puffs every 4–6 hours (1 puff every 4 hours may be sufficient in some patients)
Albuterol nebulizer solution	5 mg/mL (5%) 2.5 mg/3 mL 1.25 mg/3 mL 0.63 mg/3 mL	1.25–5 mg in 3 mL of saline every 4–8 hours	0.05 mg/kg (minimum of 1.25 mg, maximum of 2.5 mg) in 3 mL of saline every 4–6 hours
Levalbuterol (R-albuterol) nebulizer solution	0.31 mg/3 mL 0.63 mg/3 mL 1.25 mg/3 mL	0.63–2.5 mg every 4–8 hours	0.025 mg/kg (minimum of 0.63 mg; maximum of 1.25 mg every 4–8 hours
Anticholinergics			
Ipratropium	MDI CFC: 18 mcg/puff, 200 puffs MDI HFA: 17 mcg/puff, 200 puffs	2–3 puffs every 6 hours	1–2 puffs every 6 hours
	Nebulizer solution: 0.25 mg/mL (0.25%)	0.25 mg every 6 hours	0.25–0.5 mg every 6 hours
Ipratropium with albuterol	MDI: 18 mcg/puff of ipratropium bromide and 90 mcg/puff of albuterol	2–3 puffs every 6 hours	1–2 puffs every 8 hours
	Nebulizer solution: 0.5 mg/3 mL ipratropium bromide and 2.5 mg/3 mL albuterol	3 mL every 4–6 hours	1.5–3 mL every 4–8 hours
Systemic Corticosteroids			
Methylprednisolone Prednisolone	2-, 4-, 8-, 16-, 32-mg tablets 5-mg tablets 5 mg/5 mL 15 mg/5 mL	Short course "burst" to achieve control; 40–60 mg/day as single or two divided doses for 3–10 days	Short-course "burst" to achieve control; 1–2 mg/kg per day, maximum of 60 mg/day for 3–10 days
Prednisone	1-, 2.5-, 5-, 10-, 20-, 50-mg tablets 5 mg/mL 5 mg/5 mL		
Methylprednisolone acetate	Repository injection: 40 mg/mL 80 mg/mL	240 mg intramuscularly once	7.5 mg/kg intramuscularly once

[a]Children less than or equal to 12 years of age.
CFC, chlorofluorocarbon propellant; HFA, hydrofluoroalkane propellant; MDI, metered-dose inhaler.
Adapted from National Institutes of Health, National Heart Lung and Blood Institute. National Asthma Education and Prevention Program. Expert Panel Report. Guidelines for the Diagnosis and Management of Asthma. Update on Selected Topics 2002; http://www.nhlbi.nih.gov/guidelines/asthma/asthmafullrpt.pdf; accessed August 2005, used with permission.

advantage of the use of inhaled corticosteroids compared to systemic corticosteroids is the targeted delivery of drug to the lungs, which decreases the risk of systemic adverse effects.

Inhaled corticosteroids are not equivalent on a milligram basis; however, equivalent doses have been approximated (Table 11–3). Low to moderate doses have been shown to be safe and effective in all age groups. Although some effect is seen from inhaled corticosteroids within 12 hours, 2 weeks of therapy is necessary to see significant clinical effects, and longer treatment periods may be necessary to see the full effect of these agents on airway inflammation and remodeling.

Inhaled corticosteroids appear to have a flat dose-response curve, with a two-fold increase in dose having a limited additional effect on asthma control.[3,27] Although a four-fold increase in inhaled corticosteroid dose has been shown to improve asthma control, this significantly increases the risk of systemic adverse effects.[2,28] These agents are generally effective when given twice daily and may be effective when given once daily for mild asthma; however, dosing four times a day may be required to achieve asthma control in patients with severe asthma.[3]

Local adverse effects of inhaled corticosteroids include oral candidiasis and **dysphonia**. The incidence of local adverse

TABLE 11–3. Estimated Comparative Dosages for Inhaled Corticosteroids

Medication	Age[a]	Low Daily Dose	Medium Daily Dose	High Daily Dose
Beclomethasone	Adult	80–240 mcg	240–480 mcg	Greater than 480 mcg
MDI (HFA): 40–80 mcg/puff	Child	80–160 mcg	160–320 mcg	Greater than 320 mcg
Budesonide	Adult	200–600 mcg	600–1200 mcg	Greater than 1200 mcg
DPI: 200 mcg/inhalation	Child	200–400 mcg	400–800 mcg	Greater than 800 mcg
Budesonide solution for inhalation 250 mcg or 500 mcg/2 mL	Child	0.5 mg	1 mg	2 mg
Flunisolide	Adult	500–1000 mcg	1000–2000 mcg	Greater than 2000 mcg
MDI (CFC): 250 mcg/puff	Child	500–750 mcg	1000–1250 mcg	Greater than 1250 mcg
Fluticasone	Adult	88–264 mcg	264–660 mcg	Greater than 660 mcg
MDI: 44, 110, or 220 mcg/puff	Child	88–176 mcg	176–440 mcg	Greater than 440 mcg
Mometasone furoate	Adult	200–400 mcg	400–800 mcg	Greater than 800 mcg
DPI: 200 mcg/inhalation	Child	—	—	—
Triamcinolone acetonide MDI	Adult	400–1000 mcg	1000–2000 mcg	Greater than 2000 mcg
(CFC): 100 mcg/puff	Child	400–800 mcg	800–1200 mcg	Greater than 1200 mcg

[a]Children less than or equal to 12 years of age
CFC, chlorofluorocarbon; DPI, dry powder inhaler; HFA, hydrofluoroalkane propellant; MDI, metered-dose inhaler.
National Institutes of Health. National Heart, Lung and Blood Institute. National Asthma Education and Prevention Program. Expert Panel Report. Guidelines for the Diagnosis and Management of Asthma. Update on Selected Topics 2002. http://www.nhlbi.nih.gov/guidelines/astham/asthmafullrpt.pdf; accessed August 2005; and Kelly HW, Sorkness CA. Asthma. In: DiPro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw Hill; 2005:527.

effects can be reduced by using a spacer or holding chamber and by having the patient rinse their mouth with water and expectorate after using the inhaled corticosteroids. Systemic absorption occurs via the pulmonary and oral routes. Although only a fraction of the drug is delivered to the lungs, 100% of the drug reaching the lungs is absorbed systemically.[1,3] For most delivery devices, the majority of the drug is deposited in the oropharyngeal cavity and swallowed. Systemic exposure to swallowed drug is primarily determined by the degree of first-pass metabolism of the agent. Because spacers and holding chambers decrease oral deposition and increase pulmonary delivery, these devices may increase the systemic effects of inhaled corticosteroids.[15,16] Additionally, changes in drug delivery devices [e.g., from a CFC to a hydrofluoroalkane (HFA) propellant or from an MDI to a DPI] may also alter pulmonary drug deposition with a resulting change in efficacy or systemic adverse effects.[3]

Systemic adverse effects are dose-dependent and are rare at low to medium doses; however, high-dose inhaled corticosteroids have been associated with adrenal suppression, decreased bone mineral density, skin thinning, and easy bruising.[3,29] Growth suppression in children may occur even with low-dose inhaled corticosteroids; however, suppression appears to occur primarily in the first year of treatment and may be due to delayed growth with the potential of future catch-up growth.[30]

Because all inhaled corticosteroids are equally effective if given in equipotent doses, product selection should be individualized based on the available dosage form, delivery device, and patient preference. In infants, administration may require the use of a nebulizer or spacer/holding chamber with a facemask. Caregivers should use a soft, damp cloth to wipe the face of infants receiving an inhaled corticosteroid via a facemask to prevent topical candidiasis.[18]

Systemic Corticosteroids

Systemic corticosteroids are effective as both long-term control and rescue medications; however, due to the potential for serious adverse effects, systemic corticosteroids should only be used for long-term control of asthma in patients who have failed other therapies. Serious adverse effects include hypothalamic-pituitary-adrenal suppression, growth retardation, osteoporosis, aseptic necrosis of the bone, psychiatric disturbances, sodium and water retention, hyperkalemia, hyperglycemia, immunosuppression, impaired wound healing, glaucoma, posterior subcapsular cataracts, skin thinning and easy bruising, central redistribution of fat, and moon facies.

If it is necessary to use systemic corticosteroids for long-term control therapy, once-daily or every-other-day therapy should be used and repeated attempts should be made to decrease the dose or discontinue the drug. Withdrawal of chronic therapy may precipitate adrenal failure or unmask underlying inflammatory disorders such as **Churg-Strauss syndrome**.

Systemic corticosteroids are the cornerstone of the treatment of worsening asthma not responding to bronchodilators and acute severe asthma. For patients with worsening asthma not responding to bronchodilators, a short course or "burst" of systemic corticosteroids is effective for gaining control and preventing progression.[1,3] The short course should be continued until the PEF reaches 80% of personal best or symptoms resolve. Three to ten days of therapy are usually sufficient, but longer therapy may be required.[1]

In acute severe asthma, systemic corticosteroids should be given to all patients who do not respond to initial bronchodilator therapy and all patients with moderate to severe exacerbations. Corticosteroids attenuate the inflammatory

response and increase the response to β_2-agonists. They speed recovery from the exacerbation, decrease hospital admissions, and reduce relapse rates. Their onset of effects is delayed, and a clinical response may not be seen for 4 to 12 hours.[18] For this reason, systemic corticosteroids should be started early in the course of acute exacerbations or worsening asthma.

There is no evidence that intravenous corticosteroid administration is more effective than oral administration, and the oral route is preferred in acute severe asthma.[3] There are also few data to guide selection of initial corticosteroid doses. Recommended doses for acute severe asthma are shown in Table 11–5, page 227; however, recent data indicate that

TABLE 11–4. Usual Doses for Long-Term Control Medications

Medication	Dosage Form	Adult Dose	Child Dose[a]
Inhaled Corticosteroids			
See Table 11–3			
Systemic Corticosteroids			
Methylprednisolone	2-, 4-, 8-, 16-, 32-mg tablets	7.5–60 mg daily in a single dose in the morning or every other day as needed for control	0.25–2 mg/kg daily in a single dose in the morning or every other day as needed for control
Prednisolone	5-mg tablets 5 mg/5 mL 15 mg/5 mL		
Prednisone	1-, 2.5-, 5-, 10-, 20-, 50-mg tablets 5 mg/mL 5 mg/5 mL		
Long-Acting Inhaled β_2-Agonists			
Salmeterol	DPI 50 mcg/blister	1 blister every 12 hours	1 blister every 12 hours
Formoterol	DPI 12 mcg/single-use capsule	1 capsule every 12 hours	1 capsule every 12 hours
Cromolyn and Nedocromil			
Cromolyn	MDI 1 mg/puff Nebulizer: 20 mg/ampule	2–4 puffs 3–4 times a day 1 ampule 3–4 times a day	1–2 puffs 3–4 times a day 1 ampule 3–4 times a day
Nedocromil	MDI 1.75 mg/puff	2–4 puffs 2–4 times a day	1–2 puffs 2–4 times a day
Leukotriene Modifiers			
Montelukast	4 mg/pack granules 4- or 5-mg chewable tablet 10-mg tablet	10 mg at bedtime (greater than 14 years of age)	4 mg at bedtime (12 mo–5 years, granules; 2–5 years of age, chewable tablet) 5 mg at bedtime (6–14 years of age)
Zafirlukast	10- or 20-mg tablet	20 mg twice a day	10 mg twice a day (7–11 years of age)
Zileuton	300- or 600-mg tablet	600 mg four times a day	—
Methylxanthine			
Theophylline	Liquids, sustained-release tablets, capsules	Starting dose: 10 mg/kg per day up to 300 mg maximum; usual maximum dose is 800 mg/day	Starting dose: 10 mg/kg per day; usual maximum dose is: Less than 1 year of age: (0.2 × age in weeks) + 5 = dose in mg/kg per day Greater than or equal to 1 year of age: 16 mg/kg per day up to 300 mg maximum
Miscellaneous			
IgE monoclonal antibody	Lyophilized powder for reconstitution with sterile water: 150 mg/vial	Dosed every 2 or 4 weeks based on patient weight and baseline total IgE concentrations	—

[a]Children less than or equal to 12 years of age.
DPI, dry powder inhaler; MDI, metered-dose inhaler.
Adapted from National Institutes of Health, National Heart Lung and Blood Institute. National Asthma and Education Prevention Program. Expert Panel Report. Guidelines for the Diagnosis and Management of Asthma. Update on Selected Topics 2002. http://www.nhlbi.nih.gov/guidelines/asthma/asthmafullrpt.pdf; accessed August 2005; used with permission.

methylprednisolone 60 to 80 mg/day (or equivalent) is adequate for hospitalized patients, and doses as low as 40 mg/day (or equivalent) are probably adequate.[3] No advantage has been shown for higher doses in acute severe asthma.[1,3]

Although the optimal duration of systemic corticosteroids is unknown, therapy should be continued until PEF is greater than or equal to 80% of predicted or personal best. According to the NAEPP, the usual regimen is to continue frequent multiple doses until the patient's FEV_1 or PEF improves to 50% of predicted and then decrease the frequency to twice daily. In general, the duration of therapy ranges from 3 days for mild exacerbations to 14 days for severe exacerbations. It is not necessary to taper the systemic steroid dose in patients receiving short bursts of systemic corticosteroid therapy, as the adrenal suppression that occurs is transient and rapidly reversible.[18]

Anticholinergics

Anticholinergic agents act by inhibiting the effects of acetylcholine on muscarinic receptors in the airways. They only protect against cholinergic-mediated bronchoconstriction and are not as effective as bronchodilators as are β_2-agonists in asthma.[18] Administration can be associated with bothersome adverse effects such as blurred vision, dry mouth, urinary retention, and constipation. However, the anticholinergic agents currently available for inhalation are quaternary amines that are not absorbed systemically and have limited adverse effects.

Ipratropium is the most commonly used anticholinergic for treating bronchoconstriction in asthma. It is available as an MDI and solution for nebulization. Ipratropium has an onset of action of approximately 30 minutes and a duration of action of 4 to 8 hours. Care should be taken not to spray the metered-dose inhaler into or allow the nebulized solution to get in the patient's eyes, as it can cause mydriasis and blurred vision.

The addition of ipratropium bromide to inhaled β_2-agonist therapy in acute severe asthma improves pulmonary function and decreases hospitalization rates in both adult and pediatric patients.[31] The benefit of combining ipratropium and albuterol appears to be greatest in moderate to severe exacerbations, and the combination should be considered first-line therapy in severe exacerbations.

Tiotropium is a long-acting inhaled anticholinergic available in a DPI; it has an onset of action of approximately 30 minutes and a duration of action longer than 24 hours.[32] Because pure asthmatics were excluded from clinical trials for tiotropium, a paucity of data exist concerning its use in asthma.

Leukotriene Modifiers

Leukotriene modifiers either inhibit 5-lipoxygenase (zileuton) or competitively antagonize the effects of leukotriene D_4 (montelukast and zafirlukast). These agents improve FEV_1 and decrease asthma symptoms, rescue drug use, and exacerbations due to asthma. Although these agents offer the convenience of oral therapy for asthma, they are significantly less effective than low doses of inhaled corticosteroids.[2,33]

Use of zileuton is uncommon due to the need for dosing four times a day, potential drug interactions, and the potential for hepatotoxicity with the resulting need for frequent monitoring of liver enzymes. In patients started on zileuton, serum alanine aminotransferase concentrations should be monitored before treatment begins, monthly for the first 3 months, every 2 to 3 months for the remainder of the first year, and then periodically thereafter for as long as the patient continues to receive the medication. Zileuton also inhibits the cytochrome P-450 (CYP) mixed function enzyme system and has been shown to decrease the clearance of theophylline, R-warfarin and propranolol.[34]

The leukotriene inhibitors zafirlukast and montelukast are generally well tolerated and dosed twice and once a day, respectively. Significant increases in hepatic enzymes have been reported in postmarketing studies for zafirlukast but not montelukast.[34] Zafirlukast also inhibits the CYP2C9 and CYP3A4 isoenzymes and may increase prothrombin times in patients receiving warfarin. The International Normalized Ratio should be monitored if warfarin and zafirlukast are used concomitantly. Erythromycin and theophylline may decrease zafirlukast concentrations, whereas aspirin may increase zafirlukast concentrations. It is not clear if these interactions are clinically important. Montelukast does not appear to inhibit the cytochrome P-450 enzymes, but drugs that induce CYP3A4 may decrease montelukast concentrations.

Both of these agents have been associated with rare reports of Churg-Strauss syndrome. This syndrome may result from the corticosteroid dose reduction, as it has also been reported when systemic corticosteroids have been reduced or withdrawn in conjunction with the initiation of high-potency inhaled corticosteroids.[35]

Cromolyn and Nedocromil

Cromolyn and nedocromil are inhaled anti-inflammatory agents that block both the early- and late-phase response. Both agents are considered alternative therapies to inhaled corticosteroids for the treatment of mild persistent asthma; however, both are less effective than low doses of inhaled corticosteroids.[2,30] The exact mechanism of action of these agents is not understood, but they appear to inhibit mast cell mediator release as well as modulate other inflammatory responses.[3]

Patients receiving these agents may notice improvement in 1 to 2 weeks, but maximal benefit may not be seen for 4 to 6 weeks. Cromolyn and nedocromil appear to be similar in efficacy to the leukotriene antagonists and theophylline for persistent asthma.[18] Both agents are well tolerated with adverse effects limited to cough and wheezing. Bad taste and headache have also been reported with nedocromil. One dose of cromolyn or nedocromil prior to exercise or allergen exposure will provide effective prophylaxis for 1 to 2 hours. Cromolyn and nedocromil are not as effective as albuterol for prophylaxis of exercise-induced asthma.

In addition to their decreased efficacy compared to corticosteroids, a primary drawback to the use of these agents is

the need to dose them four times a day until symptoms stabilize, after which the dosage frequency can be reduced to three times a day for cromolyn and twice a day for nedocromil.[18]

Methylxanthines

Theophylline is also considered an alternative to inhaled corticosteroids for the treatment of mild persistent asthma; however, limited efficacy compared to inhaled corticosteroids, a narrow therapeutic index with life-threatening toxicity, and multiple clinically important drug interactions have severely limited its use. Theophylline causes bronchodilation through inhibition of phosphodiesterase and antagonism of adenosine and appears to have anti-inflammatory and immunomodulatory properties as well.[36]

Target serum theophylline concentrations are 5 to 15 mg/L (28 to 83 µmol/L). Adverse effects generally are not problematic at serum concentrations below 15 mg/L (83 µmol/L), but the increased risk of adverse effects outweighs the increase in bronchodilation in most patients above 15 mg/L (83 µmol/L).[36] Headache, nausea, vomiting, and irritability may occur at serum concentrations less than 20 mg/L (110 µmol/L) but are rare when the dose is started low and increased slowly. More serious adverse effects, including cardiac arrhythmias, seizures, toxic encephalopathy, and death can occur at higher concentrations.[18] Arrhythmias and seizures may occur without nausea and vomiting, particularly in chronic toxicity.

Theophylline is primarily metabolized by CYP1A2 and CYP3A4 and is involved in a large number of disease and drug interactions. Theophylline exhibits non-linear pharmacokinetics in the therapeutic range; therefore, serum concentration changes due to dosage adjustments and drug interactions may not always be predictable.[18,36] Theophylline also exhibits interpatient variability in hepatic clearance, and therefore patients receiving theophylline should have their serum theophylline concentrations monitored.

Omalizumab

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that inhibits binding of IgE to receptors on mast cells and basophils, resulting in the inhibition of mediator release and attenuation of the early- and late-phase allergic response. It may be a treatment option for moderate to severe persistent asthmatics 12 years of age or older whose asthma is not controlled by inhaled corticosteroids and who have a positive skin test or in vitro reactivity to perennial allergens.[37] Omalizumab significantly decreases inhaled corticosteroid use, number and length of exacerbations, and increases asthma-related quality of life.[37]

Omalizumab is given as a subcutaneous injection, and the dose is based on the patient's weight and initial total IgE serum concentration. The dosage should not be adjusted based on subsequent total serum IgE measurements. Drug clearance appears to depend on patient weight, and dosage should be adjusted if there is a significant change in body weight. Doses greater than 150 mg should be administered as separate injections at multiple sites. The most common adverse effects are injection site reactions and include bruising, redness, pain, stinging, itching, and burning. Anaphylactic reactions are rare.

Treatment of Chronic Asthma

The intensity of pharmacologic therapy is based on the severity of the disease, and the least amount of medications necessary to meet the goals of asthma therapy should be used.[1,3] Stepwise therapy for the treatment of chronic asthma based on disease severity is shown in Table 11–1.

Mild Intermittent Asthma

In patients with mild intermittent asthma, long-term control medications are not necessary, and patients should use a short-acting inhaled β_2-agonist to prevent or treat symptoms.[2] This classification includes patients with exercise-induced asthma, seasonal asthma, or asthma symptoms associated with infrequent trigger exposure. Patients can pre-treat with two puffs of cromolyn or nedocromil prior to exposure to a known trigger. The treatment of choice for exercise-induced asthma is two inhalations of albuterol 5 minutes prior to exercise.[1] Cromolyn and nedocromil are less effective than albuterol for prophylaxis of exercise-induced asthma.

Persistent Asthma

Patients who use their short-acting inhaled β_2-agonist more than twice a week should be treated as mild persistent asthma, and consideration should be given to treating those with a history of severe exacerbations as having moderate persistent asthma.[2,3]

Patients with persistent asthma require daily long-term control therapy (Table 11–4). The NAEPP recommends that long-term control therapy be initiated one step above the severity classification to gain quick control, and once the asthma is controlled, therapy should be stepped down to the least amount of medication necessary to maintain control.[1] This may require high-dose inhaled corticosteroids or a short course of systemic corticosteroids. However, initiating treatment at a moderate dose of inhaled corticosteroids may be as effective as initiating therapy with a high-dose inhaled corticosteroid and may decrease the chances of overmedication.[3,38] Therapy should be evaluated on a regular basis, and a gradual step down in long-term control therapy should be initiated when possible.[1] Inhaled corticosteroids are the long-term control medication of choice at all levels of severity and in all age groups.[2] Cromolyn, leukotriene modifiers, nedocromil, and theophylline are non-preferred alternatives to inhaled corticosteroids.

Mild Persistent Asthma

In mild persistent asthma, daily use of a low-dose inhaled corticosteroid is the preferred treatment in all age groups. Cromolyn,

nedocromil, and leukotriene modifiers should be reserved for patients who cannot take inhaled corticosteroids.[2,25]

Moderate Persistent Asthma

❸ *The addition of a long-acting inhaled β_2-agonist to low-dose inhaled corticosteroids is the preferred treatment of moderate asthma in adults and school-age children.*[2] Although efficacy data in pre-school children are lacking, the combination is one of the preferred treatments for moderate persistent asthma in this age group as well. Medium-dose inhaled corticosteroids have also been shown to be effective in pre-school children and are also a preferred treatment in this age group.[2] In some patients with moderate persistent asthma, particularly those with risks for severe exacerbations, the combination of a medium-dose inhaled corticosteroid plus a long-acting inhaled β_2-agonist may be preferred for asthma control.[2]

Severe Persistent Asthma

Patients with severe persistent asthma should receive high-dose inhaled corticosteroids, a long-acting inhaled β_2-agonist, and if needed, systemic corticosteroids.[2] Because of the significant adverse effects seen with long-term therapy, efforts should be made to optimize other therapies in an attempt to discontinue or limit systemic corticosteroid therapy. The Global Initiative for Asthma guidelines suggest adding a leukotriene modifier or theophylline as an alternative to starting systemic corticosteroids.[3]

Leukotriene modifiers may permit dose reduction of inhaled corticosteroids in moderate and severe asthmatics, improve surrogate markers of inflammation in patients treated with inhaled corticosteroids plus a long acting β_2-agonist, and improve asthma control in patients not controlled on low to high doses of inhaled corticosteroids.[3,39] Thus, addition of a leukotriene modifier should be considered for patients not controlled by high-dose inhaled corticosteroids and an inhaled long-acting β_2-adrenergic agonist before starting systemic corticosteroids.[3] In patients in whom systemic corticosteroids are necessary for asthma control, the lowest effective dose should be used, and repeated attempts should be made to wean the patient from systemic corticosteroids or decrease the dose.

All patients with chronic asthma should be prescribed a short-acting inhaled β-agonist to treat symptoms; however, use of these agents should be minimized. ❾ *Excessive use of inhaled short-acting β_2-agonists is an indicator of inadequately controlled asthma*, and long-term control therapy should be intensified. Excessive use can be demonstrated by daily use of these agents, use of more than one canister a month, increasing use, or lack of expected effect.[2] Additionally, failure to have a rapid and sustained response to these agents in worsening asthma indicates the need for further medical attention and intensification of therapy.[3] Use of an inhaled short-acting β_2-agonist more than twice a week to treat symptoms is cause to consider stepping up long-term control therapy.[10]



Patient Encounter, Part 2: The Medical History, Physical Exam, and Diagnostic Tests

PMH
Allergic rhinitis for 6 years
Bronchitis 3 times in the last 6 years, last episode 6 months ago
Hospitalized with viral lower respiratory tract infections twice at ages 2 and 4

FH
Mother had asthma as a child, but "outgrew" it and has had no problems with it since she was 12 or 13 years old; both her mother and father have allergic rhinitis

SH
Only child who lives at home with her mother and father in a two-bedroom duplex built on a concrete slab; neither the patient nor her parents smoke or drink alcohol; they have no animals inside or outside the home

Meds
Fexofenadine SR 180 mg PO daily

ROS
Unremarkable except as described above

PE
General appearance: Small for her age but appears to be well nourished and healthy

VS: Blood pressure 112/68 mm Hg, pulse 78 beats per minute, respiratory rate 18/minute, temperature 37.0°C (98.7°F), Ht 4′6″ (137 cm), Wt 62 lb (28 kg)
Chest: CTA bilaterally, no wheezing
CV: RRR, S_1 and S_2 normal, no rubs, gallops, or murmurs
Exts: No clubbing, cyanosis, or edema

Labs
Normal except for an eosinophil count of 7% of the total white blood cell count

Pulmonary function tests
FEV_1: 1.6 L (90% predicted)
FVC: 1.75 L (92% predicted)
FEV_1/FVC: 0.914
Post-bronchodilator FEV_1: 1.73 L (8.1% increase)
FEV_1 after exercise 1.23 L (23.1% decrease)

- Given this additional information, what is your assessment of the patient's condition?
- Identify your treatment goals for this patient.
- What nonpharmacologic and pharmacologic alternatives are feasible for this patient?
- Outline a treatment plan for this patient that includes nonpharmacologic therapy, pharmacologic therapy, and a monitoring plan. Justify your therapeutic selections.

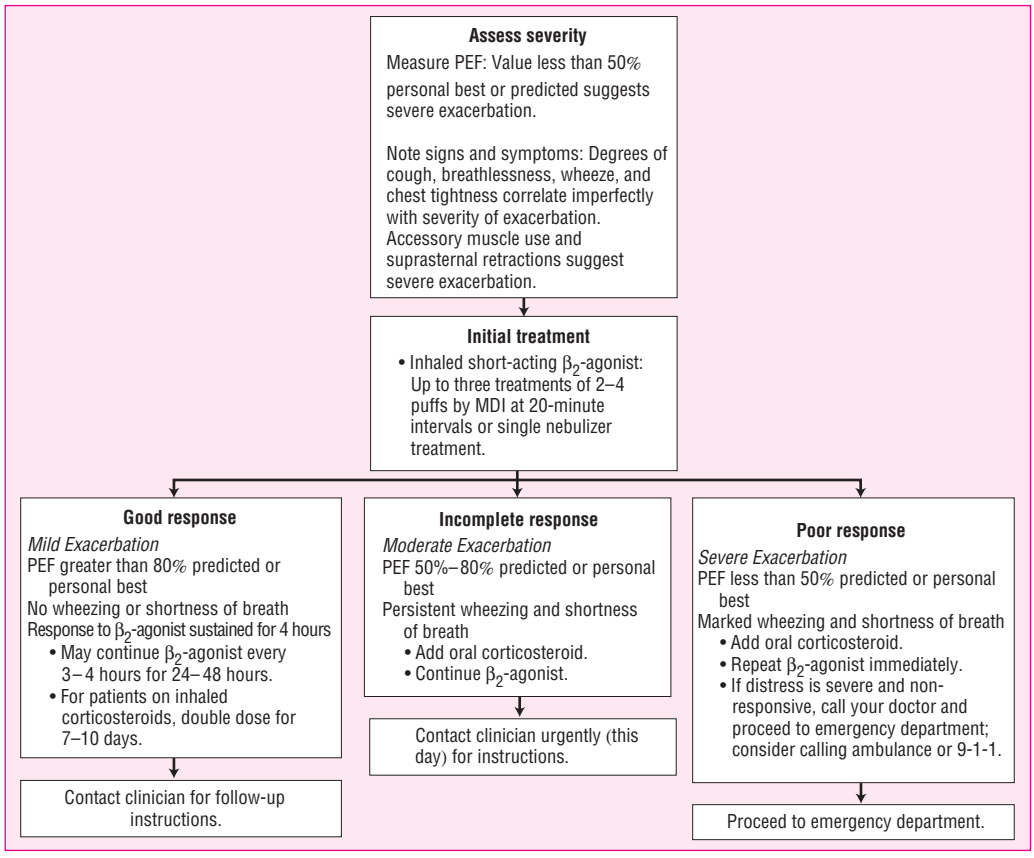


FIGURE 11–2. Home management of acute asthma exacerbation. Patients at risk for asthma-related death should receive immediate clinical attention after initial treatment. PEF, peak expiratory flow. (From Kelly HW, Sorkness CA. Asthma. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 516, with permission.)

Treatment of Acute Severe Asthma

The optimal treatment of acute severe asthma depends on the severity of the exacerbation (Figs. 11–2 and 11–3). The patient's condition usually deteriorates over several hours, days, or weeks; however, rapid deterioration can occur in some patients.[3] Gradual deterioration may indicate failure of long-term controller therapy. Patients with rapid deterioration usually respond well to bronchodilator therapy.[40] Severity at the time of the evaluation can be estimated by signs and symptoms, but patient response 30 minutes after inhalation of a bronchodilator is the best predictor of outcome.[12]

Starting therapy at home allows for rapid initiation and early assessment of response. Patients should follow their written action plan as symptoms intensify or lung function deteriorates. An algorithm for the initial treatment of an asthma exacerbation at home is shown in Fig. 11–2. Based on the initial response to β_2-agonist therapy, the severity of the exacerbation can be assessed, and treatment can be appropriately intensified.[1]

Patients with a good response to therapy should consider intensification of anti-inflammatory therapy.[1] Although guidelines recommend doubling the previous inhaled corticosteroid dose, this may not be necessary for mild exacerbations.[3,41,42] Treatment selection should be individualized based on what has worked for the patient previously.

Patients with mild exacerbations whose response to inhaled short-acting β_2-agonists lasts less than 1 hour and patients with incomplete responses should start a short course of oral prednisone. Corticosteroid therapy should continue until PEF is at least 80% of predicted or personal best.[40] Short-acting β_2-agonist therapy can be continued at two to four inhalations every 3 to 4 hours for several days until symptoms resolve. Continued reliance on short-acting β_2-adrenergic agonists for prolonged periods indicates a need to seek medical care.

Patients with incomplete responses should contact their health care provider immediately for instructions, while those with a poor response should proceed directly to the emergency department.[1] In the emergency department, baseline PEF measurements and oxygen saturation should be monitored. PEF should be monitored before and 15 to 20 minutes after bronchodilator administration. Treatment should be initiated as soon as lung function is assessed (Fig. 11–3). Dosages for emergency department and hospital use of quick relief medications are shown in Table 11–5.

Patients with an oxygen saturation less than 90% (less than 95% in children, pregnant women, and patients with co-existing heart disease) should receive oxygen with the dose adjusted to keep oxygen saturation above these levels.[3,12,40] **Hypoxemia** usually results from a ventilation/perfusion mismatch, and low oxygen levels (less than 30% of the fraction of inspired air) administered by nasal cannula or facemask are sufficient to reverse hypoxemia in most patients.

Infants and young children may present with dehydration due to increased respiratory losses and decreased intake.[1,3] Rehydration

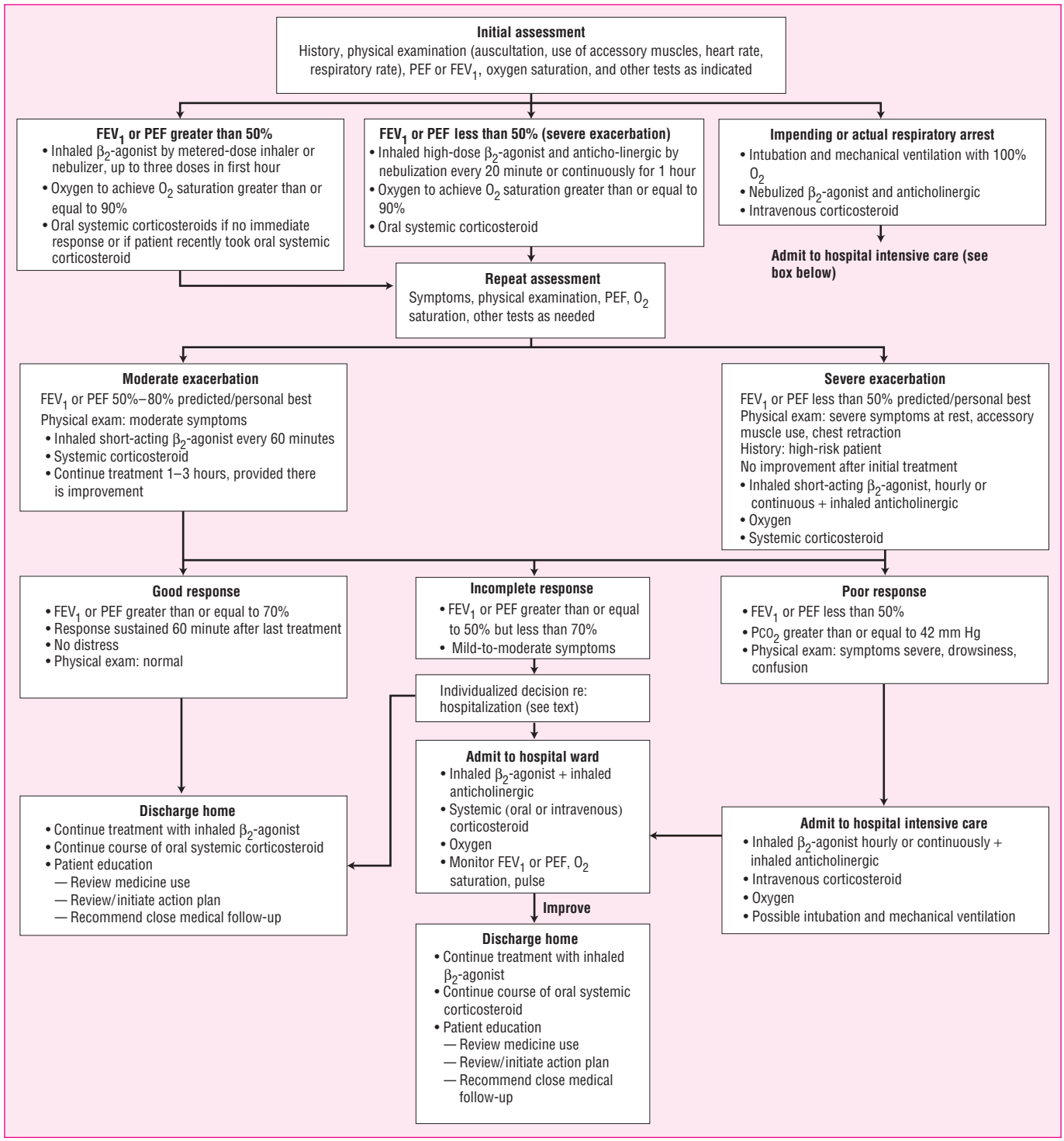


FIGURE 11–3. Emergency department and hospital-based management of asthma exacerbation. FEV_1, forced expiratory volume in 1 second; P_{CO_2}, partial arterial pressure of carbon dioxide; PEF, peak expiratory flow; O_2, oxygen. (From Kelly HW, Sorkness CA. Asthma. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 517, with permission.)

TABLE 11–5. Dosages of Selected Medications for Asthma Exacerbations in Emergency Medical Care or Hospital

Medication	Dosage Form	Adult Dose	Child Dose[a]
Short-Acting Inhaled β_2-Agonists			
Albuterol	Nebulizer solution: 5 mg/mL (5%) 2.5 mg/3 mL 1.25 mg/3 mL 0.63 mg/3 mL MDI: 90 mcg/puff	2.5–5 mg every 20 minutes for 3 doses, then 2.5–10 mg every 1–4 hours as needed, or 10–15 mg/hour continuously 4–8 puffs every 20 minutes up to 4 hours, then every 1–4 hours as needed	0.15 mg/kg (minimum dose 2.5 mg) every 20 minutes for 3 doses, then 0.15–0.3 mg/kg up to 10 mg every 1–4 hours as needed, or 0.5 mg/kg per hour by continuous nebulization 4–8 puffs every 20 minutes for 3 doses, then every 1–4 hours inhalation maneuver; use spacer/holding chamber
Levalbuterol	Nebulizer solution 0.31 mg/3 mL 0.63 mg/3 mL 1.25 mg/3 mL MDI: 45 mcg/puff	1.25–2.5 mg every 20 minutes for 3 doses, then 1.25–5 mg every 1–4 hours as needed or 5–7 mg/hour continuously See albuterol dose; thought to be twice as potent as albuterol on a mg basis	0.075 mg/kg (maximum dose 1.25 mg) every 20 minutes for 3 doses, then 0.075–0.15 mg/kg, up to 5 mg, every 1–4 hours as needed or 0.25 mg/hour by continuous nebulization See albuterol dose; thought to be twice as potent as albuterol on a mg basis
Anticholinergics			
Ipratropium bromide	Nebulizer solution 0.25 mg/mL MDI CFC: 18 mcg/puff MDI HFA: 17 mcg/puff	0.5 mg every 30 minutes for 3 doses then every 2–4 hours as needed 4–8 puffs as needed	0.25 mg every 20 minutes for 3 doses, then every 2–4 hours 4–8 puffs as needed
Ipratropium with albuterol	Nebulizer solution: 0.5 mg ipratropium bromide and 2.5 mg albuterol per 3-mL vial MDI: 18 mcg of ipratropium bromide and 90 mcg of albuterol per puff	3 mL every 30 minutes for 3 doses, then every 2–4 hours as needed 4–8 puffs as needed	1.5 mL every 20 minutes for 3 doses, then every 2–4 hours 4–8 puffs as needed
Systemic Corticosteroids			
Methylprednisolone	Tablets: 2, 4, 8, 16, 32 mg Injection: 40-mg, 125-mg, 500-mg, 1-g, and 2-g vials	120–180 mg/day in 3 or 4 divided doses for 48 hours, then 60–80 mg/day until PEF reaches 70% of predicted or personal best	1 mg/kg every 6 hours for 48 hours, then 1–2 mg/kg per day (maximum of 60 mg/day) in 2 divided doses until PEF 70% of predicted or personal best
Prednisolone	Tablets: 5 mg Oral liquid: 5 mg/5 mL, 15 mg/5 mL		
Prednisone	Tablets: 1, 2.5, 5, 10, 20, 50 mg Oral liquid: 5 mg/mL, 5 mg/5 mL		

[a]Children less than or equal to 12 years of age.
CFC, chlorofluorocarbon; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; PEF, peak expiratory flow.
Adapted from: National Institutes of Health, National Heart Lung and Blood Institute. National Asthma and Education Prevention Program. Expert Panel Report. Guidelines for the Diagnosis and Management of Asthma. Update on Selected Topics 2002. http://www.nhlbi.nih.gov/guidelines/asthma/asthmafullrpt.pdf; accessed August 2005; used with permission.

therapy is appropriate and should be guided by an assessment of fluid status from urine output, urine specific gravity, mucous membrane moisture, and serum electrolytes.[1,18] Dehydration is not problematic in older children and adults; therefore, aggressive rehydration is not recommended.

After the initiation of treatment, the health care professional should conduct an initial history that includes: (1) the time of onset of symptoms; (2) severity of the symptoms, especially compared to previous exacerbations; (3) all current medications and time of last dose; and (4) identification of risk factors for fatal asthma. These risk factors include a past history of severe asthma, use of more than two canisters of a short-acting β_2-adrenergic agonists in a month, current use of systemic corticosteroids or recent withdrawal from corticosteroids, cardiopulmonary comorbidities, serious psychiatric or psychosocial problems, low socioeconomic status and

urban residence, illicit drug use, and sensitivity to the mold allergen *Alternaria*.[1]

A focused physical exam should be conducted that includes the general presentation (level of alertness, fluid status, presence of cyanosis, and use of accessory muscles), auscultation of the lungs, heart rate, and respiratory rate.

Routine antibiotic use is not warranted because the primary infectious agents associated with asthma exacerbations are viruses.[2,3] Antibiotics should be reserved for situations when bacterial infection is strongly suspected (e.g., fever and purulent sputum, pneumonia, and suspected sinusitis).

Theophylline is not recommended for treatment of acute asthma.[2] It provides no additional benefit when optimal inhaled bronchodilators are used and increases the risk of adverse events. Similarly, although magnesium has bronchodilator activity, it offers no significant benefits when optimal bronchodilator therapy is used.[12,40]

Heliox is a mixture of helium and oxygen that results in a lower density of inspired air, thereby improving oxygen delivery. Heliox does not appear to have any significant adverse effects, but it does limit oxygen flow to approximately 30% and therefore is not useful in patients needing higher concentrations of oxygen.[12,40]

Patients who do not respond adequately to intensive therapy in the emergency department within 3 to 4 hours should be admitted to the hospital. Patients responding to therapy in the emergency department with a sustained response to inhaled β_2-agonists (PEF greater than 60%) that lasts at least an hour can be discharged home.[1,12] It is important to ensure that the patient has an inhaled short-term β_2-agonist, is restarted on maintenance medications, and receives a 3- to 10-day course of oral corticosteroids. Prior to discharge, the health care provider should instruct the patient on what to do if asthma symptoms worsen, review medication use, and instruct the patient to schedule a follow-up visit with their health care provider in 3 to 5 days.[1]

Special Populations

Pregnancy

Approximately 4% to 8% of pregnant women are affected by asthma with roughly one-third of them experiencing worsening asthma during pregnancy.[43] Because inadequate control of asthma is a greater risk to the fetus than is the risk of asthma medication use, it is safer for pregnant women to have their asthma appropriately treated with medications than to risk worsening asthma.[43] Goals for asthma therapy in pregnancy are the same as those for the general population, and recent guidelines propose a stepwise approach to asthma therapy in pregnancy that is similar to the guidelines for the general population with respect to preferred therapies for each step.[43]

Because budesonide has the most safety data in humans, it is the preferred inhaled corticosteroid and is the only inhaled corticosteroid classified as pregnancy category B; however, there are no data indicating that other inhaled corticosteroids contribute to increased risk to the mother or fetus.[43] Because of the risk to the fetus, asthma exacerbations should be managed aggressively. Albuterol is the drug of choice for the treatment of asthma symptoms and exacerbations in pregnancy.[43]

Exercise-Induced Asthma

Exercise is one of the most common precipitants of asthma symptoms, and exercise-induced asthma is commonly seen in children and adolescents. Exercise may be a precipitant in up to 90% of the population with asthma and may be the first precipitant noticed in an asthma patient.[18] Shortness of breath, wheezing, or chest tightness usually occur during or shortly after vigorous exercise and resolve within 30 to 60 minutes.

Patients with exercise-induced asthma should warm-up prior to vigorous exercise and cover their mouth and nose with a scarf or mask during cold weather. Increased physical conditioning and gradually decreasing the intensity of exercise prior to stopping may also help prevent bronchospasm. Pre-treatment with albuterol 5 minutes prior to exercise is the treatment of choice and will protect against bronchospasm for 2 to 3 hours.[1] Pretreatment with cromolyn sodium or nedocromil is also effective in preventing bronchospasm, but it is not as effective as albuterol.[18] Pretreatment with salmeterol or formoterol can protect against bronchospasm for up to 12 hours; however, tolerance to the bronchoprotective effects occurs with repeated use and a more reasonable expectation for protection is for 6 to 9 hours. Pretreatment with a leukotriene modifier and regular treatment with inhaled corticosteroids also prevents bronchospasm associated with exercise. Consideration should be given to initiating long-term control therapy in mild intermittent asthmatics using multiple weekly doses of a bronchodilator to prevent asthma symptoms associated with exercise.[3]

Aspirin Sensitivity

Patients with aspirin-sensitive asthma are usually adults and often present with the triad of rhinitis, nasal polyps, and asthma. In this population, acute asthma may occur within minutes of ingesting aspirin or another non-steroidal anti-inflammatory agent. Although acetaminophen is thought to be safe in this population, doses larger than 1 gram may cause acute asthmatic reactions in some patients, and the incidence of asthma is significantly greater in frequent users of acetaminophen compared to non-users.[44,45] Patients with aspirin-sensitive asthma may be able to tolerate cyclooxygenase-2 inhibitors; however, given the potentially serious adverse events that could occur in aspirin-sensitive asthmatics, the first dose of a cyclooxygenase-2 inhibitor should be given under the observation of a health care provider with rescue drugs available.[44]

OUTCOME EVALUATION

Chronic Asthma

- Monitor symptoms such as wheezing, shortness of breath, chest tightness, cough, and nocturnal awakenings due to asthma symptoms. Daytime symptoms should occur no

more frequently than twice a week, and nocturnal symptoms should occur twice a month or less. Patients with more frequent symptoms should have their long-term control medications increased to the next step of therapy.

- Monitor and maintain PEF above 80% of personal best; PEF variability should be less than 20%. Patients with PEF rates consistently greater than 80% over several months should be evaluated for a step down in long-term control therapy. Patients with a PEF less than 80% of personal best should begin to monitor PEF twice daily and consult their asthma action plan. Patients with a PEF less than 50% of personal best should immediately use their short-acting inhaled β_2-agonist and consult their asthma action plan.
- Monitor patient activity levels. Inability of a patient to perform routine physical activities indicates inappropriate therapy, and long-term control medications should be increased according to the next step of therapy.
- Monitor frequency of patient exacerbations. Frequent exacerbations, unscheduled clinic visits, emergency department visits, and hospitalizations due to asthma may indicate a non-adherent patient or the need to step up long-term control medications.
- Monitor patient use of long-term control medications to ensure adherence to the medication plan. Patients not adhering to the long-term control medication regimen should be re-educated on the importance of these medications for asthma control.
- Monitor use of short-acting inhaled β_2-agonists. Use of these agents more than twice a week in intermittent asthma may indicate the need to initiate long-term control therapy. Use of more than one canister per a month indicates the need to step up long-term control therapy.
- Monitor for adverse events from medications, including candidiasis and dysphonia from inhaled corticosteroids.

Acute Severe Asthma

- Monitor PEF, which should increase to greater than 60% of personal best or predicted after the first three doses of an inhaled short-acting β_2-agonist.
- Monitor patients for hypoxemia. Oxygen saturation should be greater than 90% in adults and greater than 95% in children, pregnant women, and patients with co-existing cardiovascular disease.
- In patients with severe exacerbations, monitoring of P_{CO_2} should be considered. Patients with acute asthma usually have a respiratory alkalosis, and a normal or increased P_{CO_2} indicates the potential for respiratory failure.
- Monitor serum potassium in patients receiving high-dose or continuous nebulization of a short-acting β_2-agonist. Serum potassium concentrations should be obtained upon admission, and if hypokalemic, every 4 hours (after each 30 to 40 mEq or mmol of replacement) until the patient's potassium is stable. Potassium should be monitored every 3 to 6 months after discharge.



Patient Encounter, Part 3

Follow-Up

Six months later, RB's mother brings her back for a check-up. The patient has been using her albuterol inhaler 3 to 4 times a week to treat symptoms, and she is waking up about twice a month with shortness of breath. She has developed a sore mouth. White patches on the back of her tongue and the inside of her cheek are observed on examination.

Meds

Qvar™ 84 mcg/puff, 1 puff 4 times a day
Proventil HFA 2 puffs PRN for symptoms
Flonase 1 puff in each nostril daily

- What further information do you need before altering this patient's therapy?
- How would you counsel this patient to prevent further adverse reactions?
- Assuming that the patient is currently using her medications appropriately, how would you adjust this patient's medication?



Patient Care and Monitoring

Chronic Asthma

1. Obtain a thorough medical history focusing on disease states that may worsen the severity of asthma.
2. Ask the patient about the frequency and severity of symptoms, when symptoms occur, and whether or not the symptoms are associated with exposure to known allergens. Ask the patient about previous emergency department visits and hospitalizations due to asthma.
3. Use the patient's symptoms and pulmonary function tests to classify disease severity.
4. Explain the goals of therapy to the patient and ask if (s)he has any personal therapeutic goals.
5. Develop a patient education plan that fits the patient's needs. Educate about the differences between the asthmatic and normal lung and what happens to the lung during an asthma attack. Counsel the patient on how their medications work and differentiate between long-term control and quick relief medications.
6. Provide the patient with a specific allergen avoidance plan and counsel all patients to avoid secondhand tobacco smoke.
7. Demonstrate the appropriate use of drug delivery devices and peak flow meters; then have the patient perform these activities for you. If the task is performed incorrectly, demonstrate the skill again, emphasizing the incorrect step and have the patient re-demonstrate the skill.

(*Continued*)

Patient Care and Monitoring (*Continued*)

8. Prepare a patient-specific self-monitoring plan and review it with the patient. Educate the patient on the signs and symptoms of asthma deterioration and when and how to take rescue actions.
9. Assess the patient's adherence to long-term control therapy. If the patient is non-adherent, stress the importance of adherence to this therapy. Evaluate the complexity of the patient's treatment plan and simplify it as much as possible. Determine whether the patient would benefit from an inhaled corticosteroid/inhaled long-acting β_2-agonist combination product.
10. Assess the patient for adverse effects, particularly candidiasis and dysphonia associated with inhaled corticosteroids.
11. Evaluate therapy on a regular basis. Assess the patient's control of asthma by evaluating symptoms, PEF diary entries, and rescue medication use. Step long-term control therapy up or down based on these parameters. Before stepping up therapy, reassess the patient's inhaler technique to assure appropriate drug delivery.

Acute Severe Asthma

1. Assess the patient's PEF.
2. Assess whether or not the patient can use an MDI with a spacer or holding chamber. If the patient cannot use the device, determine whether someone can assist the patient with the inhaler device, or whether a nebulizer is necessary.
3. Initiate therapy with a short-acting β_2-agonist and 2 to 6 L/minute of oxygen if needed.
4. Perform a brief medical history to determine the time of symptom onset, symptom severity, symptom severity in relation to previous exacerbations, current medications, previous emergency department visits or hospitalizations due to asthma, previous history of respiratory failure, and psychiatric or psychological disorders.
5. Assess the patient's general appearance, use of accessory muscles, respiratory rate, heart rate, lung sounds, pulsus paradoxus, PEF, and oxygen saturation.
6. Reassess pulmonary function every 20 to 30 minutes. If there was not an immediate response to the inhaled short acting β_2-agonist, initiate systemic corticosteroid therapy. If the patient is not improving, add ipratropium to the patient's therapy and continue with a high-dose inhaled short-acting β_2-agonist.
7. Assess the patient for hospitalization or discharge home.
8. If the patient is discharged home, ensure that the patient has a short-acting β_2-agonist, review the appropriate technique for inhaler use with the patient, and ensure that the patient has a prescription for 3 to 10 days of oral corticosteroids.
9. Restart the patient on maintenance therapy. Instruct the patient on what to do if asthma should worsen and to follow-up with his/her health care provider in 3 to 5 days.

ABBREVIATIONS

AHR:	airway hyperresponsiveness
CFC:	chlorofluorocarbon
CYP:	cytochrome P-450 isoenzyme
DPI:	dry powder inhaler
FEV_1:	forced expiratory volume in 1 second
FVC:	forced vital capacity
HFA:	hydrofluoroalkane
IgE:	immunoglobulin E
MDI:	metered-dose inhaler
NAEPP:	National Asthma Education and Prevention Program
Pa_{O_2}:	partial arterial oxygen pressure
P_{CO_2}:	partial arterial pressure of carbon dioxide
PEF:	peak expiratory flow
T_H2:	type 2 T helper CD4+ cell

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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12 Chronic Obstructive Pulmonary Disease

Tara R. Whetsel and Nicole D. Verkleeren



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Describe the pathophysiology of chronic obstructive pulmonary disease (COPD).
2. Identify signs and symptoms of COPD.
3. List the treatment goals for a patient with COPD.
4. Design an appropriate COPD treatment regimen based on patient-specific data.
5. Develop a monitoring plan to assess effectiveness and adverse effects of pharmacotherapy for COPD.
6. Formulate an appropriate education plan for a patient with COPD.

Key Concepts

❶ Inflammation plays a key role in the pathophysiology of COPD, but it differs from that seen in asthma; therefore, the use of and response to anti-inflammatory medications are different.

❷ An integrated approach of health maintenance (e.g., smoking cessation), drug therapy, and supplemental therapy (e.g., oxygen and pulmonary rehabilitation) should be used in a stepwise manner.

❸ Smoking cessation is the only intervention known to slow the rate of decline in pulmonary function in patients with COPD.

❹ Bronchodilators are the mainstay of treatment for symptomatic COPD. They reduce symptoms and improve exercise tolerance and quality of life.

❺ In symptomatic patients with severe COPD and frequent exacerbations, regular treatment with inhaled corticosteroids decreases the number of exacerbations per year and improves health status; however, corticosteroids do not slow the long-term decline in pulmonary function.

❻ Antibiotics should be used in patients with COPD exacerbations who have either of the following characteristics: (1) at least two of three cardinal symptoms: increased dyspnea, sputum volume, or sputum purulence; or (2) a severe exacerbation requiring mechanical ventilation.

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by airflow limitation that is not fully reversible. It is caused by exposure to noxious particles or gases, most commonly cigarette smoke. It is a major cause of morbidity and mortality and a leading cause of disability in the United States.

COPD includes chronic bronchitis and emphysema. Chronic bronchitis is defined clinically as a chronic productive cough for at least 3 months in each of two consecutive years in a patient in whom other causes have been excluded.[1] Emphysema is defined pathologically as the presence of permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls without obvious fibrosis.[1] The major risk factor for both conditions is cigarette smoking, and many patients share characteristics of each condition. Therefore, new consensus guidelines have moved away from using these subsets and instead focus on chronic airflow limitation.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) is an expert panel of health professionals who have developed a consensus document with recommendations for the diagnosis and care of patients with COPD.[2] The online document is updated annually and is commonly referred to as the GOLD guidelines. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) have jointly published standards for the diagnosis and treatment of patients with COPD.[1] The ATS/ERS guidelines provide more specific recommendations on oxygen therapy, pulmonary rehabilitation, and other treatment issues than the broader GOLD guidelines.

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EPIDEMIOLOGY AND ETIOLOGY

In 2001, 12.1 million United States adults 25 years of age and older reported having COPD.[3] The true prevalence is larger; COPD is underdiagnosed because many patients have few or no symptoms in the early stages.

COPD is the fourth leading cause of death in the United States; in 2000, 119,000 adults died from the disease.[3] In 2002, COPD was estimated to cost the United States $32.1 billion, with direct medical costs accounting for $18 billion of the total.[3] Morbidity, mortality, and costs are all expected to increase over the next decade.

Exposures and host factors play a role in the development of COPD. Cigarette smoking is the leading cause of COPD and accounts for 80% to 90% of cases in developed countries.[4] Occupational exposure to dusts and chemicals (vapors, irritants, and fumes) also plays a role. Environmental air pollution has been implicated as an etiologic factor, but its exact role is unclear. Not all smokers develop clinically significant COPD, which suggests that genetic susceptibility plays a role. The best documented genetic factor is a rare hereditary deficiency of α_1-antitrypsin (AAT). Severe deficiency of this enzyme results in premature and accelerated development of emphysema. Asthma and airway hyperresponsiveness have been identified as risk factors, but how they influence the development of COPD is unknown. Failure to reach maximal lung function, due to recurrent infections or exposure to tobacco smoke during childhood, may also increase the risk of COPD.

PATHOPHYSIOLOGY

COPD is characterized by pathologic changes in the central airways, peripheral airways, lung **parenchyma**, and pulmonary vasculature. Chronic inflammation in the lung from repeated exposure to noxious particles and gases is primarily responsible for these changes.[2] An imbalance between **proteinases** and **antiproteinases** in the lung and oxidative stress are also thought to be important in the pathogenesis of COPD. These processes may be a result of ongoing inflammation or may arise from environmental (e.g., oxidants in cigarette smoke) or genetic (e.g., AAT deficiency) factors (Fig. 12–1).[2] In addition to these destructive processes, chronic inflammation and exposure to noxious particles and gases disrupts or impairs the normal protective and repair mechanisms.

Inflammation is present in the lungs of all smokers. It is unclear why only 15% to 20% of smokers develop COPD, but susceptible individuals appear to have an exaggerated inflammatory response.[5] ❶ *The inflammation of COPD differs from that seen in asthma, so the use of anti-inflammatory medications and the response to those medications are different.* The inflammation of asthma is mainly mediated through eosinophils and mast cells. In COPD the primary inflammatory cells include neutrophils, macrophages, and $CD8^+$ T lymphocytes.

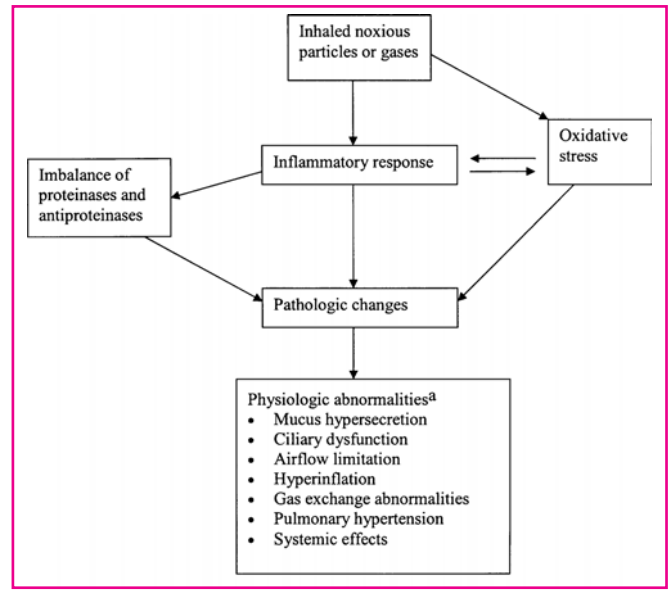


FIGURE 12–1. Pathophysiology of chronic obstructive pulmonary disease.
[a]The physiologic abnormalities usually develop in this order.

Eosinophils may be increased in some patients, particularly during exacerbations. Activated inflammatory cells release a variety of mediators, most notably leukotriene B_4, interleukin-8, and tumor necrosis factor-α (TNF-α). Various proteinases, such as elastase, cathepsin G, and proteinase-3, are secreted by activated neutrophils. These mediators and proteinases are capable of sustaining inflammation and damaging lung structures.

Proteinases and antiproteinases are part of the normal protective and repair mechanisms in the lungs. The imbalance of proteinase-antiproteinase activity in COPD is a result of either increased production or activity of destructive proteinases or inactivation or reduced production of protective antiproteinases. AAT (an antiproteinase) inhibits trypsin, elastase, and several other proteolytic enzymes. Deficiency of AAT results in unopposed proteinase activity, which promotes destruction of alveolar walls and lung parenchyma, leading to emphysema.

Markers of oxidative stress (e.g., hydrogen peroxide, nitric oxide, and isoprostane $F_2\alpha$-III) have been found in the epithelial fluid, breath, and urine of cigarette smokers and patients with COPD.[2] Increased oxidative stress contributes to COPD in a variety of ways. Oxidants (e.g., reactive oxygen species, superoxide, and nitric oxide) can react with and damage a variety of molecules leading to cell dysfunction and damage to the lung extracellular matrix. Oxidative stress promotes inflammation and contributes to the proteinase-antiproteinase imbalance by reducing antiproteinase activity. In addition, oxidants constrict airway smooth muscle, contributing to reversible airway narrowing.

In the central airways (the trachea, bronchi, and bronchioles greater than 2 to 4 mm in internal diameter), inflammatory cells and mediators stimulate mucus-secreting gland **hyperplasia**

and mucus hypersecretion. Mucus hypersecretion and ciliary dysfunction lead to chronic cough and sputum production. The major site of airflow obstruction is the peripheral airways (small bronchi and bronchioles with an internal diameter less than 2 mm). Three mechanisms are postulated to be involved in the narrowing of these small airways.[2] Airways may be blocked by inflammatory exudates and mucus hypersecretion. Loss of elasticity and destruction of alveolar attachments leads to loss of support and closure of small airways during expiration. Infiltration of inflammatory cells, increased smooth muscle tissue, and fibrosis cause thickening of airway walls. Of these mechanisms, the structural changes in the airway walls are the most important cause of fixed airflow obstruction.

As airflow obstruction worsens, the rate of lung emptying is slowed and the interval between inspirations does not allow expiration to the relaxation volume of the lungs. This leads to pulmonary hyperinflation, which initially only occurs during exercise, but later is also seen at rest. Hyperinflation contributes to the discomfort associated with airflow obstruction by flattening the diaphragm and placing it at a mechanical disadvantage.

In advanced COPD, airflow obstruction, damaged bronchioles and alveoli, and pulmonary vascular abnormalities lead to impaired gas exchange. This results in **hypoxemia** and eventually **hypercapnia**. Hypoxemia is initially present only during exercise but occurs at rest as the disease progresses. Inequality in the **ventilation/perfusion ratio (V_AQ)** is the major mechanism behind hypoxemia in COPD.

Pulmonary hypertension develops late in the course of COPD, usually after the development of severe hypoxemia. It is the most common cardiovascular complication of COPD and can result in **cor pulmonale**, or right-sided heart failure. Hypoxemia plays the primary role in the development of pulmonary hypertension by causing vasoconstriction of the pulmonary arteries and by promoting vessel wall remodeling. Destruction of the pulmonary capillary bed by emphysema further contributes by increasing the pressure required to perfuse the pulmonary vascular bed. Cor pulmonale is associated with venous stasis and thrombosis that may result in pulmonary embolism. Another important systemic effect is the progressive loss of skeletal muscle mass, which contributes to exercise limitations and declining health status.

DIAGNOSIS

A suspected diagnosis of COPD should be based on the patient's symptoms and/or history of exposure to risk factors. **Spirometry** is required to confirm the diagnosis. The presence of a postbronchodilator FEV_1/FVC ratio less than 70% [the ratio of FEV_1 to forced vital capacity (FVC)] confirms the presence of airflow limitation that is not fully reversible.[1,2] Spirometry results can further be used to classify COPD severity (Table 12–1). Full pulmonary function tests (PFTs) with lung volumes and diffusion capacity and arterial blood gases are not necessary to establish the diagnosis or severity of COPD.



Clinical Presentation of Chronic Obstructive Pulmonary Disease

General

- Patients with COPD are initially asymptomatic. The disease is usually not diagnosed until declining lung function leads to significant symptoms and prompts patients to seek medical care.

Symptoms

- The onset of symptoms is variable but often does not occur until the forced expiratory volume in one second (FEV_1) has fallen to approximately 50% of predicted.[2]
- Initial symptoms include chronic cough (duration greater than 3 months), which may be intermittent at first; chronic sputum production; and dyspnea on exertion.
- As COPD progresses, dyspnea at rest develops and the ability to perform activities of daily living declines.

Signs

- Observation of the patient may reveal use of accessory muscles of respiration (manifested as paradoxical movements of the chest and abdomen, in a "see-saw"–type motion), pursed-lips breathing, and hyperinflation of the chest with increased anterior-posterior diameter ("barrel chest").
- On auscultation of the lungs, patients may have distant breath sounds, wheezing, a prolonged expiratory phase of respiration, and **rhonchi**.
- In advanced COPD, signs of hypoxemia may include **cyanosis** and tachycardia.
- Signs of cor pulmonale include increased pulmonic component of the second heart sound, jugular venous distention (JVD), lower extremity edema, and hepatomegaly.

Laboratory Tests

- Hematocrit may be elevated and may exceed 55% (**polycythemia**).
- Arterial blood gases (ABGs) should be obtained in patients with an FEV_1 less than 40% predicted or signs or symptoms suggestive of cor pulmonale or respiratory failure.[2] COPD patients characteristically exhibit normal or increased arterial carbon dioxide tension ($PaCO_2$) and decreased arterial oxygen tension (PaO_2).
- An α_1-antitrypsin level should be obtained in younger patients (less than 45 years old) presenting with COPD signs and symptoms, especially if there is a strong family history of emphysema.

It is important to distinguish COPD from asthma because treatment and prognosis differ. Differentiating factors include age of onset, smoking history, triggers, occupational history, and degree of reversibility measured by pre- and postbronchodilator spirometry. In some patients a clear distinction between asthma and COPD is not possible. Management of these patients should be similar to that of asthma. **Bronchiectasis**, cystic fibrosis, **obliterative bronchiolitis**, congestive heart failure, and

TABLE 12–1. GOLD Classification of COPD Severity[a]

Stage	Category	FEV_1/FVC	FEV_1	Symptoms
0	At risk	Greater than or equal to 70%	Greater than or equal to 80% predicted	Chronic cough and sputum production
I	Mild	Less than 70%	Greater than or equal to 80% predicted	With or without chronic cough and sputum production
II	Moderate	Less than 70%	50%–79% predicted	With or without chronic cough and sputum production
III	Severe	Less than 70%	30%–49% predicted	With or without chronic cough and sputum production
IV	Very severe	Less than 70%	Less than 30% predicted or less than 50% predicted plus chronic respiratory failure[b]	

[a]Classification based on postbronchodilator FEV_1.
[b]Respiratory failure: Arterial partial pressure of oxygen (PaO_2) less than 60 mm Hg with or without arterial partial pressure of carbon dioxide ($Paco_2$) greater than 50 mm Hg while breathing air at sea level. FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.
Adapted from GOLD Science Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2005. Available at: www.goldcopd.com. Used with permission.

tuberculosis are other possible differential diagnoses that are usually easier to distinguish from COPD. Chest radiography or high-resolution computed tomography (CT) along with patient presentation help rule out these other lung diseases.

TREATMENT

Desired Outcomes

The goals of COPD management include: (1) smoking cessation; (2) reducing symptoms; (3) minimizing the rate of decline in lung function; (4) maintaining or improving quality of life; (5) preventing and treating exacerbations; and (6) limiting complications.



Patient Encounter, Part 1

A 49-year-old man with a past medical history of hypertension presents to the clinic complaining of shortness of breath that began about 3 to 4 years ago. His symptoms have gradually gotten worse since then. He is now unable to walk 100 yards without having to stop and rest. He also has a daily cough that is usually productive of yellowish sputum. He smokes about $1^1/_2$ packs of cigarettes a day and has done so for the past 30 years. He also drinks on average 6 to 7 beers a day. He does not have any significant occupational exposures to dust, gases, or fumes.

- What information is suggestive of COPD?
- What risk factors does he have for COPD?
- What additional information do you need to know before creating a treatment plan for this patient?

General Approach to Treatment

❷ *An integrated approach of health maintenance (e.g., smoking cessation), drug therapy, and supplemental therapy (e.g., oxygen and pulmonary rehabilitation) should be used in a stepwise manner.* Table 12–2 provides an overview of the management of stable COPD.

Nonpharmacologic Therapy

Smoking Cessation

❸ *Smoking cessation is the only intervention known to slow the rate of decline in pulmonary function in patients with COPD.*[6,7] Stopping smoking can also reduce cough and sputum production and decrease airway reactivity. Therefore, it is a critical part of any treatment plan for patients with COPD. Unfortunately, achieving and maintaining cessation is a major challenge. A clinical practice guideline from the United States Public Health Service recommends a specific action plan depending on the current smoking status and desire to quit (Fig. 12–2).[8] Brief interventions are effective and can increase cessation rates significantly. The five A's and the five R's can be used to guide brief interventions (Table 12–3).

All tobacco users should be assessed for their readiness to quit and appropriate strategies implemented. Those who are ready to quit should be treated with a combination of counseling on behavioral and cognitive strategies and pharmacotherapy (nicotine replacement therapy, sustained-release bupropion, or varenicline). In COPD patients, the likelihood of sustained abstinence is higher with nicotine replacement therapy than with sustained-release bupropion.[9]

TABLE 12–2. Treatment Algorithm for Stable Chronic Obstructive Pulmonary Disease

GOLD Stage	Recommended Therapy[2]
0: At Risk	Avoidance of risk factor(s), especially smoking cessation; influenza vaccination
	ADD
I: Mild	Short-acting inhaled bronchodilator when needed (e.g., ipratropium, albuterol, or combination inhaler)
	ADD
II: Moderate	Pulmonary rehabilitation Inhaled LABD on a scheduled basis (e.g., tiotropium,[a] salmeterol, or formoterol) ↓ Inadequate response to LABD? ↓ Yes Use alternative class or combine classes of inhaled LABD ↓ Inadequate response to LABD? ↓ Yes Add/substitute oral theophylline
	ADD
III: Severe	Inhaled corticosteroids if repeated exacerbations[b]
	ADD
IV: Very severe	Long-term oxygen if chronic respiratory failure Consider surgical treatment

[a]Albuterol should be used as rescue therapy for patients treated with tiotropium.
[b]Defined as three exacerbations in the past 3 years by GOLD and as at least one exacerbation requiring a course of oral corticosteroids or antibiotics within the last year by ATS/ERS. Other authorities define frequent exacerbations as at least two within the past year.
ATS, American Thoracic Society; ERS, European Respiratory Society; LABD, long-acting bronchodilator.

Pulmonary Rehabilitation

Pulmonary rehabilitation results in significant and clinically meaningful improvements in dyspnea, exercise capacity, health status, and health care utilization.[10] It should be considered for patients with COPD who have dyspnea or other respiratory symptoms, reduced exercise capacity, a restriction in activities because of their disease, or impaired health status.[1] A comprehensive pulmonary rehabilitation program should include exercise training, nutrition counseling, and education. It should cover a range of non-pulmonary problems including exercise deconditioning, relative social isolation, altered mood states (especially depression), muscle wasting, and weight loss.

Rehabilitation programs may be conducted in the inpatient, outpatient (most common), or home setting. The minimum length of an effective program is 2 months; the longer the program, the more sustained the results.[10] It is important for patients to continue with a home exercise program to maintain the benefits gained from the pulmonary rehabilitation program.

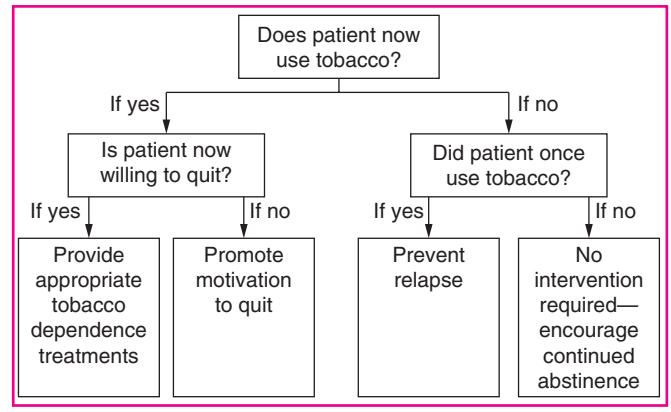


FIGURE 12–2. Algorithm for routine assessment of tobacco use status. (Reproduced from Treating Tobacco Use and Dependence—Clinician's Packet. A How-To Guide for Implementing the Public Health Service Clinical Practice Guideline, March 2003. United States Public Health Service. Available at: www.surgeongeneral.gov/tobacco/clinpack.html.)

Long-Term Oxygen Therapy

Long-term administration of oxygen (greater than 15 hours per day) to patients with chronic respiratory failure has been shown to reduce mortality and improve quality of life.[1,2] Oxygen therapy should be initiated in stable patients with very severe COPD (GOLD stage IV) who are optimized on

TABLE 12–3. Components of Brief Interventions for Tobacco Users

The 5 A's for Brief Intervention
- **A**sk: Identify and document tobacco use status for every patient at every visit.
- **A**dvise: Urge every tobacco user to quit.
- **A**ssess: Is the tobacco user willing to make a quit attempt at this time?
- **A**ssist: Use counseling and pharmacotherapy to help patients willing to make a quit attempt.
- **A**rrange: Schedule follow-up contact, preferably within the first week after the quit date.

The 5 R's to Motivate Smokers Unwilling to Quit at Present
- **R**elevance: Tailor advice and discussion to each smoker.
- **R**isks: Help the patient identify potential negative consequences of tobacco use.
- **R**ewards: Help the patient identify the potential benefits of quitting.
- **R**oadblocks: Help the patient identify barriers to quitting.
- **R**epetition: Repeat the motivational message at every visit.

drug therapy and meet one of the following criteria: (1) A resting Pa_{O_2} at or below 55 mm Hg (7.32 kPa) or oxygen saturation (Sa_{O_2}) at or below 88%; (2) Pa_{O_2} between 55 and 60 mm Hg (7.32 and 7.98 kPa) or Sa_{O_2} of 89% and evidence of pulmonary hypertension, peripheral edema suggesting congestive heart failure, or polycythemia.[1,2]

The dual-prong nasal cannula is the standard means of delivering continuous flow oxygen. The goal of therapy is to increase the baseline oxygen saturation to at least 90% and/or Pa_{O_2} to at least 60 mm Hg (7.98 kPa), allowing adequate oxygenation of vital organs. The flow rate, expressed as liters per minute (L/minute), must be increased during exercise and sleep and can be adjusted based on pulse oximetry. Hypoxemia also worsens during air travel; patients requiring oxygen should generally increase their flow rate by 2 L/minute during flight.[1]

Oxygen therapy should be continued indefinitely if it was initiated while the patient was in a stable state (rather than during an acute episode). Withdrawal of oxygen because of improved Pa_{O_2} in such a patient may be detrimental.

Surgery

Bullectomy, lung volume reduction surgery, and lung transplantation are surgical options for very severe COPD. These procedures may result in improved spirometry, lung volumes, exercise capacity, dyspnea, health-related quality of life, and possibly survival. Patient selection is critical because not all patients benefit. Refer to the ATS/ERS COPD standards for a detailed discussion of appropriate selection of surgical candidates.[1]

Pharmacologic Therapy of Stable COPD

The medications available for COPD are effective for reducing or relieving symptoms, improving exercise tolerance, reducing the number and severity of exacerbations, and improving quality of life. No medications presently available have been shown to slow the rate of decline in lung function.

Bronchodilators

❹ *Bronchodilators are the mainstay of treatment for symptomatic COPD. They reduce symptoms and improve exercise tolerance and quality of life.*[2] They can be used as needed for symptoms or on a scheduled basis to prevent or reduce symptoms. Bronchodilator drugs commonly used in COPD include β_2-agonists, anticholinergics, and theophylline. The choice depends on availability, individual response, and preferences. The inhaled route is preferred, but attention must be paid to proper inhaler technique training. Long-acting inhaled bronchodilators are more effective and convenient but more expensive than short-acting inhaled bronchodilators. Combination therapy improves efficacy and is preferred over increasing the dose of a single agent, especially since the dose-response relationship using FEV_1 as the outcome is relatively flat for single-agent therapy.

Beta$_2$-Agonists

β_2-Agonists cause airway smooth muscle relaxation by stimulating adenyl cyclase to increase the formation of cyclic adenosine monophosphate (cAMP). Other non-bronchodilator effects have been observed, such as improvement in mucociliary transport, but their significance is uncertain.[11] β_2-Agonists are available in inhalation, oral, and parenteral dosage forms; the inhalation route is preferred because of fewer adverse effects.

These drugs are also available in short-acting and long-acting formulations (Table 12–4). The short-acting β_2-agonists include albuterol, levalbuterol, pirbuterol, and terbutaline. They are used as "rescue" therapy for acute symptom relief. Most COPD patients need continuous bronchodilator therapy on a scheduled basis every day. For these patients, short-acting β_2-agonists are inconvenient because of the need for frequent dosing. In addition, short-acting β_2-agonists have been associated with a slight, but statistically significant, loss of effectiveness when used regularly for more than 3 months (tachyphylaxis).[12]

Long-acting β_2-agonists include salmeterol and formoterol. Salmeterol is a partial agonist with a slower onset of action than short-acting β_2-agonists. Formoterol is a more complete agonist and has an onset of action similar to that of albuterol. Full agonists (formoterol) produce greater response at full receptor capacity than partial agonists (salmeterol). Bronchodilator effects of salmeterol and formoterol last at least 12 hours, allowing for twice-daily dosing. Long-acting bronchodilators are superior to scheduled short-acting bronchodilators on important clinical outcomes, including frequency of exacerbations, degree of dyspnea, and health-related quality of life.[11] For symptomatic patients, these are preferred over short-acting agents for maintenance therapy. Patients should also have a short-acting β_2-agonist such as albuterol available for as-needed use ("rescue" medication).

Adverse effects of β_2-agonists are dose-related and include palpitations, tachycardia, and tremor. Sleep disturbance may also occur and appears to be worse with higher doses of inhaled long-acting β_2-agonists. Increasing doses beyond those clinically recommended is without benefit and could be associated with increased adverse effects.

Anticholinergics

Ipratropium and tiotropium are inhaled anticholinergic medications commonly used for COPD. They produce bronchodilation by competitively blocking muscarinic receptors in bronchial smooth muscle. They may also decrease mucus secretion, although this effect is variable. Tiotropium dissociates from receptors extremely slowly resulting in a half-life longer than 36 hours, allowing for once-daily dosing. Ipratropium has an elimination half-life of about 2 hours, necessitating dosing every 6 to 8 hours.

Tiotropium provides the most consistent improvements on the widest range of outcomes among all the bronchodilators. It has been shown to be superior to ipratropium and salmeterol in improving lung function and superior to ipratropium

TABLE 12–4. Maintenance Medications for COPD

	Medication	Onset	Peak	Duration	Usual dose
Short-Acting β_2-Agonists	**Albuterol**				
	Nebulization	5–15 minutes	0.5–2 hours	2–6 hours	2.5 mg every 6–8 hours (max: 30 mg/day)
	Inhalation	5–15 minutes	0.5–2 hours	2–6 hours	MDI (90 mcg/puff) 1–2 puffs every 4–6 hours (max: 1080 mcg/day)
	Oral	7–30 minutes	2–3 hours	4–6 hours ER: 8–12 hours	2–4 mg three to four times a day ER: 4–8 mg every 12 hours (max: 32 mg/day)
	Levalbuterol				
	Nebulization	10–20 minutes	1.5 hours	5–8 hours	0.63–1.25 mg three times a day, 6–8 hours apart (max: 3.75 mg/day)
	Inhalation	5–10 minutes	1–1.5 hours	3–6 hours	MDI (45 mcg/puff) 1–2 puffs every 4–6 hours (max: 540 mcg/day)
	Pirbuterol				
	Inhalation	5 minutes	0.5–1.5 hours	4–5 hours	MDI (200 mcg/puff) 1–2 puffs every 4–6 hours (max: 2400 mcg/day)
	Terbutaline				
	Oral	0.5–2 hours	1–3 hours	6–8 hours	2.5–5 mg three times a day, 6 hours apart (max: 15 mg/day)
Long-Acting β_2 Agonists	**Formoterol**				
	Inhalation	1–3 minutes	1–3 hours	12 hours	Powder (12 mcg/inhalation) 1 inhalation every 12 hours (max: 24 mcg/day)
	Salmeterol				
	Inhalation	10 minutes–2 hours	2–5 hours	12 hours	Powder (50 mcg/inhalation) 1 inhalation every 12 hours (max: 100 mcg/day)
Short-Acting Anticholinergic	**Ipratropium**				
	Nebulization	1–30 minutes	1.5–2 hours	4–6 hours	500 mcg every 6–8 hours (max: 2000 mcg/day)
	Inhalation	1–30 minutes	1.5–2 hours	4–6 hours	MDI (18 mcg/puff) 2 puffs four times a day (max: 216 mcg/day)
Long-Acting Anticholinergic	**Tiotropium**				
	Inhalation	30 minutes	1–4 hours	24 hours	Powder (18 mcg/inhalation) 1 inhalation every 24 hours (max: 18 mcg/day)
Methylxanthine	**Theophylline**				
	Oral	0.5–2 hours	Up to 24 hours, depending on formulation	6–24 hours	400–600 mg/day divided every 6–24 hours based on formulation Adjust dose to serum concentrations of 5–15 mcg/mL (28–83 µmol/L)
Inhaled Corticosteroids	**Beclomethasone**	1–7 days	1–4 weeks		MDI (40, 80 mcg/puff) 40–160 mcg twice a day (max: 640 mcg/day)
	Budesonide	1–7 days	1–2 weeks		Powder (200 mcg/inhalation) 1–2 inhalations twice a day (max: 1600 mcg/day)
	Fluticasone	1–7 days	1–2 weeks		MDI (44, 110, 220 mcg/puff) 88–440 mcg twice a day (max: 1760 mcg/day)
	Triamcinolone	1–7 days	1–2 weeks		MDI (100 mcg/puff) 2 puffs three to four times a day or 4 puffs twice a day (max: 1600 mcg/day)

MDI, metered-dose inhaler; ER, extended-release.

in relieving symptoms, reducing exacerbation frequency, and improving health status.[13,14] Because of its superior efficacy, tiotropium is considered first-line therapy for all COPD patients with persistent symptoms (e.g., dyspnea, need for rescue medication more than twice a week, and night waking). The largest drawback to widespread use of tiotropium is the high cost of therapy. Patients using tiotropium as maintenance therapy should be prescribed albuterol as their rescue therapy. The combination of ipratropium and tiotropium is not recommended because of the risks of excessive anticholinergic effects.

Inhaled anticholinergics are well tolerated with the most common adverse effect being dry mouth. Occasional metallic taste has also been reported with ipratropium. Other anticholinergic adverse effects include constipation, tachycardia, blurred vision, and precipitation of narrow-angle glaucoma symptoms. Urinary retention could be a problem, especially for those with concurrent bladder outlet obstruction.

Theophylline

Theophylline is a non-specific phosphodiesterase inhibitor that increases intracellular cAMP within airway smooth muscle resulting in bronchodilation. It has a modest bronchodilator effect in patients with COPD, and its use is limited due to a narrow therapeutic index, multiple drug interactions, and adverse effects. Theophylline should be reserved for patients who cannot use inhaled medications or who remain symptomatic despite appropriate use of inhaled bronchodilators.

Theophylline's bronchodilatory effects are dependent upon achieving adequate serum concentrations, and therapeutic drug monitoring is needed to optimize therapy because of wide interpatient variability. If theophylline is used, serum concentrations in the range of 5 to 15 mcg/mL (28 to 83 μmol/L) provide adequate clinical response with a greater margin of safety than the traditionally recommended range of 10 to 20 mcg/mL (55 to 110 μmol/L). The most common adverse effects include heartburn, restlessness, insomnia, irritability, tachycardia, and tremor. Dose-related adverse effects include nausea and vomiting, seizures, and arrhythmias.

Tobacco smoke contains chemicals that induce the cytochrome P-450 isoenzymes 1A1, 1A2, and 2E1. Theophylline is metabolized by 1A2 and 2E1, and therefore smoking leads to increased clearance and subsequently decreased plasma levels of the drug.[15] Because most patients with COPD are current or past smokers, it is important to assess current tobacco use and adjust the theophylline dose as required based on altered plasma theophylline levels if tobacco use changes.

Combinations of Bronchodilators

Patients with COPD often need maintenance treatment with two or three bronchodilators. Combining albuterol plus ipratropium, a long-acting β_2-agonist plus theophylline, or a long-acting β_2-agonist plus tiotropium produces a greater change in spirometry than either drug alone.[1,2,16,17] Administering a long-acting β_2-agonist plus ipratropium leads to fewer exacerbations than either drug alone.[18] A combination of all three bronchodilator classes (β_2-agonist, anticholinergic, and theophylline) can be used if the response to a two-drug combination is inadequate. However, this approach has not been evaluated adequately in clinical trials.

Corticosteroids

❺ *In symptomatic patients with severe COPD (FEV_1 less than 50% predicted) and frequent exacerbations, regular treatment with inhaled corticosteroids decreases the number of exacerbations per year and improves health status; however, corticosteroids do not slow the long-term decline in pulmonary function.*[2,19–23] A combination inhaler device is recommended when using a long-acting β_2-agonist with an inhaled corticosteroid [e.g., Advair (fluticasone/salmeterol)]. Patients should be reassessed 6 to 8 weeks after initiating inhaled corticosteroids to determine whether there has been a positive response. A positive response is indicated by an increase in FEV_1 of 15% or more, improvement in symptoms, and/or improvement in 6-minute walking distance.[24] Treatment should be discontinued if no substantial clinical or physiologic improvement is seen.[1,24]

Upon discontinuation of inhaled corticosteroids some patients may experience deterioration in lung function and an increase in dyspnea and mild exacerbations; it is reasonable to reinstitute the medication in these patients.[25] Completion of ongoing clinical trials assessing mortality should help to clarify the role of corticosteroid treatment of COPD.

The most common adverse effects from inhaled corticosteroids include oropharyngeal candidiasis and hoarse voice. These can be minimized by rinsing the mouth after use and by using a spacer device with metered-dose inhalers. Increased bruising and decreased bone density have also been reported; the clinical importance of these effects remains uncertain.[1,2,19]

Long-term use of oral corticosteroids should be avoided due to an unfavorable risk/benefit ratio. The steroid myopathy that can result from long-term use of oral corticosteroids weakens muscles, further decreasing the respiratory drive in patients with advanced disease.

Immunizations

Serious illness and death in COPD patients can be reduced by about 50% with annual influenza vaccination. The optimal time for vaccination is usually from early October through mid-November. All patients with COPD should also receive a one-time vaccination with the pneumococcal polysaccharide vaccine, even though sufficient data supporting its use in COPD patients are lacking.[1,2] Patients over 65 years of age should be revaccinated if it has been more than 5 years since initial vaccination and they were less than 65 years of age at the time.

$Alpha_1$-Antitrypsin Augmentation Therapy

The American Thoracic Society and the European Respiratory Society have published standards for the diagnosis and management of individuals with AAT deficiency.[26] They recommend intravenous augmentation therapy for individuals with AAT

deficiency and moderate airflow obstruction (FEV_1 35% to 60% predicted). In these patients, augmentation therapy appears to reduce overall mortality and slow the decline in FEV_1, although large randomized controlled trials have not been conducted. Augmentation therapy consists of weekly transfusions of pooled human AAT with the goal of maintaining adequate plasma levels of the enzyme. The benefits of augmentation therapy are unclear in patients with severe (FEV_1 less than 35% predicted) or mild (FEV_1 greater than 60% predicted) airflow obstruction. Augmentation therapy is not recommended for individuals with AAT deficiency who do not demonstrate lung disease.

Other Pharmacologic Therapies

Leukotriene modifiers (e.g., zafirlukast and montelukast) have not been adequately evaluated in COPD patients and are not recommended for routine use. Small, short-term studies showed improvement in pulmonary function, dyspnea, and quality of life when leukotriene modifiers were added on to inhaled bronchodilator therapy.[27,28] Additional long-term studies are needed to clarify their role.

Nedocromil, a mast cell stabilizer, has not been adequately tested in COPD patients and is not included in the GOLD recommendations.

N-acetylcysteine has antioxidant and mucolytic activity, which makes it a promising agent for COPD treatment, but clinical trials have produced conflicting results. One of the largest trials found N-acetylcysteine to be ineffective at reducing the decline in lung function and preventing exacerbations.[29] Routine use cannot be recommended at this time.

Prophylactic, continuous use of antibiotics has no effect on the frequency of exacerbations; antibiotics should only be used for treating infectious exacerbations. Antitussives are contraindicated because cough has an important protective role. Opioids may be effective for dyspnea in advanced disease but may have serious adverse effects; they may be used to manage symptoms in terminal patients.

Pharmacologic Therapy of COPD Exacerbations

An exacerbation is a sustained worsening of the patient's symptoms from his or her usual stable state that is beyond normal day-to-day variations. It is acute in onset and sufficient to warrant a change in management. Commonly reported symptoms are worsening of dyspnea, increased sputum production, and change in sputum color. The most common causes of an exacerbation are respiratory infection and air pollution, but the cause cannot be identified in about one-third of severe exacerbations.[2]

Treatment depends on the symptoms and severity of the exacerbation. Mild exacerbations can often be treated at home with an increase in bronchodilator therapy with or without oral corticosteroids (Fig. 12–3). Antibiotics are indicated only if there are clinical signs of airway infection (e.g., increased volume and change in color of sputum and/or fever). Moderate to severe exacerbations require management in the emergency department or hospital. Management should consist of controlled oxygen therapy, bronchodilators, oral or intravenous corticosteroids, antibiotics if indicated, and consideration of mechanical ventilation (non-invasive or invasive).



Patient Encounter, Part 2: The Medical History, Physical Exam, and Diagnostic Tests

PMH
Hypertension for 6 years, currently controlled

SH
Patient works as an accountant; married with two children

FH
Father with emphysema and lung cancer. There is no family history of type 2 diabetes or heart disease

Meds
Lisinopril 40 mg PO once daily
Hydrochlorothiazide 25 mg PO once daily

ROS
(–) skin rash; (–) nasal congestion, drainage; (–) chest pain, paroxysmal nocturnal dyspnea, orthopnea; (+) shortness of breath, cough, intermittent wheezing; (–) hemoptysis; (–) heartburn, reflux symptoms, N/V/D, change in appetite, change in bowel habits; (–) joint pain or swelling; (–) pedal edema

PE
VS: blood pressure 134/82 mm Hg, pulse 80 beats per minute, respiratory rate 20/minute, temperature 35.8°C, Wt 132 lb (60 kg), Ht 64 in. (163 cm), body mass index 22.7 kg/m^2
HEENT: EOMI; mucosal membranes are moist; no evidence of JVD; no palpably enlarged cervical lymph nodes
Lungs: Barrel-shaped chest; hyperresonant percussion noted bilaterally; lung sounds are fairly distant, no rhonchi or crackles.
CV: RRR, normal S_1, S_2; no murmur, gallop, or rub
Abd: Soft, non-tender, no hepatosplenomegaly
Exts: No cyanosis, edema, or finger clubbing; evidence of onychomycosis on all fingernails

PFTs

	Prebronchodilator		Postbronchodilator	
	Actual	% Predicted	Actual	% Predicted
FVC (L)	4.4	107%	4.0	97%
FEV_1 (L)	1.68	50%	1.59	47%
FEV_1/FVC (%)			39%	

Chest x-ray: Hyperlucency and hyperinflation of the lungs suggestive of emphysematous change

- Given this additional information, what is your assessment of the patient's condition?
- This patient's COPD can be classified as what stage?
- What are the treatment goals for this patient?
- What nonpharmacologic and pharmacologic alternatives are feasible for this patient?
- Develop a treatment plan for this patient.

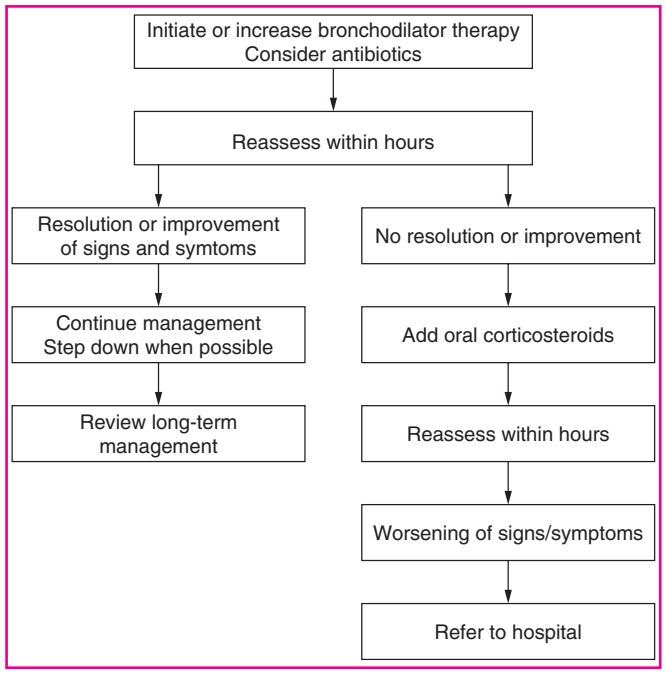


FIGURE 12–3. Algorithm for the management of an exacerbation of COPD at home. (Reproduced from GOLD Science Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2005. Available at: www.goldcopd.com. Used with permission.)

Bronchodilators

Albuterol is the preferred bronchodilator for treatment of acute exacerbations because of its rapid onset of action. Ipratropium can be added to allow for lower doses of albuterol, thus reducing dose-dependent adverse effects such as tachycardia and tremor. Delivery can be through metered-dose inhaler (MDI) and spacer or nebulizer. The nebulizer route is preferred in patients with severe dyspnea and/or cough that would limit delivery of medication through an MDI with spacer. If response is inadequate, theophylline can be considered; however, clinical evidence supporting its use is lacking.

Oral Corticosteroids

Systemic corticosteroids shorten the recovery time, help to restore lung function more quickly, and may reduce the risk of early relapse.[30] The GOLD guidelines recommend that corticosteroids be considered in addition to bronchodilators in all hospitalized patients and in outpatients with baseline FEV_1 less than 50% predicted.[2] Other authorities recommend corticosteroids for all patients experiencing a COPD exacerbation.[1] Oral prednisone 30 to 40 mg/day for 10 to 14 days is recommended. Prolonged treatment does not result in greater efficacy and increases the risk of adverse effects. If inhaled corticosteroids are part of the patient's usual treatment regimen, they should be continued during systemic therapy.

Antibiotics

The role of bacterial infections in COPD exacerbations is controversial, and there are limited data on the efficacy of antibiotics in treating COPD exacerbations. Recent studies suggest that bacteria cause 40% to 50% of acute exacerbations.[31]

❻ *Antibiotics should be used in patients with COPD exacerbations who have either of the following characteristics: (1) at least two of three cardinal symptoms: increased dyspnea, sputum volume, or sputum purulence; or (2) a severe exacerbation requiring mechanical ventilation.*[2]

The predominant bacterial organisms in patients with mild exacerbations are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. In patients with more severe underlying COPD, other bacteria, such as enteric gram-negative bacilli (*Escherichia coli, Klebsiella pneumoniae,* and *Enterobacter cloacae*) and *Pseudomonas aeruginosa* may be more common. Selection of empiric antibiotic therapy should be based on the most likely organism(s) thought to be responsible for the infection and on local resistance patterns. A risk stratification approach has been advocated to help guide antibiotic selection.[1,2,31] This approach is based on risk factors found to be predictive of treatment failure or early relapse. Patients at risk for poor outcome are candidates for more aggressive initial antibiotic treatment. Table 12–5 provides recommended antibiotic treatment based on this risk stratification approach.[2,31] Antibiotic treatment for most patients should be maintained for 3 to 10 days, until the patient has been afebrile for 3 consecutive days. Exacerbations due to certain infecting organisms (*P. aeruginosa, E. cloacae,* and methicillin-resistant *Staphylococcus aureus*), while not common, require more lengthy courses of therapy (21 to 42 days) when they occur. If there is worsening clinical status or inadequate clinical response in 48 to 72 hours, re-evaluate the patient, consider sputum Gram's stain and culture if not already obtained, and adjust antimicrobial therapy. If Gram's stain and culture results are available, narrow the antibiotic therapy according to cultured organism(s) and sensitivities. If no cultures have been obtained, or cultures remain negative, consider additional antibiotics and/or change to antibiotics with a broader spectrum of activity.

Oxygen

The goal of oxygen therapy is to maintain PaO_2 above 60 mm Hg (8 kPa) or SaO_2 above 90% in order to prevent tissue hypoxia and preserve cellular oxygenation.[1] Increasing the PaO_2 much further confers little added benefit and may increase the risk of CO_2 retention, which may lead to respiratory acidosis. An arterial blood gas should be obtained after 1 to 2 hours to assess for hypercapnia.

In advanced COPD, caution should be used since overly aggressive administration of oxygen to patients with chronic hypercapnia may result in respiratory depression and respiratory failure. In these patients, mild hypoxemia, rather than carbon dioxide accumulation, triggers their drive to breathe.

TABLE 12–5. Recommended Antibiotic Therapy in Acute Exacerbations of COPD

Patient Characteristics	Likely Pathogens	Recommended Antibiotics[a,b]
Uncomplicated exacerbation Not requiring hospitalization Less than 3 exacerbations per year No comorbid illness FEV_1 greater than 50% predicted No recent antibiotic therapy	*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*	*Oral:* Macrolide (azithromycin, clarithromycin) Second- or third-generation cephalosporin (cefuroxime, cefpodoxime, cefdinir, cefprozil) Doxycycline Ketolide (telithromycin) β-Lactam/β-lactamase inhibitor (amoxicillin-clavulanate) *Intravenous:* Not recommended
Complicated exacerbation FEV_1 less than 50% predicted Comorbid cardiac disease Greater than or equal to 3 exacerbations per year Antibiotic therapy in the previous 3 months	Above organisms plus: drug-resistant pneumococci, β-lactamase-producing *H. influenzae* and *M. catarrhalis, Escherichia coli, Proteus* spp., *Enterobacter* spp., *Klebsiella pneumoniae*	*Oral:* β-Lactam/β-lactamase inhibitor (amoxicillin-clavulanate) Fluoroquinolone with enhanced pneumococcal activity (levofloxacin, gemifloxacin, moxifloxacin) *Intravenous:* β-lactam/β-lactamase inhibitor (ampicillin-sulbactam) Second- or third-generation cephalosporin (cefuroxime, ceftriaxone) Fluoroquinolone with enhanced pneumococcal activity (levofloxacin, moxifloxacin)
Complicated exacerbation with risk factors for P. aeruginosa Recent hospitalization Greater than or equal to 4 courses of antibiotics in the last year Very severe COPD (GOLD stage IV) Previous isolation of *P. aeruginosa*	Above organisms plus: *P. aeruginosa*	*Oral*[c]: Antipseudomonal fluoroquinolone (ciprofloxacin, high-dose levofloxacin) *Intravenous:* Antipseudomonal β-lactamase resistant penicillin (piperacillin-tazobactam) Third- or fourth-generation cephalosporin with antipseudomonal activity (ceftazidime, cefepime) Antipseudomonal fluoroquinolone (ciprofloxacin, high-dose levofloxacin)

[a]Antibiotics indicated if patient has at least two of three cardinal symptoms: increased dyspnea, sputum volume, or sputum purulence; or a severe exacerbation requiring mechanical ventilation.
[b]Trimethoprim-sulfamethoxazole, amoxicillin, first-generation cephalosporins, and erythromycin are not recommended due to susceptibility and resistance patterns of the likely infectious organisms.
[c]Double coverage (e.g., use of two antipseudomonal antibiotics) should be considered for likely pseudomonal infection. Additional antipseudomonal antibiotic choices to add for double coverage include aminoglycosides, imipenem, meropenem, and aztreonam.
COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second.

Assisted Ventilation

Mechanical ventilation can be administered as follows: (1) invasive (conventional) mechanical ventilation through an endotracheal tube; (2) non-invasive mechanical ventilation using either negative (e.g., iron lung—not recommended) or positive pressure devices. Non-invasive positive pressure ventilation (NPPV) is preferred whenever possible. NPPV improves signs and symptoms, decreases the length of hospital stay, and most importantly, reduces mortality.[32] Appropriate patients to consider for NPPV include those with the following characteristics: (1) moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion; (2) moderate to severe acidosis (pH between 7.25 and 7.35) and hypercapnia ($PaCO_2$ between 45 and 60 mm Hg [6–8 kPa]); and (3) respiratory rate between 25 and 35 breaths per minute.[2] Invasive mechanical ventilation should be used in patients with more severe symptoms and in those failing NPPV.

OUTCOME EVALUATION

- Monitor the patient for improvement in symptoms (dyspnea, cough, sputum production, and fatigue).
- Changes in FEV_1 should not be the main outcome assessed. FEV_1 changes are weakly related to symptoms, exacerbations, and health-related quality of life (outcomes that are important to patients).
- The Medical Research Council (MRC) dyspnea scale can be used to monitor physical limitation due to breathlessness

(Table 12–6). The scale is simple to administer and correlates well with scores of health status.[33]

- The BODE Index is a validated predictor of mortality and is a better predictor than FEV_1 alone.[34] It is a composite score derived from body mass index or BMI (**B**), FEV_1 or degree of airflow obstruction (**O**), modified Medical Research Council (MMRC) dyspnea scale (**D**), and 6-minute walking distance (**E**, exercise capacity). All of these variables predict important outcomes such as health-related quality of life, the rate of exacerbations, and the risk of death. The composite score is based on a 10-point scale in which higher scores indicate a higher risk of death (Table 12–7). The BODE Index can be used clinically to monitor disease progression. Its usefulness in measuring outcomes of drug therapy, pulmonary rehabilitation, and the degree of health care resource utilization needs further study.
- Assess quality of life using the St. George's Respiratory Questionnaire, which has been validated and is specific for COPD patients.[35]
- Monitor theophylline levels with goal serum concentrations in the range of 5 to 15 mcg/mL (28 to 83 µmol/L). Trough levels should be obtained 1 to 2 weeks after initiation of treatment and after any dosage adjustment. Routine levels are not necessary unless toxicity is suspected or disease has worsened.

TABLE 12–6. Medical Research Council (MRC) Dyspnea Scale

Grade	Modified Grade[a]	Statement about Perceived Breathlessness[b]
1	0	"I only get breathless with strenuous activity."
2	1	"I get short of breath when hurrying on the level or up a slight hill."
3	2	"I walk slower than people of the same age on the level because of breathlessness or I have to stop for breath after a mile or so on the level at my own pace."
4	3	"I stop for breath after walking 100 yards or after a few minutes on the level."
5	4	"I am too breathless to leave the house or I get breathless while dressing."

[a]The modified grade is used in the BODE index.
[b]The last statement to which the patient answers "yes" is their grade.



Patient Care and Monitoring

1. Assess the patient's symptoms and history of exposure to risk factors. For new patients obtain a detailed medical history including:
   - Past medical history, especially history of respiratory conditions
   - Immunization status (pneumococcal and influenza)
   - Family history of COPD or other chronic respiratory disease
   - History of exacerbations or previous hospitalizations for respiratory disorders
   - Impact of disease on the patient's life, including limitation of activity, missed work, and feelings of depression or anxiety
2. Obtain spirometry measurements to assess airflow limitation and aid in severity classification and treatment decisions. Measure arterial blood gases if FEV_1 is less than 40% predicted or if the patient has clinical signs suggestive of respiratory failure or right heart failure.
3. Obtain a thorough history of prescription, non-prescription, and dietary supplement use. Assess inhaler technique and adherence to the medication regimen. Ask the patient about effectiveness of medications at controlling symptoms and adverse effects.
4. Ask current tobacco users about daily quantity, past quit attempts, and current readiness to quit.
5. Design a therapeutic plan including lifestyle modifications (e.g., smoking cessation) and optimal drug therapy. Consider need for pulmonary rehabilitation, oxygen therapy, and/or surgery.
6. Provide patient education about the disease state and therapeutic plan:
   - What COPD is and the natural course of the disease
   - Smoking cessation counseling
   - Role of regular exercise and healthy eating
   - How and when to take medications; importance of adherence to the medication plan; adverse effects and how to minimize them
   - Signs and symptoms of an exacerbation and what to do if one occurs
   - Advanced directives and end-of-life issues for patients with more severe disease
7. Determine the follow-up period based on patient status and needs (typically 3 to 6 months).
8. Follow-up visits should include:
   - Assessment of tobacco use and/or quit attempts
   - Assessment of change in symptoms. Obtain spirometry if there is a substantial increase in symptoms or a complication
   - Review of drug therapy (dosages, adherence, inhaler technique, effectiveness, adverse effects, and drug interactions)
   - Evaluation of exacerbation frequency, severity, and likely causes
9. Perform spirometry at least annually to assess disease progression.
10. Provide annual influenza vaccination.
11. Assess inhaler technique at every visit. Have the patient demonstrate proper use of each device using a placebo inhaler or personal inhaler. Proper use of these devices is critical for therapeutic success.

TABLE 12–7. The BODE Index

	Points on BODE Index[a]			
Variable	**0**	**1**	**2**	**3**
FEV_1 (% of predicted)	Greater than or equal to 65	50–64	36–49	Less than or equal to 35
Distance walked in 6 minute (meters)	Greater than or equal to 350	250–349	150–249	Less than or equal to 149
MMRC dyspnea scale	0–1	2	3	4
Body mass index (kg/m^2)	Greater than 21	Less than or equal to 21		

[a]The cutoff values for the assignment of points are shown for each variable.
FEV_1, forced expiratory volume in one second; MMRC, modified Medical Research Council. From Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004;350:1005–1012. Copyright © 2004 Massachusetts Medical Society. All rights reserved. Used with permission.

ABBREVIATIONS

AAT: α_1-antitrypsin
ABG: arterial blood gas
ATS: American Thoracic Society
BMI: body mass index
cAMP: cyclic adenosine monophosphate
COPD: chronic obstructive pulmonary disease
CT: computed tomography
ERS: European Respiratory Society
FEV_1: forced expiratory volume in one second
FVC: forced vital capacity
GOLD: Global Initiative for Chronic Obstructive Lung Disease
JVD: jugular venous distention
LABD: long-acting bronchodilator
MDI: metered-dose inhaler
MMRC: modified Medical Research Council
MRC: Medical Research Council
NPPV: non-invasive positive pressure ventilation
$PaCO_2$: partial pressure of arterial carbon dioxide
PaO_2: partial pressure of arterial oxygen
PFT: pulmonary function test
PO: orally
Sa_{O_2}: arterial oxygen saturation
TNF-α: tumor necrosis factor-α
V_A/Q: ventilation/perfusion ratio

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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13 Cystic Fibrosis

Kimberly J. Novak



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Explain the pathophysiology of cystic fibrosis (CF) and its multi–organ system involvement.
2. Describe the common clinical presentation and diagnosis of CF.
3. Consider long-term treatment goals with respect to clinical course and prognosis of CF.
4. Identify nonpharmacologic therapies for CF management.
5. Recommend appropriate pharmacologic therapies for chronic CF management.
6. Design appropriate antibiotic regimens for acute pulmonary exacerbations of CF.
7. Employ pharmacokinetic principles when calculating drug doses in CF patients.
8. Formulate monitoring plans for acute and chronic CF pharmacologic therapies.

Key Concepts

❶ In CF, the cystic fibrosis transmembrane regulator (CFTR) chloride channel is dysfunctional and usually results in decreased chloride secretion and increased sodium absorption, leading to altered viscosity of fluid excreted by the exocrine glands and mucosal obstruction.

❷ Pulmonary disease is characterized by thick mucus secretions, impaired mucus clearance, chronic airway infection and colonization, obstruction, and an exaggerated neutrophil-dominated inflammatory response.

❸ Maximizing nutritional status through pancreatic enzyme replacement and vitamin and nutritional supplements is necessary for normal growth and development and for maintaining long-term lung function.

❹ Airway clearance therapy is a necessary routine for all CF patients to clear secretions and control infection. It is typically performed once or twice daily for maintenance care and three or four times per day for acute exacerbations.

❺ Antibiotic therapy is indicated in three distinct situations over the course of CF: (1) early eradication and delay of colonization; (2) suppression of bacterial growth once colonization occurs; and (3) reduction of bacterial load in acute overgrowth.

❻ Antibiotic selection is based on periodic culture and sensitivity data, typically covering all organisms identified over the preceding year. If no culture data are available, empiric antibiotics should cover the most likely organisms for the patient's age group.

❼ Antibiotic regimens in severe CF exacerbations include an intravenous antipseudomonal β-lactam plus an aminoglycoside.

❽ CF patients have a larger volume of distribution and enhanced total body clearance of many antibiotics, which often results in the need for higher doses to attain target levels.

❾ Titration of pancreatic enzyme doses is based on control of steatorrhea, stool output, and abdominal symptoms.

❿ Because CF-related diabetes (CFRD) results from insulin insufficiency, exogenous insulin replacement is required.

Cystic fibrosis (CF) is an inherited multi–organ system disorder affecting children and an ever-growing adult population. It is the most common life-threatening genetic disease among Caucasians and the major cause of severe chronic lung disease and pancreatic insufficiency in children. The disease generally manifests as mucosal obstruction of exocrine glands caused by defective ion transport within epithelial cells. Due to the array of affected organ systems and complicated medical therapies, appropriate CF treatment necessitates multidisciplinary team collaboration.

EPIDEMIOLOGY AND ETIOLOGY

In the United States, CF most commonly occurs in the Caucasian population, ranging from 1 in 1900 to 3700 individuals. CF is less common in Hispanics (1 in 9000), African-Americans

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(1 in 15,000), and Asian Americans (1 in 32,000).[1] CF is inherited as an autosomal recessive trait, and approximately 1 in 25 Caucasians are **heterozygous** carriers. For example, offspring of a carrier couple (each parent being heterozygous) have a one in four chance of having the disease (**homozygous**), a one in two chance of being a carrier (heterozygous), and a one in four chance of receiving no trait. The gene mutation is found on the long arm of chromosome 7 and encodes for the cystic fibrosis transmembrane regulator (CFTR) protein, which functions as a chloride channel to transport water and electrolytes. Over 1000 mutations have been described in the CF gene; however, the ΔF508 mutation is the most common and is present in 70% to 90% of CF patients in the United States.[2]

PATHOPHYSIOLOGY

CF is a disease of exocrine gland epithelial cells where CFTR is largely expressed. Normally, these cells transport chloride through CFTR chloride channels with sodium and water accompanying this flux across the cell membrane (Fig. 13–1). CFTR is regulated by protein kinases in response to varying levels of the intracellular second messenger cyclic-3′, 5′-adenosine monophosphate (cAMP). CFTR also downregulates the epithelial sodium channel, regulates calcium-activated chloride and potassium channels, and may function in exocytosis and formation of plasma membrane molecular complexes and proteins important in inflammatory responses.[2] ❶ *In CF, the CFTR chloride channel is dysfunctional and usually results in decreased chloride secretion and increased sodium absorption, leading to altered viscosity of fluid excreted by the exocrine glands and mucosal obstruction.*

Pulmonary System

Chronic lung disease is a hallmark of CF, leading to death in 90% of patients.[3] ❷ *Pulmonary disease is characterized by thick mucus secretions, impaired mucus clearance, chronic airway infection and colonization, obstruction, and an exaggerated neutrophil-dominated inflammatory response.*[4] Over time, chronic obstruction and inflammation lead to air trapping, **atelectasis**, mucus plugging, **bronchiectasis**, cystic lesions, pulmonary hypertension, and eventual respiratory failure. In the United States CF population, pulmonary function declines at an average yearly rate of 2%, as measured by forced expiratory volume in 1 second (FEV_1). The rate in an individual patient may be higher or lower depending on severity of CFTR dysfunction and comorbidities. Patients may show a slow steady decline over time, or they may have stable lung function for several years and then experience periods of sharp decline.[1] In the upper airways, sinusitis and nasal polyps are also common, and microbial colonization is similar to that of the lungs.

Bacterial pathogens are often acquired in an age-dependent sequence, and prevalence is tracked in the Cystic Fibrosis Foundation Patient Registry. Early infection is most often caused by *Staphylococcus aureus* and non-typeable *Haemophilus influenzae* (and thus is not prevented by childhood *H. influenzae* type b immunization). *Pseudomonas aeruginosa* infection also occurs early in life and is the most significant CF pathogen among all age groups. *P. aeruginosa* expresses extracellular toxins that perpetuate lung inflammation. Mucoid strains of *P. aeruginosa* produce an alginate biofilm layer that interferes with antibiotic penetration. Other organisms identified later in the disease course include *Stenotrophomonas maltophilia*, *Alcaligenes xylosoxidans*, *Burkholderia cepacia*, fungi including *Candida* and *Aspergillus* species, and non-tuberculous mycobacteria.[1] Other organisms may also present chronically or intermittently. Similarly, cultured organisms may represent an initial infection, chronic colonization, or microbial overgrowth in an acute exacerbation.

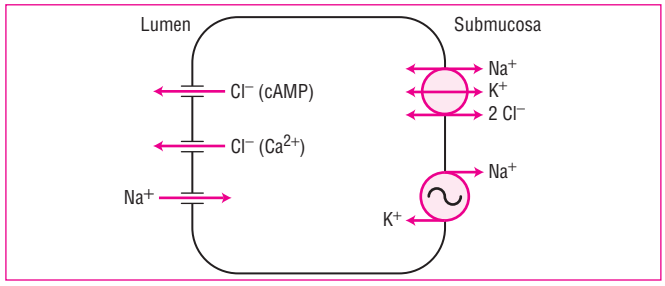


FIGURE 13–1. Electrolyte transport in the airway epithelial cell. Ca, calcium; cAMP, cyclic-3′, 5′-adenosine monophosphate; Cl, chloride; Na, sodium; K potassium. (From Milavetz G, Smith JJ. Cystic fibrosis. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 592, with permission.)

Gastrointestinal System

Gastrointestinal involvement may present initially as small bowel obstruction shortly after birth (known as meconium ileus) due to abnormally thick **meconium** that cannot be passed. Older CF patients may develop distal intestinal obstruction syndrome (DIOS), formerly called meconium ileus equivalent, which occurs due to fecal impaction in the terminal ileum and cecum.

Maldigestion due to pancreatic enzyme insufficiency is present in about 85% to 90% of CF patients.[5] Thick pancreatic secretions and cellular debris obstruct the pancreatic ducts and lead to fibrosis. Volume and concentration of pancreatic enzymes and bicarbonate are reduced, leading to maldigestion of fat and protein. Subsequently, absorption of fat-soluble vitamins (A, D, E, and K) is often impaired. Maldigestion is characterized by abdominal distention, numerous large foul-smelling loose stools (**steatorrhea**), flatulence, and malnourishment and hunger despite voracious intake. Maldigestion is progressive and may develop later in a previously pancreatic sufficient patient.

Other complications may include gastroesophageal reflux, dysmotility, **intussusception**, **volvulus**, **atresia**, **rectal prolapse**, and complications related to corrective surgery for meconium ileus.[6]

Hepatobiliary disease occurs due to bile duct obstruction from abnormal bile composition and flow. Hepatomegaly, splenomegaly, and cholecystitis may be present. Hepatic **steatosis** may also be present due to effects of malnutrition. The progression from cholestasis (impaired bile flow) to portal fibrosis and to focal and multilobar cirrhosis, esophageal varices, and portal hypertension takes several years. Many patients are compensated and asymptomatic but may be susceptible to acute decompensation in the event of extrinsic hepatic insult from viruses, medications, or other factors.[7]

Endocrine System

CF-related diabetes shares characteristics of both type 1 and type 2 diabetes mellitus but is categorized separately. The primary cause of CFRD is insulin deficiency resulting from both reduced functional pancreatic islet cells and increased islet **amyloid** deposition. Insulin secretion is delayed in response to glucose challenge, and absolute insulin secretion over time is reduced. Some insulin resistance may also be present in CFRD; however, sensitivity may be increased in CF patients without diabetes.[8]

Postprandial hyperglycemia is common, but because some basal insulin secretion is maintained, fasting hyperglycemia is less severe and ketosis is rare.[5] Diet, acute and chronic infection, and corticosteroid use lead to fluctuations in glucose tolerance over time.[8] CFRD is associated with greater nutritional failure, increased pulmonary disease, and earlier death. The average age of onset is 18 to 21 years; but underdiagnosis is thought to be common.

Reproductive System

CF patients often experience delayed puberty. In females, menarche occurs 18 months later than average, and menstrual irregularity is common. Females also have reduced fertility due to increased viscosity of cervical mucus. Due to increasing life expectancy, pregnancy is becoming more common; however, outcomes depend on pre-partum nutritional and pulmonary status.

Almost all males with CF are **azoospermic** due to congenital absence of the vas deferens with resultant obstruction; however, conception still occurs occasionally. Conception can also occur through application of assisted reproductive technologies.[9]

Musculoskeletal System

Several factors contribute to development of bone disease in CF: (1) malabsorption of vitamins D and K and calcium; (2) poor nutrition and decreased body mass; (3) physical inactivity; (4) corticosteroid therapy; and (5) delayed puberty. Chronic pulmonary infection, through release of inflammatory cytokines, can cause increased bone resorption and decreased formation. **Osteopenia**, osteoporosis, pathologic fractures, and **kyphosis** can then occur.[10]

Episodic or chronic arthritis and hypertrophic pulmonary osteoarthropathy may also occur due to immune complex formation in response to chronic inflammation.[11] Digital **clubbing** is commonly observed and is a marker for hypoxia.

Hematologic System

Anemia may be present in some patients due to impaired erythropoietin regulation, nutritional factors (vitamin E and iron malabsorption), or chronic inflammation. With chronic pulmonary disease, increased cytokine production can lead to shortened red blood cell survival, reduced erythropoietin response, and impaired mobilization of iron stores.

Additionally, with chronic hypoxia, normal hemoglobin and hematocrit values may represent relative anemia.[12] Increased red blood cell production is a physiologic response to hypoxia; however, this response may be blunted in CF and may result in symptoms of anemia despite normal lab values. Abnormal bleeding may also be observed as a result of vitamin K malabsorption or antibiotic-associated depletion of gastrointestinal flora and vitamin K synthesis.

Miscellaneous Systems

Abnormally high concentrations of sodium and chloride are found in sweat due to impaired reabsorption within the sweat duct from loss of CFTR channels. Patients are usually asymptomatic (other than a characteristic salty taste to the skin).[2] In rare instances such as hot weather or excessive sweating during physical activity, patients may become dehydrated and experience symptoms of hyponatremia (nausea, headache, lethargy, and confusion). Similar CFTR defects are also seen in the salivary glands, manifested by increased saliva viscosity and impaired salivary function.

CLINICAL PRESENTATION AND DIAGNOSIS

Diagnosis

Diagnosis of CF is based on two separate elevated sweat chloride concentrations of greater than or equal to 60 mEq/L (or mmol/L) obtained through pilocarpine **iontophoresis** (referred to as the "sweat test"). Genetic testing (CFTR mutation analysis) may be performed to confirm the diagnosis, screen in utero, or detect carrier status. More than 70% of diagnoses are made by 12 months of age and almost all are made by age 12.



Clinical Presentation of Cystic Fibrosis

General

- CF is usually diagnosed in neonates or during early childhood. Some patients may present much later in life due to less severe symptoms or misdiagnosis.

Symptoms

- Pulmonary symptoms may include chronic cough, sputum production, and decreased exercise tolerance.
- Patients with intestinal obstruction may complain of abdominal pain, abdominal distention, and/or decreased bowel movements.
- Maldigestion may be manifested by the presence of numerous large foul-smelling loose stools (steatorrhea) and flatulence.
- Patients with vitamin A deficiency may report visual disturbances, night blindness, and dry skin.
- Acute infection may be marked by increased cough, changes in sputum (darker and thicker), dyspnea, and fever.

Signs

- Signs of obstructive airway disease include tachypnea, dyspnea, **cyanosis**, wheezes, crackles, sternal retractions, digital clubbing, and barrel chest.
- Infants and children with maldigestion may have evidence of failure to thrive (below age-based normals in both height and weight), and adults may be near or below their ideal body weight despite apparent adequate caloric intake.
- Salty taste to the skin may be noticed.
- Biliary cirrhosis may be asymptomatic or evidenced by hepatomegaly, splenomegaly, or prolonged bleeding.
- Recurrent pancreatitis (usually in pancreatic-sufficient patients) may present with episodes of epigastric abdominal pain, persistent vomiting, and fever.

Laboratory Tests

- Maldigestion results in decreased serum levels of the fat-soluble vitamins A, D, E, and K.
- Decreased vitamin K levels may result in elevated prothrombin time (PT) and International Normalized Ratio (INR).
- There may be glucose intolerance, as indicated by blood glucose between 140 and 199 mg/dL (7.77 to 11.04 mmol/L) 2 hours after an oral glucose tolerance test.
- Patients may have CFRD, as indicated by blood glucose greater than or equal to 200 mg/dL (greater than or equal to 11.1 mmol/L) 2 hours after an oral glucose tolerance test.
- Some patients have CFRD with fasting hyperglycemia (fasting blood glucose greater than or equal to 126 mg/dL (greater than or equal to 6.99 mmol/L) regardless of the post–glucose challenge level).
- Serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyl transferase, and bilirubin may be elevated in patients with hepatobiliary disease.
- White blood cell count with an associated increase in polymorphonuclear (PMN) leukocytes and bands may occur in acute pulmonary infection; however, infection may occur without these laboratory abnormalities.

Other Tests

- Pulmonary function tests (PFTs) indicate decreased forced expiratory volume in 1 second (FEV_1), decreased forced vital capacity (FVC), and increased residual volume. Values are typically worse during acute pulmonary exacerbations.
- Chest x-ray or chest computed tomography scan may reveal infiltrates, atelectasis, bronchiectasis, and mucus plugging.
- Intestinal obstruction may be manifested as meconium ileus, distal intestinal obstruction syndrome, or intussusception on abdominal x-ray or computed tomography scan. Rectal prolapse may be noted on physical exam.
- In recurrent pneumonia or sinusitis, *P. aeruginosa*, *S. aureus*, *S. maltophilia*, and other CF-related organisms may be isolated in sputum, throat, or sinus cultures.

Clinical Course and Prognosis

Life expectancy has greatly increased from a predicted survival of 16 years in 1970 to more than 40 years for patients born in the 1990s.[5] The average age of patients in the Cystic Fibrosis Foundation Registry is now more than 16 years, and many are living far into adulthood. More than 40% of CF patients in the 2004 Registry annual report are over 18 years old, and the oldest is age 74.[13]

The clinical course varies greatly among patients because of the multiple genetic mutations and heterogeneous profile of the ΔF508 mutation. Some patients develop severe lung disease early in childhood and reach end-stage lung disease by their teens, whereas others maintain near-normal lung function into adulthood. Newly-diagnosed adults tend to present with chronic respiratory symptoms but usually have milder lung disease, less frequent *Pseudomonas* infection, and less severe pancreatic insufficiency.[5] Life expectancy and quality of life are expected to continue to increase with aggressive treatment strategies, lung transplantation when appropriate, and new therapies being investigated.

TREATMENT

Desired Outcomes

Therapeutic outcomes in CF care relate to both chronic and acute treatment goals. With chronic management, the primary goals are to delay disease progression and optimize quality of life. ❸ *Maximizing nutritional status through pancreatic enzyme replacement and vitamin and nutritional supplements is necessary for normal growth and development and for maintaining long-term lung function.* Reduction of airway



Patient Encounter, Part 1

Jessica is an 18-month-old female who is brought to her pediatrician because of difficulty gaining weight. Her mother states that Jessica has had four to five loose stools daily "ever since I can remember." She was previously diagnosed with reflux and milk allergy. Oral ranitidine and elimination of cow's milk–based dairy products have not helped. Jessica is plotted on the growth chart at less than the third percentile for both height and weight. Mom also reports that she has been treated in the emergency department for pneumonia twice since birth. Mom is concerned since her mother's older sister died from some strange "wasting illness" when she was a young child.

- What information is consistent with a diagnosis of CF?
- What other information would you like to gather?
- How would you pursue making the diagnosis of CF?

inflammation and infection and aggressive preventive therapies minimize acute pulmonary exacerbations and delay pulmonary decline. In pulmonary exacerbations, therapy is directed toward reducing acute airway inflammation and obstruction. This is accomplished through more aggressive air clearance regimens and antibiotic therapy with a goal of returning lung function to pre-exacerbation levels or greater.

General Approach to Treatment

The intensity of the daily chronic maintenance regimen varies based on patient age, baseline lung function, other organ system involvement, and social factors such as time available for therapy and patient-selected care choices. Generally, with more severe lung disease and multi–organ system involvement, therapies become more complicated and time intensive. Additionally, therapy is intensified when pulmonary symptoms are increased with acute exacerbations or even mild viral upper respiratory illness such as the common cold. The approach to treatment is best described by the organ system affected.

Nonpharmacologic Therapy

Airway Clearance Therapy

❹ *Airway clearance therapy is a necessary routine for all CF patients to clear secretions and control infection, even at diagnosis prior to becoming symptomatic.* Waiting until development of a first pneumonia or until daily symptoms are present delays benefits and may contribute to a faster pulmonary decline.

The traditional form of chest physiotherapy (CPT) is known as percussion and postural drainage. Areas of the patient's chest, sides, and back are rapidly "clapped" by hand in different patient positions, followed by cough or forced expiration to mobilize secretions. Patients may also be taught autogenic drainage, which consists of deep breathing exercises followed by forced cough.

Several devices are also available to promote airway clearance. Flutter valve devices employ oscillating positive expiratory pressure (OPEP) to cause vibratory air flow obstruction and an internal percussive effect to mobilize secretions. Intrapulmonary percussive ventilation (IPV) provides continuous oscillating pressures during inhalation and exhalation. Finally, the most commonly used technique is high-frequency chest compression (HFCC) with an inflatable vest that provides external oscillation. Vest therapy is often preferred by patients because they can independently perform the therapy even from an early age.[5,14]

If performed appropriately, airway clearance techniques provide similar clearance results, so choice should be based on patient preference and compliance. Airway clearance therapy is typically performed once or twice daily for maintenance care and is increased to three or four times per day for acute exacerbations. Inhaled medications are usually given with the therapies and will be discussed in a later section.

Nutrition

Most CF patients have an increased caloric need due to increased energy expenditure through increased work of breathing and increased basal metabolism. Prevention of malnutrition requires early nutritional intervention. In patients with mild lung disease and well-controlled absorption, required caloric intake is approximately 100% to 120% of the recommended daily allowance (RDA) for age.[15] As lung disease progresses, caloric requirements increase.

Nutrition in malnourished patients consists of baseline required calories plus additional calories for weight gain. Even with aggressive diet and oral supplements, the caloric requirement may not be achieved. Placement of a **gastrostomy** or **jejunostomy** tube to allow for nighttime bolus or continuous formula feeds in addition to daytime meals may be required to meet caloric goals.[5] Patients with continued malabsorption on appropriate pancreatic enzyme supplementation or diabetes are especially challenging due to their unique caloric needs. Collaboration with a dietician specially trained in CF nutrition is essential.

Pharmacologic Therapy

Pulmonary System

Treating Obstruction and Inflammation

Airway clearance therapy is usually accompanied by bronchodilator treatment [albuterol (also known as salbutamol outside the United States) by nebulizer or metered-dose inhaler] to stimulate mucociliary clearance and prevent bronchospasm associated with other inhaled agents. A mucolytic agent may be administered to reduce sputum viscosity and enhance clearance.

Dornase alfa (Pulmozyme®) is a recombinant human (rh) DNase that selectively cleaves extracellular deoxyribonucleic acid (DNA). This DNA is released during neutrophil degradation and contributes to the high viscosity of CF sputum. Nebulization of dornase alfa 2.5 mg once or twice daily improves daily pulmonary symptoms and function, reduces pulmonary exacerbations, and improves quality of life.[16] N-acetylcysteine and hypertonic saline are other mucolytic agents that are occasionally used; however, they are not preferred agents due to a greater incidence of bronchospasm and unpleasant odor and taste.[5]

Many patients with CF also have a reactive airways component or concurrent asthma and benefit from long-acting β_2-agonists.[5] Patients with recurrent wheezing or dyspnea who have demonstrated improvement with albuterol should be considered for maintenance therapy, as should patients with bronchodilator-responsive pulmonary function tests. Inhaled corticosteroids may also attenuate reactive airways and reduce airway inflammation in some patients. While many patients appear to respond clinically to these agents, clear benefit in CF has not been established.[1,17] Drug delivery to the site of inflammation is limited by the severity of lung disease, which may prevent maximal efficacy in CF. CF patients who are on inhaled corticosteroids and/or long-acting β_2-agonists should be advised to administer these medications after airway clearance therapies to optimize drug delivery. Montelukast, antihistamines, and/or intranasal steroids are sometimes used for CF patients with a reactive airways or allergic rhinitis component to their disease.

Several systemic therapies aim at reducing airway inflammation. Long-term oral corticosteroids, namely prednisone and prednisolone, have been shown to reduce airway inflammation and improve lung function; however, beneficial effects diminish upon discontinuation. Concern for long-term adverse effects including diabetes, osteoporosis, cataracts, cushingoid effects, growth suppression, and infection limits their use as maintenance therapy.[17] In clinical practice, systemic steroids may be added for short courses in acute exacerbations or for longer treatment of the allergic response to *Aspergillus* colonization (allergic bronchopulmonary aspergillosis or ABPA); however, dose and duration of therapy should be minimized.[1,18]

High-dose ibuprofen to achieve peak concentrations of 50 to 100 mcg/mL (243 to 485 μmol/L) has been shown to slow progression of disease. At high doses, ibuprofen inhibits the lipoxygenase pathway, reducing neutrophil migration and function as well as release of lysosomal enzymes. At the lower concentrations achieved with analgesic dosing, neutrophil migration increases, potentially increasing inflammation.[19,20] The greatest benefit with high-dose ibuprofen is in children 5 to 13 years of age with mild lung disease (FEV_1 greater than 60%). A dose of 20 to 30 mg/kg given twice daily is usually needed to attain these levels, but serum concentration monitoring is necessary due to interpatient variability.[19] Due to the need for therapeutic drug monitoring and concerns regarding long-term safety and tolerability, only a few CF centers currently prescribe high-dose ibuprofen.[1,17]

Azithromycin is a macrolide antibiotic commonly used in CF as an anti-inflammatory agent. The exact mechanism for this activity is unclear, but azithromycin has been shown to improve overall lung function. Proposed mechanisms include interference with *Pseudomonas* alginate biofilm production, bactericidal activity during stationary *Pseudomonas* growth, neutrophil inhibition, interleukin-8 reduction, and reduction in sputum viscosity.[22,23] Due to its long tissue half-life, azithromycin is typically dosed 3 days per week (Monday, Wednesday, and Friday), with a dose of 500 mg for patients weighing at least 40 kg and 250 mg for patients weighing 25 to 39 kg. Alternatively, patients may take 500 mg or 250 mg either every day or only Monday through Friday, based on the same weight parameters. To minimize the risk of selecting for macrolide-resistant non-tuberculous mycobacteria, patients should have a screening acid-fast bacillus sputum culture obtained prior to starting therapy and then every 6 months. Confirmed mycobacterial colonization is usually a contraindication to chronic azithromycin therapy.[17]

Antibiotic Therapy

❺ *Antibiotic therapy is used in three distinct clinical settings within the course of CF. First, in early lung disease, the primary goals are to detect infection early and institute appropriate antibiotic therapy to eradicate infection and delay colonization. Second, once colonization is present, chronic maintenance antibiotics are used to suppress bacterial growth. Third, in acute exacerbations, intensive antibiotics are administered in an attempt to drastically reduce bacterial load and return lung function to pre-exacerbation levels or greater.*[1] ❻ *Antibiotic selection is based on periodic culture and sensitivity data, typically covering all organisms identified over the preceding year. If no culture data are available, empiric antibiotics should cover the most likely organisms for the patient's age group.* Due to altered pharmacokinetics and microorganism resistance, care must be taken to ensure that optimal doses are prescribed (Table 13–1).

Severity of pulmonary symptoms also guides selection of antibiotic regimens for treatment of acute exacerbations. If symptoms are recent in onset and/or mild in severity (e.g., slight increase in cough and sputum production without fever), patients may be treated with oral and inhaled antibiotics for 14 to 21 days on an outpatient basis. Outpatient fluoroquinolone use is common among CF patients infected with *P. aeruginosa*, even in children. Despite concerns regarding cartilage and tendon toxicity in animal studies, clinical practice has not shown an increased risk in children.[23]

To prevent development of resistance and promote synergy, inhaled tobramycin or colistin is usually added to an oral fluoroquinolone for *P. aeruginosa* coverage.[1,3] Methicillin-sensitive *S. aureus* (MSSA) may be treated with oral amoxicillin-clavulanic acid, dicloxacillin, first- or second-generation cephalosporins, trimethoprim-sulfamethoxazole, or clindamycin, depending on sensitivity. Likewise, methicillin-resistant *S. aureus* (MRSA) may be treated with oral trimethoprim-sulfamethoxazole, clindamycin, minocycline, or linezolid. *H. influenzae* often produces

TABLE 13–1. Antibiotic Dosing in Cystic Fibrosis[a]

Antibiotic	Pediatric Dose (mg/kg per day)	Adult Maximum Daily Dose	Interval (Hours)
Intravenous			
Tobramycin, gentamicin[b]	10	None	8–12
Amikacin[b]	30	None	8–12
Ceftazidime	150	6 g	8
Cefepime	150	6 g	8
Piperacillin-tazobactam	400	16 g	6
Ticarcillin-clavulanate	400	12 g	6
Meropenem	120	6 g	8
Aztreonam	200	8 g	6
Ciprofloxacin	30	1.2 g	8–12
Levofloxacin	—	750 mg	24
Nafcillin	200	12	4–6
Vancomycin[b]	40–60	None	8–12
Linezolid	20–30	1.2 g	8–12
Colistin	5–8	480 mg	8
Chloramphenicol[b]	60–80	4 g	6
Oral			
Amoxicillin ± clavulanic acid	45–90	4 g	12
Dicloxacillin	100	2 g	6
Cephalexin	50–100	4 g	6–8
Cefuroxime	30	1 g	12
Trimethoprim-sulfamethoxazole[c]	10–20	640 mg	6–12
Clindamycin	30	1.8 g	6–8
Ciprofloxacin	40	2 g	12
Levofloxacin	—	750 mg	24
Minocycline[d]	4	200 mg	12
Linezolid	20–30	1.2 g	8–12
Inhaled			
Tobramycin	160–600 mg/day	600 mg	12
Colistin	75–150 mg/day	300 mg	12

[a]All doses assume normal renal and hepatic function. Consult a specialized drug reference for dosage adjustment if function is impaired.
[b]Empiric starting doses only. Adjust dose per therapeutic drug monitoring.
[c]Dose based on trimethoprim component.
[d]Children greater than 8 years of age.

β-lactamases but can usually be treated with amoxicillin-clavulanic acid, a cephalosporin, or trimethoprim-sulfamethoxazole. Oral trimethoprim-sulfamethoxazole or minocycline may be used to treat *S. maltophilia*.

For more severe infections or patients failing outpatient therapy, intravenous (IV) antibiotic therapy is started and continued for 2 to 3 weeks. Most patients are admitted to the hospital for initiation of IV antibiotics; however, depending on the availability of home health services, patients may be discharged to finish their course or even receive their entire course at home. ❼ *Typical regimens for severe infections include an antipseudomonal β-lactam plus an aminoglycoside for added synergy and delay of resistance development.*[1,3] Cephalosporins tend to be better tolerated and offer the benefit of administration every 8 hours. Extended-spectrum penicillins have been associated with a higher incidence of allergy. Aztreonam offers the added benefit of little cross-reactivity in penicillin- or cephalosporin-allergic patients; however, it has no gram-positive coverage. Meropenem should be reserved for organisms resistant to all other antibiotics to minimize development of resistance in the carbapenem drug class, as it is the last line of defense against extended-spectrum β-lactamase (ESBL)-producing organisms.

Intravenous tobramycin is generally the first-line aminoglycoside. Isolates are usually resistant to gentamicin, and amikacin is reserved for tobramycin-resistant strains. Pharmacokinetic goals are listed in Table 13–2. In general, higher peak serum concentrations are targeted in CF. As a result, lower serum trough levels are desirable to reduce toxicity.

Some centers use once-daily aminoglycoside dosing to achieve higher peaks and minimize troughs. Since aminoglycosides exhibit concentration-dependent killing, once-daily dosing may optimize this effect; however, time below the minimum inhibitory concentration (MIC) is prolonged with once-daily administration, possibly leading to loss of synergy for a substantial portion of the dosing interval. With once-daily administration, tobramycin is typically dosed at 10 to 15 mg/kg per day and amikacin at 35 mg/kg per day. Long-term studies are needed to examine the efficacy and resistance patterns associated with once-daily aminoglycosides in the CF population.[1,3]

TABLE 13–2. Pharmacokinetic Goals in Cystic Fibrosis

	Traditional Units of Measurement		SI Units of Measurement	
Antibiotic	Goal Peak[a] (mcg/mL)	Goal Trough[b] (mcg/mL)	Goal Peak[a] (μmol/L)	Goal Trough[b] (μmol/L)
Tobramycin, gentamicin	10–12	Less than 1.5	21.4–25.7	Less than 3.2
Amikacin	30–40	Less than 5.0	35.1–46.8	Less than 5.85
Vancomycin	—[c]	10–15	—[c]	7–10.35

[a]Peaks calculated 30 minutes after end of infusion for aminoglycosides. Higher peaks may be targeted with corresponding lower trough concentrations for aminoglycosides.
[b]Troughs calculated immediately prior to the time the dose is due.
[c]Not routinely measured.

Routine use of once-daily aminoglycosides in CF is not recommended and should be limited to adults and older teens, in whom the time below the MIC can be minimized. Due to a shorter half-life, once-daily aminoglycoside dosing does not appear to be optimal for use in younger children.

Most other serious gram-negative infections are also treated with combination therapy. *S. maltophilia* is highly resistant and is most often treated with trimethoprim-sulfamethoxazole or ticarcillin-clavulanate. *A. xylosoxidans* and *B. cepacia* are also highly resistant and may have minimal therapeutic options. In some cases, fluoroquinolones may be substituted for aminoglycosides based on sensitivity data or if renal dysfunction is present. Due to excellent bioavailability, oral fluoroquinolones, trimethoprim-sulfamethoxazole, minocycline, and linezolid should be used whenever possible. Due to toxicity risk, colistin and chloramphenicol are reserved for life-threatening, highly resistant infections. Additional combinations of two or three drugs may be used for highly-resistant organisms based on synergy studies that test susceptibility of different antibiotic combinations.

Inpatient treatment of methicillin-resistant *S. aureus* can consist of IV vancomycin or oral agents as described above, depending on the severity of infection and concomitant organisms. IV vancomycin may also be converted to oral step-down therapy upon discharge.

Chronic maintenance antibiotic therapy may be used in patients with *Pseudomonas* colonization in an attempt to prevent bacterial overgrowth. Some centers advocate regular scheduled CF "clean-outs" with IV or oral antibiotics regardless of symptoms.[5] However, long-term systemic antibiotics are not recommended due to emergence of resistant isolates.[1] Chronic or rotating inhaled antibiotic maintenance therapy has become a more common practice for preventing, treating, and suppressing *P. aeruginosa* colonization.

Inhaled tobramycin (TOBI®) is typically administered to patients 6 years of age and older in alternating 28-day cycles of 300 mg nebulized twice daily, followed by a 28-day washout or "off" period to minimize development of resistance. Long-term intermittent administration improves pulmonary function, decreases microbial burden, and reduces the need for hospitalization for IV therapy.[24,25] Due to minimal systemic absorption, pharmacokinetic monitoring is not necessary with normal renal function. Lower doses of nebulized tobramycin solution for injection have been used in younger children, and studies are underway using 300 mg twice daily in children under age 6.

Nebulized colistin using the IV formulation may be an option in patients with tobramycin-resistant strains or intolerance to inhaled tobramycin. Due to an increased risk of bronchoconstriction after colistin inhalation, patients should pre-treat with albuterol and administer the first doses under medical observation.[1,5]

Inhaled antibiotics are typically stopped during an acute exacerbation requiring IV therapy. Drug delivery is reduced with increased sputum production, and concomitant use of IV aminoglycosides may increase risk of toxicity.

Pharmacokinetic Considerations

CF patients have larger volumes of distribution of many antibiotics due to an increased ratio of lean body mass to total body mass and lower fat stores. CF patients also have an enhanced total body clearance, although the exact mechanism has not been determined. Increased renal clearance, increased glomerular filtration rate, decreased protein binding, increased tubular secretion, decreased tubular reabsorption, extrarenal elimination, and increased metabolism have all been proposed as possible reasons for the increased clearance.

As a result of these pharmacokinetic changes, higher doses of aminoglycosides are needed to achieve target serum levels and promote adequate tissue penetration. Higher doses of β-lactam antibiotics are also needed to achieve and sustain levels above the MIC. Trimethoprim-sulfamethoxazole displays enhanced renal clearance and hepatic metabolism in the CF population. Fluoroquinolones and vancomycin have fewer pharmacokinetic deviations in the CF population; however, higher doses are typically needed to attain inhibitory serum and tissue concentrations against CF pathogens.[26]

Although most CF patients have shorter half-lives and larger volumes of distribution than non-CF patients, some patients exhibit decreased clearance. Possible causes include concomitant use of nephrotoxic medications, presence of diabetic nephropathy, history of transplantation (with immunosuppressant use and/or procedural hypoxic injury), and age-related decline in renal function in older adult patients. Additionally, CF patients are repeatedly exposed to multiple courses of IV aminoglycosides, which can result in decreased renal function. Evaluation of previous pharmacokinetic parameters and trends, along with incorporation of new health information, is key to providing appropriate dosage recommendations.

Gastrointestinal System

Pancreatic enzyme replacement is the mainstay of gastrointestinal therapy. Most enzyme products are formulated as capsules containing enteric-coated microspheres or microtablets to avoid inactivation of enzymes in the acidic stomach; instead, they dissolve in the more alkaline environment of the duodenum. Capsules may be opened and the microbeads swallowed with food, as long as they are not chewed. A powder form is available for patients unable to swallow the capsules or microbeads, but bioavailability is poor. While products may contain similar enzyme ratios, they are not bioequivalent and cannot be substituted. Generic enzyme products generally display poor dissolution and should not be used.[5] Table 13–3 lists commonly used enzyme replacement products.

Pancreatic enzyme doses are initiated at 500 to 1000 units/kg per meal of lipase component with half-doses given with snacks. Infants are typically started at 1500 to 2500 units of

TABLE 13–3. Common Pancreatic Enzyme Replacement Products

Trade Name[a]	Lipase (Units)	Amylase (Units)	Protease (Units)
Enteric-Coated			
Creon® 5	5,000	16,600	18,750
Creon® 10	10,000	33,200	37,500
Creon® 20	20,000	66,400	75,000
Pancrease®	4,500	20,000	25,000
Pancrease® MT 4	4,000	12,000	12,000
Pancrease® MT 10	10,000	30,000	30,000
Pancrease® MT 16	16,000	48,000	48,000
Pancrease® MT 20	20,000	56,000	44,000
Pancreacarb® MS-4	4,000	25,500	25,000
Pancreacarb® MS-8	8,000	40,000	45,000
Ultrase®	4,500	20,000	25,000
Ultrase® MT 12	12,000	39,000	39,000
Ultrase® MT 18	18,000	58,500	58,500
Ultrase® MT 20	20,000	65,000	65,000
Non-Enteric Coated			
Viokase® 87 tablet	8,000	30,000	30,000
Viokase® 16 tablet	16,000	60,000	60,000
Viokase® powder (amount per 0.7 g)	16,800	70,000	70,000

[a]The number after a trade name refers to the number of thousands of units of lipase contained per dosage form.

lipase per 120 mL of formula or breast milk. Capsules may be opened and beads divided to obtain appropriate doses. Enzymes should be taken at the beginning or divided throughout the meal and must be given with any fat-containing snack. They should not be mixed with alkaline or hot foods, as enzymes may be denatured.

❾ *Titration of pancreatic enzyme doses is based on control of steatorrhea, stool output, and abdominal symptoms.* Doses up to 2500 units/kg per meal may be needed. Higher doses should be used with caution due to the risk of fibrosing colonopathy.[5,6] Patients who respond poorly to maximal doses of one product may benefit from changing to another product.[6] Patients may also benefit from addition of a histamine H_2-receptor antagonist or proton pump inhibitor to boost effective enzyme dose if duodenal pH is not alkaline enough to neutralize residual gastric acid. Antacid therapy is also often used to treat concomitant gastroesophageal reflux, which is common in the CF population.[5,6]

Fat-soluble vitamin supplementation is usually required in pancreatic insufficiency. Specially-formulated products for CF patients (ADEKs® and Vitamax®) are usually sufficient to attain normal serum vitamin levels at a dose of 1 tablet daily for younger children and 2 tablets daily for teenagers and adults. Additional supplementation may be needed in uncontrolled malabsorption or for replacement of severe vitamin deficiency.[5,15] Appetite stimulants such as cyproheptadine may be an option for promoting nutrition and weight gain, but efficacy has not been established.

Ursodiol may slow progression of liver disease. It improves bile flow and may displace toxic bile acids that accumulate in a cholestatic liver, stimulate bicarbonate secretion into the bile, offer a cytoprotective effect, and reduce elevated liver tests. Ursodiol is typically dosed at 15 to 20 mg/kg per day in two divided doses and may be rounded to the nearest tablet size.[5,7]

Treatment of distal intestinal obstruction syndrome (DIOS) consists of oral or nasogastric administration of polyethylene glycol electrolyte (PEG) solutions. Enemas may also be used to facilitate stool clearance. IV fluids are often required to correct dehydration due to vomiting or decreased oral intake. Re-evaluation of enzyme compliance and dosing is essential to prevent further episodes. Patients with recurrent symptoms may require daily PEG administration (Miralax®).[5] Severe presentations of DIOS or initial meconium ileus may require surgical resection.

Endocrine System

Patients with mild CFRD may be managed with dietary modification if their nutritional status will allow carbohydrate control. However, most patients present with poor nutrition and weight loss and require more aggressive treatment. ❿ *Because CFRD results from insulin insufficiency, exogenous insulin replacement is required in most cases.* Many patients can be successfully managed by meal coverage with short- or rapid-acting insulin (regular, lispro, or aspart) dosed by carbohydrate counting. Patients with fasting hyperglycemia or patients receiving nighttime tube feedings typically also require longer-acting basal insulin. Regular home glucose monitoring is essential to appropriate therapy. Little information is available regarding use of oral antidiabetic agents in CFRD, and routine use is not recommended.[5,8]

Musculoskeletal System

CF patients with low bone mineral density and low serum vitamin D levels may improve bone health through supplemental vitamin D analogs beyond those found in standard CF vitamins. The optimal dose and analog have not been determined. For ergocalciferol, a minimum of 400 IU and 800 IU



Patient Encounter, Part 2

Laboratory testing confirms the diagnosis of CF, and Jessica has been referred to her regional CF center for treatment. Additional stool studies indicate the presence of severe fat maldigestion. The pulmonologist indicates that she would like to start Jessica (weight 8.2 kg) on pancreatic enzyme replacement therapy.

- What formulation and dose would you recommend?
- How would you administer the enzymes?
- How would you titrate the dose?

should be taken daily by infants and patients over 1 year of age, respectively. Total weekly doses of 12,000 IU for children less than 5 years of age and 50,000 IU for patients 5 years of age and older may be required to achieve target vitamin D concentrations. Supplemental calcium should be provided if 1300 to 1500 mg of elemental calcium intake cannot be achieved through diet.

Antiresorptive agents (oral or IV bisphosphonates) may be used to treat adult CF patients with osteoporosis. Remaining upright for 30 minutes may be difficult in patients needing to perform airway clearance therapy, so once-weekly dosing should be considered. A high incidence of gastroesophageal reflux and presence of cirrhosis-associated esophageal varices may also complicate therapy and increase the risk of erosive esophagitis. IV pamidronate, dosed at 30 mg every 3 months, has increased bone mineral density in adult CF patients. Studies using IV bisphosphonates in children with CF are underway.

Androgen replacement in male CF patients with documented hypogonadism may also benefit bone health but should be decided on an individual basis.[10,27]

Short courses of non-steroidal anti-inflammatory drugs (NSAIDs) can be used to treat CF-related arthritis and hypertrophic pulmonary osteoarthropathy.[5] The impact on neutrophil recruitment in the lung with long-term NSAID therapy at lower analgesic doses is unknown.

Future Direction of Therapy

Significant strides have been made in past decades with development of new therapies that have led to the ever-lengthening CF life-span. Since the discovery of the CF gene and the CFTR protein defect, research has focused on gene therapy as a way to restore normal CFTR function through DNA transfer.

Pharmacologic approaches are being investigated to correct dysfunctional CFTR by suppressing premature stop codons in the CFTR gene and to activate alternative chloride channels, effectively bypassing dysfunctional CFTR. Additional research is being conducted with anti-inflammatory therapies, anti-pseudomonal vaccines, and development of exogenous cationic antimicrobial peptides to mimic those found naturally in the lung.[1] Development of more effective systemic and inhaled antibiotic agents continues to be a major focus as well.

OUTCOME EVALUATION

Pulmonary System

- Monitor for changes in pulmonary symptoms such as cough, sputum production, respiratory rate, and oxygen saturation. Symptoms of an acute exacerbation should improve with antibiotics and aggressive airway clearance therapy. Pulmonary function tests should be markedly increased after 1 week and trend back to pre-exacerbation levels after 2 weeks of therapy. If improvement lags, 3 weeks of therapy may be needed.
- Obtain serum drug levels for aminoglycosides and/or vancomycin and perform pharmacokinetic analysis. Adjust the dose, if needed, according to the parameters in Table 13–2. Obtain follow-up trough levels at weekly intervals or sooner if renal function is unstable. Follow serum creatinine levels if renal function is unstable. Hearing tests may be scheduled yearly or per patient preference.

Gastrointestinal System

- Monitor short- and long-term nutritional status through evaluation of height, weight, and body mass index. Ideally, parameters should be near the normals for non-CF patients.
- Evaluate the patient's stool patterns. Steatorrhea indicates suboptimal enzyme replacement or non-compliance. Infants should have two to three well-formed stools daily, while older children and adults may have one or two stools.
- Monitor efficacy of vitamin supplementation through yearly serum vitamin levels. Obtain levels more frequently if an identified deficiency is being treated.

Endocrine System

- Monitor blood glucose several times daily in patients with CFRD or those taking systemic corticosteroids. Follow glycosylated hemoglobin levels on an outpatient basis to assess long-term glucose control. Levels may be falsely low in CF due to a shorter red blood cell half-life.



Patient Encounter, Part 3

At Jessica's follow-up appointment 1 month later, her weight is up to 8.8 kg. Her mother reports that she seems to have caught a cold and has been coughing quite a bit of late and has not been eating as well as usual. In clinic, the following vitals are noted: respiratory rate 40/minute, temperature 38.3°C (101°F), and oxygen saturation 92%. The throat culture from her previous visit was positive for *S. aureus* (sensitive to cefazolin, nafcillin, trimethoprim-sulfamethoxazole, clindamycin, vancomycin, and linezolid; resistant to erythromycin) and *P. aeruginosa* (sensitive to ceftazidime, cefepime, piperacillin, aztreonam, meropenem, ciprofloxacin, tobramycin, and amikacin; resistant to gentamicin).

- What antibiotic(s) and dose(s) would you recommend for outpatient therapy?
- What antibiotic(s) and dose(s) would you recommend for inpatient therapy?
- Develop a monitoring plan to assess antibiotic response.



Patient Care and Monitoring

1. Perform a thorough history of prescription, nonprescription, and alternative medications. Assess adherence to the prescribed regimen, including timing of inhaled medications with respect to airway clearance therapies and timing of enzymes and insulin with regard to meals. Is the patient taking any medications not prescribed by the CF center team?
2. Is the patient on all appropriate maintenance medications? Are medications at the appropriate doses for weight and/or age? If the patient is admitted, are maintenance medications ordered?
3. Evaluate the medication regimen for drug interactions, adverse reactions, and allergies.
4. Assess pulmonary symptoms. Review the incidence and quality of cough, dyspnea, respiratory rate, sputum production, and fever. Are the patient's PFTs decreased? Is there an oxygen requirement?
5. Review culture and sensitivity history over the last 1 to 2 years. What antibiotics were used in the past, and did the patient appear to respond better to a particular regimen? Is the patient currently on antibiotics, and if so, are the symptoms improving? Recommend an appropriate antibiotic regimen based on culture and sensitivity data.
6. Review the pharmacokinetic history. Are there any possible changes in clearance since the last antibiotic course? Will the patient be discharged home on IV antibiotics? Can the IV regimen be simplified or made more convenient for home administration? Recommend appropriate doses based on the patient's clearance and an appropriate but convenient schedule.
7. Perform pharmacokinetic adjustments as necessary. Recommend a monitoring plan for the antibiotic course. Are any other laboratory tests necessary? Are signs of toxicity present?
8. Assess nutritional status. Is the patient gaining or maintaining weight according to age? Are any oral supplements or tube feedings being used?
9. Assess gastrointestinal symptoms. What is the quantity and quality of bowel movements? Does the patient have bloating, flatulence, or abdominal pain?
10. Assess quality-of-life measures such as physical, psychological, and social well-being.
11. Understand that CF therapy is complicated, and recommend regimens to ease the care burden if possible.
12. Educate the patient and family, stressing the importance of adherence to the regimen.

ABBREVIATIONS

ABPA:	allergic bronchopulmonary aspergillosis
cAMP:	cyclic-3′,5′-adenosine monophosphate
CF:	cystic fibrosis
CFRD:	cystic fibrosis–related diabetes
CFTR:	cystic fibrosis transmembrane regulator
CPT:	chest physiotherapy
DIOS:	distal intestinal obstruction syndrome
DNA:	deoxyribonucleic acid
ESBL:	extended-spectrum β-lactamase
FEV_1:	forced expiratory volume in 1 second
FVC:	forced vital capacity
HFCC:	high-frequency chest compression
INR:	International Normalized Ratio
IPV:	intrapulmonary percussive ventilation
IV:	intravenous
MIC:	minimum inhibitory concentration
MRSA:	methicillin-resistant *Staphylococcus aureus*
MSSA:	methicillin-sensitive *Staphylococcus aureus*
NSAID:	non-steroidal anti-inflammatory drug
OPEP:	oscillating positive expiratory pressure
PEG:	polyethylene glycol
PFT:	pulmonary function test
PT:	prothrombin time
RDA:	recommended daily allowance

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

KEY REFERENCES AND READINGS

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14 Gastroesophageal Reflux Disease

Dianne B. Williams and Marie A. Chisholm-Burns



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Explain the underlying causes of gastroesophageal reflux disease (GERD).
2. Differentiate between typical, atypical, and complicated symptoms of GERD.
3. Determine which diagnostic test should be recommended based on the patient's clinical presentation.
4. Identify the desired therapeutic outcomes for patients with GERD.
5. Recommend appropriate lifestyle modifications and pharmacotherapy interventions for patients with GERD.
6. Discuss other nonpharmacologic interventions that may be appropriate for patients with GERD.
7. Formulate a monitoring plan to assess the effectiveness and safety of pharmacotherapy for GERD.
8. Educate patients on appropriate lifestyle modifications and drug therapy issues including compliance, adverse effects, and drug interactions.

Key Concepts

❶ GERD can be divided into three distinct categories: erosive esophagitis, non-erosive reflux disease, and Barrett's esophagus.
❷ Patients with GERD may display symptoms described as (1) typical, (2) atypical, or (3) complicated.
❸ Patients presenting with uncomplicated, typical symptoms of reflux (heartburn and regurgitation) do not usually require invasive esophageal evaluation.
❹ The goals of treatment of GERD are to alleviate symptoms, decrease the frequency of recurrent disease, promote healing of mucosal injury, and prevent complications.
❺ Treatment for GERD involves one or more of the following modalities: (1) lifestyle changes and patient-directed therapy; (2) pharmacologic intervention primarily with acid-suppressing agents; (3) anti-reflux surgery, or (4) endoscopic therapies.
❻ Acid-suppressing therapy is the mainstay of GERD treatment and should be considered for anyone not responding to lifestyle changes and patient-directed therapy after 2 weeks.
❼ Anti-reflux surgery or endoscopic therapies offer an alternative treatment for refractory GERD or when pharmacologic management is undesirable.
❽ Many patients with GERD experience relapse if medication is withdrawn, and long-term maintenance treatment is required in such patients.
❾ Patient medication profiles should be reviewed for drugs that may aggravate GERD.

Gastroesophageal reflux disease (GERD) refers to symptoms or mucosal damage that result from abnormal reflux of gastric contents into the esophagus.[1] ❶ *GERD can be divided into three distinct categories: (1) erosive* ***esophagitis****, (2) non-erosive reflux disease, and (3) Barrett's esophagus.*[2] Erosive esophagitis occurs when the esophagus is repeatedly exposed to refluxed material for prolonged periods (Fig. 14–1). The inflammation that occurs progresses to erosions of the squamous epithelium. Non-erosive reflux disease, also referred to as "symptomatic" GERD or **endoscopy**-negative reflux disease, is associated with severe reflux symptoms with normal endoscopic findings. Barrett's esophagus is a complication of GERD characterized

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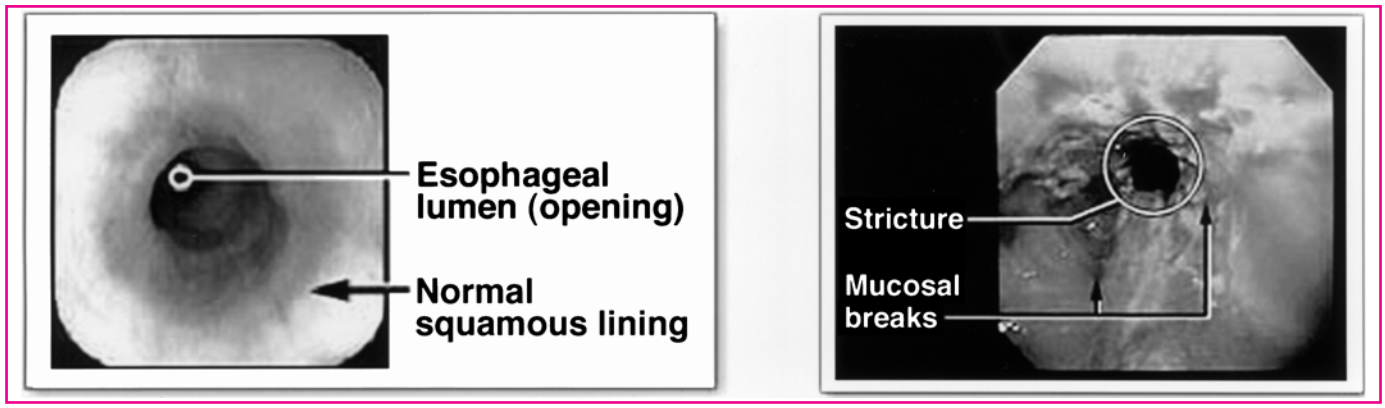


FIGURE 14–1. Endoscopic images of the esophagus. *Left:* Image taken during an endoscopy of the esophagus revealing normal smooth squamous cell lining. *Right:* Narrowed esophageal lumen (stricture) due to chronic GERD with inflammation and scarring. The surrounding esophageal lining has ulcerations and erosions from chronic acid injury. (From Barrett's esophagus website: http://www.barrettsinfo.com.; reprinted with permission.)

by replacement of the normal squamous epithelial lining of the esophagus by specialized columnar-type epithelium. Barrett's esophagus is more likely to occur in patients with a long history (years) of symptomatic reflux and may be a risk factor for developing adenocarcinoma of the esophagus.

EPIDEMIOLOGY AND ETIOLOGY

GERD is prevalent in patients of all ages. Although mortality associated with GERD is rare, symptoms can significantly decrease quality of life. The true prevalence and incidence of GERD are unknown because: (1) many patients do not seek medical treatment; (2) symptoms do not always correlate well with disease severity; and (3) there is no gold standard for diagnosing the disease. The prevalence of erosive esophagitis increases in adults older than 40 years of age. However, non-erosive reflux disease may begin approximately a decade sooner. There does not appear to be a major difference in incidence between men and women except for its association with pregnancy and possibly the non-erosive reflux disease seen in females. Although gender does not play a major role in the development of GERD, it is an important factor in the development of Barrett's esophagus, which occurs more frequently in males.

PATHOPHYSIOLOGY

The retrograde movement of acid or other noxious substances from the stomach into the esophagus is a major factor in the development of GERD.[3] Commonly, gastroesophageal reflux is associated with defective lower esophageal sphincter pressure or function. Problems with other normal mucosal defense mechanisms such as anatomic factors, esophageal clearance, mucosal resistance, gastric emptying, epidermal growth factor, and salivary buffering may also contribute to the development of GERD. Aggressive factors that may promote esophageal damage upon reflux into the esophagus include gastric acid, pepsin, bile acids, and pancreatic enzymes. Therapeutic regimens for GERD are designed to maximize normal mucosal defense mechanisms and attenuate the aggressive factors.

Lower Esophageal Sphincter Pressure

The lower esophageal sphincter is a manometrically-defined zone of the distal esophagus with an elevated basal resting pressure. The sphincter is normally in a tonic, contracted state, preventing the reflux of gastric material from the stomach. It relaxes on swallowing to permit the free passage of food into the stomach.

Mechanisms by which defective lower esophageal sphincter pressure may cause gastroesophageal reflux are three-fold. First, and probably most important, reflux may occur after spontaneous transient lower esophageal sphincter relaxations that are not associated with swallowing.[4] Esophageal distention, vomiting, belching, and retching can cause relaxation of the lower esophageal sphincter. These transient relaxations, which are normal postprandially, may play an important role in intermittent non-erosive reflux.[5] Transient decreases in sphincter pressure are responsible for approximately 65% of the reflux episodes in patients with GERD.

Second, reflux may occur after transient increases in intra-abdominal pressure (stress reflux).[3] An increase in intra-abdominal pressure such as that occurring during straining, bending over, coughing, eating, or a Valsalva maneuver may overcome a weak lower esophageal sphincter, and thus may lead to reflux.

Third, the lower esophageal sphincter may be atonic, thus permitting free reflux. Although transient relaxations are more likely to occur when there is normal lower esophageal sphincter pressure, the latter two mechanisms are more likely

TABLE 14–1. Foods and Medications that may Worsen GERD Symptoms

Decreased Lower Esophageal Sphincter Pressure	
Foods	
Fatty meal	Garlic
Carminatives (peppermint, spearmint)	Onions
Chocolate	Chili peppers
Coffee, cola, tea	
Medications	
Anticholinergics	Isoproterenol
Barbiturates	Narcotics (meperidine, morphine)
Benzodiazepines (e.g., diazepam)	Nicotine (smoking)
Caffeine	Nitrates
Dihydropyridine calcium channel blockers	Phentolamine
Dopamine	Progesterone
Estrogen	Theophylline
Ethanol	
Direct Irritants to the Esophageal Mucosa	
Foods	
Spicy foods	Tomato juice
Orange juice	Coffee
Medications	
Alendronate	Quinidine
Aspirin	Potassium chloride
Iron	
Non-steroidal anti-inflammatory drugs	

Adapted from Williams DB, Schade RR. Gastroesophageal reflux disease. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. McGraw-Hill, New York: McGraw-Hill; 2005: 615, with permission.

when the lower esophageal sphincter pressure is decreased by such factors as fatty foods, gastric distention, smoking, or medications.[3] Certain foods and medications may worsen esophageal reflux by decreasing lower esophageal sphincter pressure or by irritating the esophageal mucosa (Table 14–1).[6]

Anatomic Factors

Disruption of the normal anatomic barriers by a hiatal hernia was once thought to be a primary etiology of gastroesophageal reflux and esophagitis. It is now believed that lower esophageal sphincter pressure is a more important factor related to symptoms in patients with hiatal hernia. Although anatomic factors are considered significant by some clinicians, the diagnosis of hiatal hernia is generally considered a separate entity with which reflux may or may not simultaneously occur.

Esophageal Clearance

Many patients with GERD produce normal amounts of acid, but the acid produced spends too much time in contact with the esophageal mucosa. The contact time is dependent on the rate at which the esophagus clears the noxious material, as well as the frequency of reflux. The esophagus is cleared by primary peristalsis in response to swallowing, or by secondary peristalsis in response to esophageal distention and gravitational effects.

Swallowing contributes to esophageal clearance by increasing salivary flow. Saliva contains bicarbonate that buffers the residual gastric material on the surface of the esophagus. The production of saliva decreases with increasing age, making it more difficult to maintain a neutral intra-esophageal pH. Therefore, esophageal damage due to reflux occurs more often in the elderly and patients with **Sjögren's syndrome** or **xerostomia**. Swallowing is also decreased during sleep, which contributes to nocturnal GERD in some patients.

Mucosal Resistance

The esophageal mucosa and submucosa consist of mucus-secreting glands that contain bicarbonate. Bicarbonate moving from the blood to the lumen can neutralize acidic refluxate in the esophagus. When the mucosa is repeatedly exposed to the refluxate in GERD, or if there is a defect in the normal mucosal defenses, hydrogen ions diffuse into the mucosa, leading to the cellular acidification and necrosis that ultimately cause esophagitis.[3]

Gastric Emptying

Gastric volume is related to the amount of material ingested, rate of gastric secretion, rate of gastric emptying, and amount and frequency of duodenal reflux into the stomach. Delayed gastric emptying can lead to increased gastric volume and contribute to reflux. An increase in gastric volume may increase both the frequency of reflux and the amount of gastric fluid available to be refluxed. Factors that increase gastric volume and/or decrease gastric emptying, such as smoking and high-fat meals, are often associated with gastroesophageal reflux. This partially explains the prevalence of postprandial gastroesophageal reflux.

Composition of Refluxate

The composition, pH, and volume of the refluxate are aggressive factors associated with gastroesophageal reflux. Duodenogastric reflux esophagitis or "alkaline esophagitis" refers to esophagitis induced by the reflux of bilious and pancreatic fluid. Although bile acids have both a direct irritant effect on the esophageal mucosa and an indirect effect of increasing hydrogen ion permeability of the mucosa, symptoms are more often related to acid reflux than to bile reflux. The percentage of time that esophageal pH is below 4 is greater for patients with severe disease than for those with mild disease.

The pathophysiology of GERD is a complex process. It is difficult to determine which occurs first: gastroesophageal reflux leading to defective peristalsis with delayed clearing, or an incompetent lower esophageal sphincter pressure leading

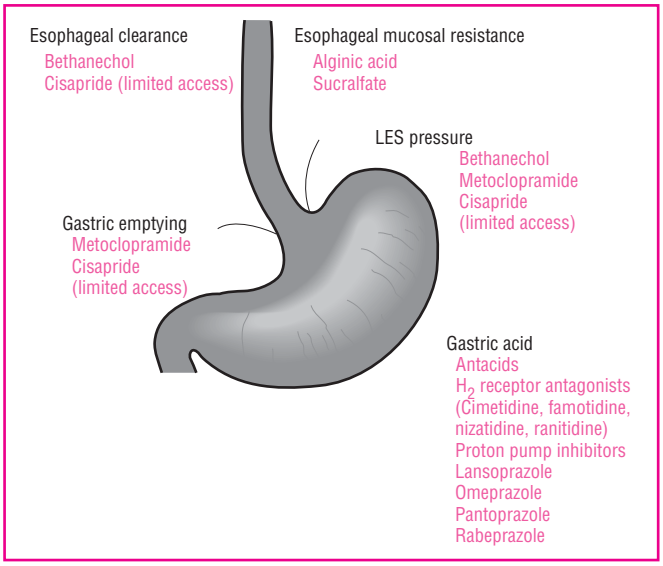


FIGURE 14–2. Therapeutic interventions in the management of gastroesophageal reflux disease. Pharmacologic interventions are targeted at improving defense mechanisms or decreasing aggressive factors. LES, lower esophageal sphincter. (Adapted from Williams DB, Schade RR. Gastroesophageal reflux disease. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 617, with permission.)

to gastroesophageal reflux. Understanding factors associated with the development of GERD is essential to providing effective treatment (Fig. 14–2).

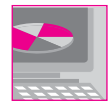
CLINICAL PRESENTATION AND DIAGNOSIS

❷ *Patients with GERD may display symptoms described as (1) typical, (2) atypical, or (3) complicated (see Clinical Presentation Box).*[7]

Complications of GERD

The severity of symptoms of gastroesophageal reflux does not always correlate with the degree of esophagitis, but it does correlate with the duration of reflux. Patients who are not adequately treated for GERD can develop complications from long-term acid exposure. Long-term, recurrent reflux symptoms that are not adequately treated may lead to Barrett's esophagus and may be an independent risk factor for esophageal adenocarcinoma.[8] Esophageal strictures (Fig. 14–1) may be present in patients presenting with dysphagia.

The use of non-steroidal anti-inflammatory drugs or aspirin is an additional risk factor that may contribute to the development or worsening of esophageal strictures. These complicated symptoms must be distinguished from other esophageal disorders such as esophageal diverticulum, achalasia, obstruction, esophageal spasm, esophageal infections, scleroderma, and malignancy.



Clinical Presentation of GERD

Typical Symptoms

- Heartburn is the hallmark symptom of GERD and is generally described as a substernal sensation of warmth or burning rising up from the abdomen that may radiate to the neck. It may be waxing and waning in character.
- Regurgitation is also very common.
- Symptoms may be worse after a fatty meal, when bending over, or when lying in a recumbent position.[1]
- Other symptoms include water brash (hypersalivation) and belching.

Atypical Symptoms

- Atypical symptoms include non-allergic asthma, chronic cough, hoarseness, pharyngitis, chest pain, and dental erosions.
- In some cases, these extra-esophageal symptoms may be the only ones present, making it more difficult to recognize GERD as the cause, especially when endoscopic studies are normal.
- It is important to distinguish GERD symptoms from those of other diseases, especially when chest pain or pulmonary symptoms are present.

Complicated Symptoms

- These include continual pain, dysphagia (difficulty swallowing), odynophagia (painful swallowing), bleeding, unexplained weight loss, and choking.
- These symptoms may be indicative of complications of GERD such as Barrett's esophagus, esophageal strictures, or esophageal cancer.

Diagnosis of GERD

The most useful tool in the diagnosis of GERD is the clinical history, including both the presenting symptoms and associated risk factors. ❸ *Patients presenting with uncomplicated,*



Patient Encounter, Part 1

A 42-year-old man with a history of diabetes and hypertension presents complaining of "heartburn." He reports a burning sensation in his upper chest and some regurgitation of sour-tasting material into his throat. The symptoms began about 1 month ago, occur about twice a week, and are associated with heavy meals and lying down after eating. He says that he smokes about one pack of cigarettes per day and drinks coffee and alcohol-containing beverages on most days.

- What information is suggestive of GERD?
- Does he have any factors contributing to GERD?
- What additional information do you need before creating a treatment plan for this patient?

typical symptoms of reflux (heartburn and regurgitation) do not usually require invasive esophageal evaluation. These patients generally benefit from a trial of lifestyle modifications and empiric acid-suppressing therapy.[1] A clinical diagnosis of GERD can be assumed in patients who respond to appropriate therapy.

More specific diagnostic tests may be warranted in patients not responding to empiric (prescription) therapy, those with complicated or "alarm" symptoms (e.g., weight loss or dysphagia), or those with long-standing symptoms who are at risk for Barrett's esophagus.

More definitive diagnostic tests include endoscopy (via endoscope or Pillcam™ ESO capsule), 24-hour ambulatory pH monitoring, diagnostic proton pump inhibitor (PPI) administration, or esophageal manometry.

Upper gastrointestinal endoscopy is the preferred diagnostic test for assessing the mucosa for esophagitis and Barrett's esophagus.[1] It enables visualization and biopsy of the esophageal mucosa. Endoscopy should be considered upon initial presentation in any patient who presents with complicated symptoms and those at risk for Barrett's esophagus.[1]

The Pillcam™ ESO allows for visualization of the esophagus via a camera-containing capsule that is swallowed by the patient. Sensors are placed on the chest and are connected to a data collector that downloads images of the esophagus. The entire procedure takes less than 15 minutes and can be done in the physician's office. The camera-containing capsule is eliminated in the stool.

24-Hour ambulatory pH monitoring may be the only way to objectively prove that symptoms are reflux-related in patients with atypical symptoms or non-erosive reflux disease. Ambulatory pH monitoring may also be useful in patients whose symptoms are not improving on adequate doses of acid-suppressing therapy.

The empiric use of a standard-dose (or double-dose) PPI as a therapeutic trial may be used in diagnosing GERD. This approach is less expensive, more convenient, and more readily available than ambulatory pH monitoring. Problems with this diagnostic approach include lack of a standardized dosing regimen and duration of the diagnostic trial.

Esophageal manometry involves placing a multi-lumen tube into the stomach. Pressures are measured as the tube is pulled back across the lower esophageal sphincter, esophagus, and pharynx. Manometry may be useful in determining which surgical procedure is best for a given patient. A newer tubeless pH monitoring system does not require full manometry.

Barium radiography involves the ingestion of barium followed by x-rays of the esophagus. It is more cost effective than endoscopy but is no longer recommended for routine diagnosis of GERD. Barium radiography lacks the sensitivity and specificity needed to determine the presence of mucosal injury, especially in less severe cases, and it cannot distinguish between Barrett's esophagus and esophagitis.

TREATMENT

Desired Outcomes

❹ *The goals of treatment of GERD are to alleviate symptoms, decrease the frequency of recurrent disease, promote healing of mucosal injury, and prevent complications.*

General Approach to Treatment

❺ *Treatment for GERD involves one of the following modalities: (1) lifestyle changes and patient-directed therapy; (2) pharmacologic intervention primarily with acid-suppressing agents; (3) anti-reflux surgery, or (4) endoscopic therapies.* The first therapeutic option used depends upon the patient's condition (i.e., frequency of symptoms, degree of esophagitis, and presence of complications; Table 14–2).

❻ *Acid-suppressing therapy is the mainstay of GERD treatment and should be considered for anyone not responding to lifestyle changes and patient-directed therapy after 2 weeks.* PPIs provide the greatest relief of symptoms and highest rates of healing, especially in patients with erosive disease or moderate to severe symptoms.

Maintenance therapy is generally necessary to control symptoms and to prevent complications. GERD that is refractory to adequate acid suppression is rare. In these cases, the diagnosis should be confirmed through further diagnostic tests before long-term, high-dose therapy or anti-reflux surgery or endoscopic therapies are considered.[1]

Nonpharmacologic Therapy

Nonpharmacologic treatment of GERD includes lifestyle modifications, anti-reflux surgery, or endoscopic therapies.

Lifestyle Modifications

Although most patients do not respond to lifestyle changes alone, the importance of maintaining these lifestyle changes throughout the course of GERD therapy should be stressed to patients on a routine basis. The most common lifestyle changes that a patient should be educated about include: (1) losing weight; (2) elevating the head of the bed; (3) eating smaller meals and avoiding meals 3 hours before sleeping; (4) avoiding foods or medications that exacerbate GERD; (5) smoking cessation; and (6) avoiding alcohol.

A meal high in fat decreases lower esophageal sphincter pressure for 2 hours or more postprandially. In contrast, a high-protein, low-fat meal elevates lower esophageal sphincter pressure. Elevating the head of the bed about 6 to 10 inches with an under-mattress foam wedge (not just elevating the head with pillows) decreases nocturnal esophageal acid contact time and should be recommended.[3]

Patient medications and food histories should be evaluated to identify potential factors that may exacerbate GERD symptoms

TABLE 14–2. Therapeutic Approach to GERD

Patient Presentation	Recommended Treatment Regimen	Comments
Intermittent, mild heartburn	A. Lifestyle modifications **PLUS** B. Antacids • Magnesium/aluminum hydroxide 30 mL after meals and at bedtime as needed • Antacid/alginic acid (Gaviscon) 2 tablets or 15 mL after meals and at bedtime **AND/OR** C. Patient-directed therapy • Over-the-counter H_2RAs (each taken up to twice daily) - Cimetidine 200 mg - Famotidine 10 mg - Nizatidine 75 mg - Ranitidine 75 mg **OR** • Over-the-counter PPI (taken once daily) - Omeprazole 20 mg	• Start lifestyle changes initially and continue throughout the treatment course. • If symptoms are unrelieved with lifestyle changes and over-the-counter medications after 2 weeks, begin therapy with a standard dose acid-suppressing agent.
Symptomatic GERD	A. Lifestyle modifications **PLUS** B. Standard dose acid-suppressing therapy • H_2RAs (taken twice daily) for 6–12 weeks - Cimetidine 400 mg - Famotidine 20 mg - Nizatidine 150 mg - Ranitidine 150 mg **OR** • PPIs (taken once daily) for 4–8 weeks - Esomeprazole 20 mg - Lansoprazole 15–30 mg - Omeprazole 20 mg - Pantoprazole 40 mg - Rabeprazole 20 mg	• For typical symptoms, treat empirically with standard doses of acid-suppressing therapy. • Mild GERD can usually be treated effectively with H_2RAs. Patients with moderate to severe symptoms should receive a PPI as initial therapy. If symptoms are relieved, treat recurrences on an as-needed basis. • If symptoms recur frequently, consider maintenance therapy with the lowest effective dose. • Most patients require standard doses for maintenance therapy.
Healing of erosive esophagitis or treatment of moderate to severe symptoms or complications	A. Lifestyle modifications **PLUS** B. PPIs (taken once-twice daily) for 4–16 weeks - Esomeprazole 20–40 mg - Lansoprazole 30 mg - Omeprazole 20 mg - Rabeprazole 20 mg - Pantoprazole 40 mg	• For atypical symptoms, give a trial of a PPI or H_2RA. • If symptoms are relieved, consider maintenance therapy. • PPIs are the most effective maintenance therapy in patients with atypical symptoms, complicated symptoms, or erosive disease. • Patients not responding to acid-suppressing therapy, including those with persistent atypical symptoms, may be candidates for anti-reflux surgery or endoscopic therapies.

H_2RA, histamine$_2$-receptor antagonist; PPI, proton pump inhibitor.
Adapted from Williams DB, Schade RR. Gastroesophageal reflux disease. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 618, with permission.

(Table 14–1).[6,9,10] Patients should be closely monitored for symptoms when medications known to worsen GERD are started.

Anti-Reflux Surgery and Endoscopic Therapies

❼ *Anti-reflux surgery or endoscopic therapies offer alternative treatments for refractory GERD or when pharmacologic management is undesirable.*

Anti-Reflux Surgery

Surgical intervention is a viable alternative for selected patients with well-documented GERD.[1] The goal of surgery is to re-establish the anti-reflux barrier, to position the lower esophageal sphincter within the abdomen where it is under positive (intra-abdominal) pressure, and to close any associated hiatal defect.[11] It should be considered in patients who (1) fail to respond to pharmacologic treatment; (2) opt for

surgery despite successful treatment because of lifestyle considerations including age, time, or expense of medications; (3) have complications of GERD (Barrett's esophagus or strictures); or (4) have atypical symptoms and reflux documented on 24-hour ambulatory pH monitoring.[11]

Endoscopic Therapies[12]

Three endoscopic approaches to the management of GERD are available. They include: (1) application of radiofrequency energy to the lower esophageal sphincter area; (2) endoscopic suturing to produce a **plication**; and (3) endoscopic injection of a biopolymer at the gastroesophageal junction.[1] More studies and experience are needed to determine their exact role in the management of GERD.

Pharmacologic Therapy

Antacids and Antacid–Alginic Acid Products

Antacids are an appropriate component of treating mild GERD, as they are clearly effective for immediate, symptomatic relief. They are often used concurrently with other acid-suppressing therapies. Patients who require frequent use of antacids for chronic symptoms should be treated with prescription acid-suppressing therapy.

An antacid product combined with alginic acid (Gaviscon) is not a potent neutralizing agent but forms a highly viscous solution that floats on the surface of the gastric contents. This viscous solution serves as a protective barrier for the esophagus against reflux of gastric contents. It also reduces the frequency of the reflux episodes.[13]

Dosage recommendations for antacids vary and range from hourly dosing to administration on an as-needed basis. In general, antacids have a short duration of action, which requires frequent administration throughout the day to provide continuous acid neutralization.

Antacids also have clinically significant drug interactions with tetracycline, ferrous sulfate, isoniazid, quinidine, sulfonylureas, and quinolone antibiotics. Antacid-drug interactions are influenced by antacid composition, dose, dosage schedule, and formulation.

H_2-Receptor Antagonists

The histamine$_2$-receptor antagonists (H_2RAs) cimetidine, famotidine, nizatidine, and ranitidine decrease acid secretion by inhibiting the histamine$_2$-receptors in gastric parietal cells. When given in divided doses, they are effective for patients with mild to moderate GERD.[1] Standard doses provide symptomatic improvement in about 60% of patients after 12 weeks of therapy.[1] Healing rates per endoscopy tend to be lower (50%).[1] Response to the H_2RAs is dependent on (1) the severity of disease, (2) the dosage regimen used, and (3) the duration of therapy.

For symptomatic relief of mild GERD, low-dose, nonprescription H_2RAs may be beneficial. For patients not responding to patient-directed therapy with over-the-counter agents after 2 weeks, standard-dose acid-suppressing therapy is warranted. Although higher doses of H_2RAs may provide greater symptomatic and endoscopic healing rates, limited information exists regarding the safety of these regimens and they can be less effective and more costly than once-daily PPIs.

Because all H_2RAs have similar efficacy, selection of the specific agent should be based on factors such as differences in dosage regimen, safety profile, and cost. In general, H_2RAs are well tolerated. Patients should be monitored for adverse effects and potential drug interactions. Cimetidine may inhibit the metabolism of certain medications such as theophylline, warfarin, phenytoin, nifedipine, or propranolol. An alternate H_2RA should be selected if the patient is taking any of these medications.

Proton Pump Inhibitors

The PPIs esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole block gastric acid secretion by inhibiting gastric H^+/K^+-adenosine triphosphatase in gastric parietal cells.[14] This produces a profound, long-lasting antisecretory effect capable of maintaining the gastric pH above 4, even during acid surges seen postprandially.[3,5]

The PPIs are superior to H_2RAs in patients with moderate to severe GERD. This includes not only patients with erosive esophagitis or complicated symptoms (Barrett's esophagus or strictures), but also those with non-erosive reflux disease who have moderate to severe symptoms. Symptomatic relief is seen in approximately 83% of patients and healing rates at 8 weeks as judged by endoscopy are 78%.[1]

Whether PPIs can reverse Barrett's esophagus remains a topic for debate. The use of high-dose omeprazole (40 mg twice daily) caused partial regression of Barrett's esophagitis, but no change was noted in patients receiving ranitidine 150 mg twice daily.[14] Others propose that islands of normal squamous cells that appear in patients with Barrett's esophagus after high-dose PPIs may be covering gastric mucosa and may mask the development of cancerous changes in the mucosa.[15] It is unknown whether regression of Barrett's esophagus reduces the risk of adenocarcinoma, but aggressive therapy to suppress acid reflux early in the disease may help prevent Barrett's esophagus.

Comparable daily doses of PPIs are omeprazole 20 mg = esomeprazole 20 mg = lansoprazole 30 mg = rabeprazole 20 mg = pantoprazole 40 mg. The PPIs degrade in acidic environments and are therefore formulated in delayed-release capsules or tablets.[16] Lansoprazole, esomeprazole, and omeprazole contain enteric-coated (pH-sensitive) granules in a capsule form. For patients unable to swallow the capsule or in pediatric patients, the contents of the capsule can be mixed in applesauce or placed in orange juice. If a patient has a nasogastric tube, the contents of an omeprazole capsule can be

mixed in 8.4% sodium bicarbonate solution. Esomeprazole can be mixed with water. Lansoprazole is contained in a packet for oral suspension and a delayed-release orally disintegrating tablet. While lansoprazole dosage forms are beneficial for those who cannot swallow the capsule, such as elderly or pediatric patients, they should not be placed into nasogastric tubes due to potential clogging. Patients taking pantoprazole or rabeprazole should be instructed not to crush, chew, or split the delayed-release tablets.

Pantoprazole, lansoprazole, and esomeprazole are available in intravenous formulations, which offer an alternative route for patients unable to take oral medications. The intravenous product is not more effective than the oral forms and is significantly more expensive.

Patients should be instructed to take their PPI in the morning, 15 to 30 minutes before breakfast to maximize efficacy, because these agents inhibit only actively secreting proton pumps.[5,17] While usually given prior to breakfast, patients with nighttime symptoms may benefit from taking their PPI prior to the evening meal.[1] If a second dose is needed, it should be administered before the evening meal and not at bedtime.[1] Regardless of the time of day, PPIs should be given prior to a meal to gain the most benefit.

The PPIs are generally well tolerated, and the choice of a particular agent is often based on cost. All PPIs can decrease the absorption of drugs (such as ketoconazole or itraconazole) that require an acidic environment to be absorbed. All PPIs are metabolized by the cytochrome P-450 system to some extent, specifically by the CYP2C19 and CYP3A4 enzymes. However, no interactions with lansoprazole, pantoprazole, or rabeprazole have been seen with CYP2C19 substrates such as diazepam, warfarin, or phenytoin.[18] Esomeprazole does not appear to interact with warfarin or phenytoin. Pantoprazole is metabolized by a cytosolic sulfotransferase and is therefore less likely to have significant drug interactions than other PPIs.[17]

While generally not of major concern, omeprazole may inhibit the metabolism of warfarin, diazepam, and phenytoin; lansoprazole may decrease theophylline concentrations. Drug interactions with omeprazole are of particular concern in patients who are considered "slow metabolizers," as are approximately 3% of the Caucasian population. Unfortunately, it is unclear which patients have the polymorphic gene variation that makes them slow metabolizers.[17] The metabolism of esomeprazole may also be altered in patients with this polymorphic gene variation. Patients on potentially interacting drugs should be monitored for development of drug-related problems.

Prolonged hypergastrinemia leading to the development of colonic polyps and potentially adenocarcinoma in rats was a concern that has proven to be unfounded with long-term use in humans.[19] The FDA has stated that there is insufficient evidence linking PPI use to atrophic gastritis, intestinal metaplasia, or gastric cancer.[20]

Prokinetic Agents

The prokinetic agents include cisapride, metoclopramide, and bethanechol. The inferior efficacy and side-effect profiles of metoclopramide and bethanechol limit their use in the treatment of GERD. Metoclopramide may cause tardive dyskinesia, especially with long-term use. In contrast, cisapride has comparable efficacy to H_2RAs in patients with mild esophagitis. Unfortunately, cisapride is no longer available for routine use because of life-threatening arrhythmias that may occur when given with certain medications and other disease states.

Mucosal Protectants

Sucralfate, a non-absorbable aluminum salt of sucrose octasulfate, has very limited value in the treatment of GERD and is not routinely recommended.

Combination Therapy

Two agents of different therapeutic classes should not be routinely used together unless a patient has esophagitis with known motor dysfunction occurring concurrently. In this case, an acid-suppressive agent and a prokinetic agent may be appropriate. Only modest improvements have been shown when a prokinetic agent is combined with a standard dose of an H_2RA. Therefore, patients not responding to standard H_2RA doses should have the dose increased, or they should be switched to a PPI instead of adding a prokinetic agent.

Monotherapy with a PPI is not only more effective in patients not responding to an H_2RA or prokinetic agent alone, but it also improves compliance with once-daily dosing and is ultimately more cost-effective.

Maintenance Therapy

❽ *Many patients with GERD relapse if medication is withdrawn, and long-term maintenance treatment is required in such patients.*[1] Candidates for maintenance therapy include patients whose symptoms return once therapy is discontinued or decreased, patients with complications such as Barrett's esophagus or strictures, and perhaps patients with atypical symptoms.

The goal of maintenance therapy is to improve quality of life by controlling symptoms and preventing complications. These goals cannot generally be achieved by decreasing the dose or switching to a less potent acid-suppressing agent. Most patients require standard doses to prevent relapses.[21] Patients should be counseled on the importance of complying with lifestyle changes and long-term maintenance therapy to prevent recurrence or worsening of disease.

The H_2RAs may be effective maintenance therapy for patients with mild disease.[5] The PPIs are first choice for maintenance treatment of moderate to severe GERD.[22] Preliminary data suggest that "on demand" maintenance therapy may be effective for some patients.[1] With on-demand therapy, patients takes their PPIs only when symptoms occur. However,

patients with more severe disease and/or complications should be maintained on standard daily doses of PPIs for maximum benefit.

Long-term use of higher PPI doses is not indicated unless the patient has complicated symptoms, has erosive esophagitis per endoscopy, or has had further diagnostic evaluation to determine degree and frequency of acid exposure. Anti-reflux surgery and endoscopic therapies may be viable alternatives to long-term drug use for maintenance therapy in selected patients.



Patient Encounter, Part 2: The Medical History, Physical Exam, and Diagnostic Tests

PMH
Type 2 diabetes mellitus since age 36; it is often not well controlled because of poor patient compliance
Hypertension x 3 years, currently controlled
History of hepatitis B

FH
Father died of MI at the age of 68 years; mother is still alive with history of colon cancer and diabetes

SH
Works as a laborer in a warehouse; drinks alcohol most days but denies any alcohol-related problems

Meds
Metformin 1000 mg orally twice daily
Hydrochlorothiazide 25 mg orally once daily
Nifedipine XL 60 mg orally once daily
Regular insulin 4 units SC 3 times daily with meals
Insulin glargine 20 units SC at bedtime

ROS
(+) Heartburn, regurgitation; (–) chest pain, nausea, vomiting, diarrhea, weight loss, change in appetite, shortness of breath or cough, difficulty or painful swallowing

PE
VS: Blood pressure 134/84 mm Hg, pulse 82 beats per minute, respiratory rate 16/minutes, temperature 37°C (98.6°F)
CV: RRR, normal S_1, S_2; no murmurs, rubs, or gallops
Abdomen: Soft, non-tender, non-distended; (+) bowel sounds, (–) hepatosplenomegaly, heme (–) stool
Endoscopy: Diffuse erythema and several isolated erosions in the distal esophagus; no evidence of ulceration, obstruction, or stricture

- Given this additional information, what findings are consistent with a diagnosis of GERD?
- Could any of the medications listed aggravate GERD symptoms in this patient?
- Identify your treatment goals for this patient.
- What nonpharmacologic and pharmacologic options are possible for this patient?

Special Population Considerations

Patients with Atypical GERD Symptoms

Patients presenting with atypical symptoms may require higher doses and longer treatment courses than patients with typical symptoms. These patients are best diagnosed with ambulatory pH testing or an empiric trial with a PPI.[23] These tests can confirm reflux in patients who have persistent symptoms without evidence of mucosal damage by endoscopy.[1] In patients presenting with non-cardiac chest pain, a short course (1 to 8 weeks) of omeprazole 20 mg twice daily has been advocated.[23]

In patients with asthma, anti-reflux medications may improve asthma symptoms and even decrease asthma medication use but cause little or no improvement in lung function.[24] A trial of 3 months has been advocated using twice-daily proton pump inhibitor therapy for asthma symptoms thought to be associated with GERD. Omeprazole doses as high as 60 mg daily have been used.[23] In patients with chronic cough, 24-hour ambulatory pH testing is the preferred approach for evaluation of GERD when available because many patients do not have erosive disease by endoscopy.[25] Maintenance therapy is generally indicated in patients who respond to the therapeutic trial or have evidence of reflux. Anti-reflux surgery or endoscopic therapies may be indicated in selected patients not responding to medical management.

Patients with Endoscopy-Negative Reflux Disease

Although endoscopy is the best diagnostic tool to evaluate the integrity of the esophageal mucosa, it cannot prove that the patient's symptoms are caused by GERD. Patients with typical symptoms and increased acid exposure may have no evidence of esophageal damage. Many patients with persistent, severe symptoms but normal endoscopy require therapy similar to those with positive endoscopic findings.

Patients presenting with normal esophageal mucosa on endoscopy may undergo 24-hour ambulatory pH testing or a therapeutic trial with a PPI to further confirm the diagnosis of GERD.

Pediatric Patients with GERD

Gastroesophageal reflux occurs in approximately 18% of infants. As in adults, transient lower esophageal sphincter relaxations appear to be the most common cause of GERD.[26] This is due to developmental immaturity of the lower esophageal sphincter.[27] Other causes include impaired luminal clearance of gastric acid, neurologic impairment, and type of infant formula.

Most infants have physiologic reflux with no clinical consequence.[26] Complications, although rare, include distal esophagitis, **failure to thrive**, esophageal strictures, and Barrett's esophagus.[27]

Uncomplicated GERD usually resolves by 12 to 18 months of life and responds to supportive therapy, including dietary

adjustments such as smaller meals, more frequent feedings, or thickened infant formula. Postural management (e.g., positioning the infant in an upright position, especially after meals), and reassurance for the parents may also be helpful.[27] Medical therapy may be indicated if there is no improvement.

The combination of a prokinetic agent and acid-suppressing drug is used commonly in pediatric patients with GERD.[27] Monotherapy with an H_2RA is also used frequently; ranitidine 2 to 4 mg/kg/day is effective in neonates and pediatric patients.

Use of PPIs is becoming more common in pediatrics. Lansoprazole is FDA-approved for treating symptomatic and erosive GERD in patients 1 through 11 years of age. The recommended dose is 15 mg once daily for children weighing less than or equal to 30 kg and 30 mg once daily for those weighing greater than 30 kg. Although omeprazole is not FDA-approved for use in children, evidence supports its effectiveness in children with GERD. A common dose for esophagitis is omeprazole 1 mg/kg/day (given once or twice daily).[28] Although no major adverse events have been noted in children receiving PPIs for up to 7 years, the safety of prolonged use in children is unknown.[28] There are no data evaluating the use of esomeprazole, pantoprazole, or rabeprazole in treating GERD in children.

Elderly Patients with GERD

Older individuals have decreased host defense mechanisms such as slowed gastric emptying and decreased saliva production. They may present with atypical symptoms such as chest pain, asthma, hoarseness, coughing, wheezing, or poor dentition. These patients often do not seek medical attention because they believe their symptoms are part of the normal aging process.

A PPI may be warranted in patients older than 60 years of age.[29] Proton pump inhibitors are the most useful option because they have superior efficacy and are dosed once daily. Elderly patients may be sensitive to the central nervous system effects of metoclopramide and H_2RAs.



Patient Encounter, Part 3: Creating a Care Plan

Based on the information presented, create a care plan for this patient's GERD. Your plan should include: (1) a statement of the drug-related needs and/or problems; (2) the goals of therapy; (3) a patient-specific detailed therapeutic plan; and (4) a plan for follow-up to determine whether the goals have been achieved and adverse effects avoided.

OUTCOME EVALUATION

- Monitor for symptom relief and the presence of complicated symptoms, such as difficulty swallowing, painful swallowing, or unexplained weight loss.
- Record the frequency and severity of symptoms by interviewing the patient after 6 to 8 weeks of acid-suppressing therapy. Continued symptoms may indicate the need for long-term maintenance therapy.
- Monitor for adverse drug reactions, drug-drug interactions, and compliance with the therapeutic regimen initially and any time there is a change in symptoms or medications.
- Educate patients about symptoms that suggest the presence of complications requiring immediate medical attention, such as dysphagia or odynophagia.
- Refer patients who present with atypical symptoms such as cough, non-allergic asthma, or chest pain to their physician for further diagnostic evaluation.



Patient Care and Monitoring

1. Assess patient symptoms to determine if further diagnostic evaluation is necessary. Does the patient have any GERD-related complications such as difficulty swallowing, painful swallowing, or unexplained weight loss?
2. ❾ *Perform a thorough medication history (nonprescription, prescription, and natural drug products), food, and patient history to determine exacerbating factors.*
3. Determine what treatments have been helpful in the past.
4. Instruct the patient to avoid foods that aggravate GERD symptoms.
5. Educate the patient on lifestyle modifications to improve symptoms.
6. Review the results of diagnostic tests.
7. Recommend appropriate therapy and develop a plan to assess effectiveness.
8. Evaluate the patient for the presence of adverse drug reactions, drug allergies, and drug interactions.
9. Stress the importance of compliance with the therapeutic regimen.
10. Determine if long-term maintenance treatment is necessary.
11. Assess improvement in quality-of-life measures such as physical, psychological, and social functioning and well-being.
12. Provide patient education on disease, lifestyle modifications, and drug therapy:
    - What causes GERD and what are things to avoid?
    - What are possible complications of GERD?
    - When should medications be taken?
    - What potential adverse effects may occur?
    - Which drugs may interact with their therapy?
    - What warning signs should be reported to the physician?

ABBREVIATIONS

GERD: gastroesophageal reflux disease
H_2RA: histamine$_2$-receptor antagonist
LES: lower esophageal sphincter
PPI: proton pump inhibitor

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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15 Peptic Ulcer Disease

Jeffrey J. Fong and John W. Devlin



Learning Objectives

Upon completion of the chapter the reader will be able to:

1. Recognize differences between ulcers induced by *Helicobacter pylori* (HP) and non-steroidal anti-inflammatory drugs (NSAIDs) in terms of risk factors, pathogenesis, signs and symptoms, clinical course, and prognosis.
2. Identify desired therapeutic outcomes for patients with HP-associated ulcers and NSAID-induced ulcers.
3. Identify factors that guide selection of an HP eradication regimen and improve compliance with these regimens.
4. Determine the appropriate management for a patient taking a non-selective NSAID who is at high risk for ulcer-related gastrointestinal complications or who develops an ulcer.
5. Devise an algorithm for evaluation and treatment of a patient with signs and symptoms suggestive of an HP-associated or NSAID-induced ulcer.
6. Given patient-specific information and the prescribed drug treatment regimen, formulate a monitoring plan for a patient who is receiving drug therapy to either eradicate HP or to treat an active NSAID-induced ulcer or gastrointestinal complication.

Key Concepts

❶ Patients with peptic ulcer disease should avoid exposure to factors known to worsen the disease, exacerbate symptoms, or lead to ulcer recurrence [e.g., non-steroidal anti-inflammatory drug (NSAID) use or cigarette smoking].

❷ Reliance on conventional antiulcer drug therapy as an alternative to *Helicobacter pylori* (HP) eradication is discouraged because it is associated with a higher incidence of ulcer recurrence and side effects.

❸ Eradication therapy with a proton pump inhibitor–based three-drug regimen should be considered for all patients who test positive for HP and have an active ulcer or a documented history of either an ulcer or ulcer-related complication. Different antibiotics should be used if a second course of HP eradication therapy is required.

❹ In patients at risk for NSAID-induced ulcers, proton pump inhibitors (PPIs) at standard doses reduce the risk of both gastric and duodenal ulcers as effectively as misoprostol and are generally better tolerated.

❺ Selective cyclooxygenase-2 (COX-2) inhibitors have not been shown to be any more effective than the combination of a PPI and a non-selective NSAID in reducing the incidence of ulcers, and questions regarding their long-term cardiovascular safety remain.

❻ Low-dose maintenance therapy with a proton pump inhibitor or histamine$_2$-receptor antagonist is only indicated for patients who fail HP eradication, have HP-negative ulcers, or develop severe complications related to their ulcer disease.

Peptic ulcer disease (PUD) refers to an ulcer that forms on the muscular mucosa in the wall of the gastrointestinal tract. These **ulcerations** are usually located in the duodenum or stomach but can be found elsewhere in the gastrointestinal tract. Peptic ulcer disease is common and may adversely affect quality of life unless properly diagnosed and treated. The high prevalence and relapse rate associated with PUD pose a substantial economic burden. Peptic ulcers are most commonly caused by one of three etiologies: (1) HP infection, (2) use of NSAIDs; or (3) stress-related mucosal damage (SRMD). A number of pathophysiologic variables can be used to distinguish these three common types of peptic ulcer (Table 15–1). This chapter will focus on strategies to optimize pharmacotherapy for patients with PUD related to HP or NSAID therapy.

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TABLE 15–1. Characteristics of Common Causes of Peptic Ulcer Disease

	H. pylori	NSAID	SRMD
Onset	Chronic	Chronic	Acute
Primary location of damage	Duodenum	Stomach	Stomach
Presence of symptoms	Frequent	Rare	Rare
Primary mechanism for ulceration	Infection resulting in inflammatory state	Loss of defense mechanisms	Loss of defense mechanisms
Depth of ulcers	Superficial	Deep	Superficial
Dependence on acid for mucosal damage	Greater	Lesser	Lesser
Characterization of GI bleeding	Minor	Major	Major
Responsive to acid-suppressive therapy	No	Yes	Yes

GI, gastrointestinal; *H. pylori, Helicobacter pylori*; NSAID, non-steroidal anti-inflammatory drug; SRMD, stress-related mucosal damage.

Stress-related mucosal damage occurs most frequently in critically ill patients and is thought to be caused by factors such as compromised mesenteric perfusion rather than HP or NSAIDs. Its onset is usually acute, and in a small proportion of patients may progress to deep ulceration and hemorrhage.

Less common causes of peptic ulceration include Zollinger-Ellison syndrome (ZES), cancer chemotherapy, radiation, and vascular insufficiency. ZES is caused by a gastrin-producing tumor called a gastrinoma and results in gastric acid hypersecretion. High-dose oral proton pump inhibitor (PPI) therapy is the initial treatment of choice for ZES; intermittent intravenous PPI therapy may be required for any patient in whom oral therapy is contraindicated.[1]

EPIDEMIOLOGY AND ETIOLOGY

Approximately, 25 million Americans are affected by PUD, with the lifetime prevalence estimated to be 12% in men and 10% in women.[2] Annual direct and indirect costs associated with PUD in the United States are estimated to be more than $9 billion. Despite the widespread use of conventional anti-ulcer therapy that effectively reduces gastric acid secretion, ulcers frequently recur, with 1-year recurrence rates (after ulcer initial healing) estimated to range from 60% to 100%.[1]

Helicobacter pylori infection and NSAID use account for most cases of PUD. The relatively high incidence of PUD in the elderly may be due to higher NSAID use. Although hospitalizations related to PUD have decreased over the past two decades, the incidence of PUD-related complications such as bleeding and perforation remain unchanged.

In general, ulcers related to HP infection more commonly affect the duodenum whereas ulcers related to NSAIDs more frequently affect the stomach. However, ulcers may be found in either location from either cause. Gastric ulcers (GUs) tend to occur much later in life than duodenal ulcers (DUs), with the peak incidence of GU occurring in patients over 60 years of age. Malignancy is more commonly found with GU than DU.

Helicobacter pylori

Since its discovery nearly 25 years ago, the role of HP in PUD has been increasingly recognized, and it is now one of the most common causes of PUD.[3] While HP causes **gastritis** in all infected patients, only a small proportion of patients actually develop PUD.

Helicobacter pylori normally resides in the human stomach and is transmitted via the fecal-oral route or through ingestion of fecal-contaminated water or food. Infection with HP is more common in developing countries because of crowded conditions and the presence of contaminated food and water. HP colonization does not necessarily reflect an active infection since the organism can attach itself to the gastric epithelium



Patient Encounter 1

PUD Secondary to *Helicobacter pylori*

A 51-year-old woman presents to the emergency department complaining of abdominal pain for the past 3 days and dark tarry stools over the past 2 days. She states that she has never had these symptoms before and that she has been feeling weak and tired for the past 2 weeks. She denies having bright red blood in her stools or vomiting. She does not take any prescription medications and only takes extra-strength acetaminophen for occasional headaches.

PMH

Hypertension × 10 years

FH

Mother died of a stroke at age 81, father died of pneumonia at age 71

SH

Denies alcohol, tobacco, or illicit drug use

Allergies: No known drug allergies

Meds

Acetaminophen extra-strength 2 tablets every 6 hours as needed for occasional headache

- Which signs and symptoms are suggestive of PUD?
- What are this patient's risk factors for PUD?
- What additional information do you need to know before creating a treatment plan for this patient?

without invading cells. Cellular invasion by HP is necessary for an active infection, which is usually asymptomatic and leads to chronic active gastritis.

Non-steroidal Anti-Inflammatory Drugs

NSAIDs are one of the most widely used classes of medications in the United States, particularly in the elderly.[4] More than 20,000 deaths occur in the United States per year as a direct result of adverse events related to NSAID use. Chronic NSAID ingestion leads to symptoms of nausea and dyspepsia in nearly half of patients. Peptic ulceration occurs in up to 30% of patients who use NSAIDs chronically, with gastrointestinal bleeding or perforation occurring in 1.5% of patients who develop an ulcer. NSAID-related peptic ulcers usually occur in the stomach; duodenal ulcers are much less common.

Risk factors for NSAID-induced peptic ulcers and complications are presented in Table 15–2. Several important principles should be considered when estimating the risk for developing PUD in a patient taking an NSAID (1) risk factors are generally additive; (2) some risk factors (e.g., corticosteroid therapy) are not by themselves a risk factor for ulceration but increase PUD risk substantially when combined with NSAID therapy; and (3) many of the risk factors postulated to increase PUD risk in a patient taking an NSAID (e.g., rheumatoid arthritis, tobacco smoking, alcohol consumption) remain unproven and thus should not generally be considered independent risk factors for NSAID-induced ulceration.[5]

TABLE 15–2. Established Risk Factors for Ulcers and Gastrointestinal Complications Related to NSAID Use

Age over 60
Concomitant anticoagulant use
Preexisting coagulopathy (elevated INR or thrombocytopenia)
Concomitant corticosteroid therapy
Previous peptic ulcer disease or upper gastrointestinal bleeding
Cardiovascular disease and other comorbid conditions
Multiple NSAID use (e.g., low-dose aspirin in conjunction with another NSAID)
Duration of NSAID use (greater than 1 month)
High-dose NSAID use
NSAID-related dyspepsia

INR, International Normalized Ratio; NSAID, non-steroidal anti-inflammatory drug.



Patient Encounter 2

PUD Secondary to NSAID use

A 65-year-old man with a history of osteoarthritis and chronic obstructive pulmonary disease (COPD) comes to your clinic complaining of burning abdominal pain. The pain has worsened over the past 2 weeks; it is worse at night and after meals.

PMH

Osteoarthritis for 5 years, started diclofenac within the past 2 months
COPD for 15 years

FH

Non-contributory

SH

Tobacco 1 pack per day × 40 years; drinks 2 beers/day

Meds

Ipratropium metered dose inhaler (MDI) 2 puffs every 6 hours
Albuterol MDI 2 puffs every 4 hours as needed
Prednisone 10 mg daily
Diclofenac 75 mg two times a day
Aspirin 81 mg daily

- Which signs and symptoms are suggestive of PUD?
- What are this patient's risk factors for PUD?
- What additional information do you need to know before creating a treatment plan for this patient?

Other Causative Factors

Cigarette smoking is associated with a higher prevalence of ulcers and may also impair healing of ulcers that develop.[6] The exact mechanism(s) for the detrimental effects of smoking on the gastric mucosa are unclear but may involve increased pepsin secretion, duodenogastric reflux of bile salts, elevated levels of free radicals, and reduced bicarbonate and **prostaglandin** production.[7,8] It is unknown whether nicotine or one of the many other ingredients found in cigarettes is responsible for these deleterious effects.

Until the discovery of HP, psychological stress was considered one of the primary causes of PUD. Although psychosocial factors such as life stress, baseline personality patterns, and depression may influence PUD prevalence, a clear causal relationship has not been demonstrated.

Dietary factors such as coffee, tea, cola, beer, and a highly-spiced diet may cause dyspepsia, but they have not been shown to independently increase PUD risk. Although caffeine increases gastric acid secretion and alcohol ingestion causes acute gastritis, there is inconclusive evidence to confirm that either of these substances are independent risk factors for peptic ulcers.

PATHOPHYSIOLOGY

Ulcer formation is the net result of a lack of homeostasis between factors within the gastrointestinal tract responsible for the breakdown of food (e.g., gastric acid and pepsin) and factors that promote epithelial defense and repair (e.g., bicarbonate, mucus secretion, and prostaglandins).

Gastric Acid and Pepsin

Hydrochloric acid and pepsin are the primary substances that cause gastric mucosal damage in PUD. Three different stimuli

(i.e., histamine, acetylcholine, and gastrin) are responsible for acid secretion through their interactions with the histaminic, cholinergic, and gastrin receptors on the surface of parietal cells. Gastric acid output occurs in two stages: (1) basal acid output (BAO), which reflects the baseline output of acid during the fasting state; and (2) maximal acid output (MAO), which occurs in response to meals. Basal acid secretion follows a **circadian** cycle in which it is highest at night and lowest in the morning and is modulated by the effects of acetylcholine and histamine acting on the parietal cell.

Food can cause maximal gastric acid secretion in two ways. In the cephalic phase of acid secretion, the vagus nerve stimulates acid secretion in response to the sight, smell, or taste of food. In both the gastric and intestinal phases of acid secretion, the physical distention caused by food in the gastric fundus and small intestine induces gastrin secretion resulting in acid production. After stimulation by histamine, acetylcholine, and gastrin, acid is secreted by the H^+-K^+-ATPase (proton) pump, located on the luminal side of parietal cells. Acid secretion in PUD is usually normal or slightly elevated. NSAID ingestion usually does not affect acid secretion, whereas HP infection usually leads to a slight increase in acid output. This is in contrast to ZES, in which acid secretion is substantially elevated.

Pepsinogen released during food digestion is converted to pepsin in the presence of an acidic environment and plays a key role in the initiation of protein digestion, **proteolysis** of collagen, and as a signal for the release of other digestive enzymes such as gastrin and cholecystokinin. The proteolytic activity of pepsin appears to influence ulcer formation.

Mucosal Defense and Repair

Several defense and repair mechanisms are responsible for preventing mucosal damage and subsequent ulcer formation. Mucus gel, through its buffering action, is the primary source of defense for the gastric epithelial surface against gastric acid. It allows an acidic environment to be maintained in the lumen but a near neutral pH to be maintained on the epithelial lining. On the epithelial lining, a number of protective mechanisms are responsible for the repair of damaged cells, production of defense mechanisms, and the promotion of epithelial growth.

Prostaglandins, one of the most important epithelial growth factors, inhibit gastric acid secretion and have numerous mucosal protective effects, the most important of which include the stimulation of both mucus and phospholipid production, promotion of bicarbonate secretion, and increased mucosal cell turnover. Damage to the mucosal defense system is the primary method by which HP or NSAIDs cause peptic ulcers.

Helicobacter pylori

Helicobacter pylori is a gram-negative microaerophilic rod that has a number of adaptive functions allowing it to live within the acidic environment of the stomach. It is an S-shaped bacterium with multiple flagella that initially inhabits the gastric antrum but migrates to the more proximal sections of the stomach over time. The motility provided by the flagella allows it to penetrate the mucous gel barrier, thus permitting a direct interaction with epithelial cells—the site where acute infection occurs. HP is able to survive in the acidic conditions of the stomach because of its ability to induce a transient **hypochlorhydria** via production of urease, an enzyme that hydrolyzes urea into carbon dioxide and ammonia.

A number of host and pathogenic factors contribute to the ability of HP to cause gastroduodenal mucosal injury including: (1) direct mucosal damage; (2) alterations to host inflammatory responses; and (3) hypergastrinemia leading to a state of elevated acid secretion. Bacterial-surface adhesion components facilitate binding of HP to epithelial cells, and vacuolating cytotoxin (vac A) facilitates the binding of HP to the cell membrane, thus enabling the HP organism better access to nutrients. The cag pathogenicity island (*cag*-PAI) leads to the release of cytokines thus leading to a chronic inflammatory state in HP-infected patients.[3] The complex interplay between bacterial virulence factors and an enhanced inflammatory response results in a chronic HP infection that elevates acid production and reduces various protective factors.

Non-steroidal Anti-Inflammatory Drugs

Non-selective NSAIDs [those that inhibit both cyclooxygenase-1 and -2 (COX-1 and COX-2)] cause gastric mucosal damage by two primary mechanisms: (1) a direct toxic interaction; and (2) systemic pharmacologic actions.

Direct irritation of the mucosal lining by NSAIDs occurs because NSAIDs are weak acids. Topical irritation is therefore most pronounced with more acidic NSAIDs such as aspirin. While the direct irritant effects of NSAIDs play a contributory role in the development of NSAID-induced gastritis, this mechanism generally plays a minor role in the evolution of NSAID-induced PUD.

The systemic effects of NSAIDs are the primary cause of PUD. Cyclooxygenase (COX) is the rate-limiting enzyme in the prostaglandin synthesis pathway (Fig. 15–1). Inhibition of prostaglandin production is the primary therapeutic effect of NSAIDs. COX is responsible for the conversion of arachidonic acid to prostaglandins (PGs) such as PGG_2 and PGH_2. There are two forms of the COX enzyme, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is routinely found in body tissues that produce prostaglandins for normal physiologic maintenance. In contrast, COX-2 is an inducible enzyme that is expressed during states in which cytokines and inflammatory mediators are elevated (e.g., fever and pain). Inhibition of the COX-1 isoenzyme decreases production of endogenous prostaglandins, particularly PGE_1, PGE_2, and PGI_2. Administration of NSAIDs parenterally (e.g., ketorolac) or rectally (e.g., indomethacin) is associated with an incidence of PUD that is similar to that with oral NSAIDs.

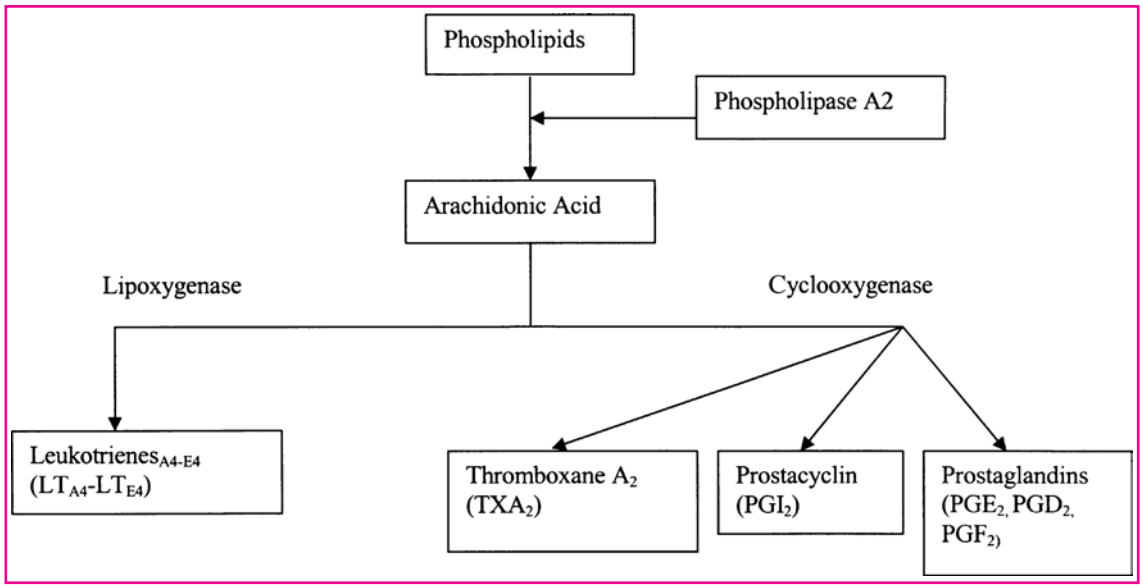


FIGURE 15–1. The arachidonic acid pathway.

Prostaglandins, through their effects on mucous cell secretion, basal bicarbonate secretion, and mucosal growth, are important factors in gastric healing and protection. Inhibition of prostaglandin production by NSAIDs compromises these important protective mechanisms. Finally, the antiplatelet effects of NSAIDs may worsen bleeding complications associated with PUD.

COMPLICATIONS

Hemorrhage is the most common complication of PUD and may occur when an ulcer erodes the wall of a gastric or duodenal artery. Bleeding occurs in approximately 15% of PUD patients and is more frequently seen in patients greater than 60 years of age, particularly those who ingest NSAIDs. Up to 20% of patients who develop a PUD-related hemorrhage do not have prior symptoms.

Gastric outlet obstruction occurs in approximately 2% of patients with PUD and is usually caused by ulcer-related inflammation or scar formation near the peripyloric region. Signs and symptoms of outlet obstruction include early satiety after meals, nausea, vomiting, abdominal pain, and weight loss. Ulcer healing with conventional acid-suppressive therapy is the primary treatment, but if this is unsuccessful then an endoscopic procedure (e.g., balloon dilation) is required.

CLINICAL PRESENTATION AND DIAGNOSIS

Diagnosis

Diagnostic tests for the presence of HP can be either endoscopic or non-endoscopic. Endoscopic diagnosis requires the extraction of gastric tissue samples that are subsequently tested for HP.[9] Although endoscopy is the gold standard for detecting HP infections, it may be associated with rare but severe complications and greater expense than non-endoscopic diagnostic methods. Endoscopy is therefore usually reserved for patients greater than 50 years of age who have anemia, gastrointestinal bleeding, or unexplained weight loss.

Non-endoscopic testing methods include the urea breath test, serologic testing, and the stool antigen assay. Compared to endoscopic procedures, these tests are more comfortable, less expensive, and do not require a special procedure. The urea breath test is usually the first-line test to detect active



Presentation of Peptic Ulcer Disease

Symptoms

- Mild epigastric pain that may be described as burning, gnawing, or aching in character.
- Abdominal pain may be described as burning or a feeling of discomfort.
- Some patients report nocturnal pain.
- The severity of pain often fluctuates.
- The intensity of pain can vary widely (e.g., from dull to sharp).
- Pain often occurs 1 to 3 hours after meals.
- Patients may also complain of heartburn, belching, bloating, nausea, or vomiting.

Signs

- Weight loss may be associated with nausea and vomiting.
- Complications such as bleeding, perforation, or obstruction may occur.
- Alarm signs and symptoms include: bleeding, anemia, tarry stools or "coffee-grounds" emesis, and weight loss.



Patient Encounter 1, Part 2: Physical Examination, Laboratory Tests, and Diagnostic Procedures

PE
VS: blood pressure 135/90 mm Hg, pulse 89 beats per minute, respiratory rate 14/minutes, temperature 37.5°C
Gen: NAD
Skin: Normal turgor
HEENT: PERRL
CV: RRR; S_1, S_2 normal; no S_3 or S_4
Lungs: CTA bilaterally
ABD: Soft, non-tender, non-distended, (+) bowel sounds × 4 quadrants, 7/10 pain
Neuro: A&O × 3, Cranial nerves intact, DTR 2+

Labs
WBC 4.6 x $10^3/mm^3$, Hemoglobin 8.5 g/dL (5.3 mmol/L), Hematocrit 24.7%, Platelets 327 x $10^3/mm^3$, aPTT 32.5 seconds, PT 12.1 seconds, INR 1.02

Fecal occult blood: (+)
EGD: Multiple superficial ulcerations in the duodenum; largest ulcer measures 2 cm in diameter; no active bleeding noted.

CLO test (urease test): (+) for *H. pylori*

- Given this information, what is your assessment of the patient's condition?
- What are your treatment goals?
- What nonpharmacologic and pharmacologic alternatives are available for this patient?



Patient Encounter 2, Part 2: Physical Examination, Laboratory Tests, and Diagnostic Procedures

PE
VS: blood pressure 125/85 mm Hg, pulse 72 beats per minute, respiratory rate 12/minutes, temperature 37.5°C
Gen: NAD
Skin: dry, intact
HEENT: PERRL
CV: RRR, S_1, S_2
Lungs: CTA B/L
ABD: Soft, non-tender, non-distended, (+) bowel sounds, 5/10 pain on the epigastric region
Neuro: A&O × 3, Cranial nerves intact, DTR 2+

Labs
WBC 9.9 x $10^3/mm^3$, Hemoglobin 12.1g/dL (7.5 mmol/L), Hematocrit 38.3%, Platelets 108 x $10^3/mm^3$, aPTT 27.9 seconds, PT 12.4 seconds, INR 1.09

EGD: One ulcer located on the antrum of the stomach measuring 3 cm in diameter; no bleeding or obstruction noted

- Given this information, what is your assessment of the patient's condition?
- What are your treatment goals?
- What nonpharmacologic and pharmacologic treatment alternatives are available for this patient?

HP infection because it has a sensitivity and specificity greater than 95% and a short turnaround time (2 days). Concomitant acid-suppressive or antibiotic therapy may give false-negatives with this test.

Office-based serologic testing provides a quick assessment (within 15 minutes) of an exposure to HP, but patients can remain seropositive for up to 1 year after eradication, making the clinical utility of this test limited. Stool antigen assays can be useful for the initial diagnosis or to confirm HP eradication, and unlike the urea breath test, are less affected by concomitant medication use.[9]

Radiologic and/or endoscopic procedures are usually required to objectively document the presence of ulcers. Barium studies have a high sensitivity and are considered first-line tests to radiographically document an ulcer. However, the cost and complexity of all of these tests has led to the promotion of an early empiric treatment strategy for patients at low risk for PUD-related sequelae (e.g., malignancy). An empiric treatment strategy is appropriate for patients less than 50 years of age who have mild or intermittent epigastric symptoms and no evidence of PUD-related systemic symptoms or complications.

TREATMENT

The treatment selected for PUD depends on the following factors: (1) the etiology of the ulcer; (2) whether the ulcer is new or recurrent; and (3) the presence of any ulcer-related complications. Figure 15–2 contains an algorithm for the evaluation and treatment of a patient with signs and symptoms suggestive of an *H. pylori*–associated or NSAID-induced ulcer.

Desired Outcomes

The goals of PUD therapy are to: (1) resolve symptoms; (2) reduce acid secretion; (3) promote epithelial healing; (4) prevent ulcer-related complications; and (5) prevent ulcer recurrence. For HP-related PUD, eradication of HP is an additional outcome.

Nonpharmacologic Therapy

❶ *Patients with PUD should avoid exposure to factors known to worsen the disease, exacerbate symptoms, or lead to ulcer recurrence.* Patients should be advised to reduce psychological

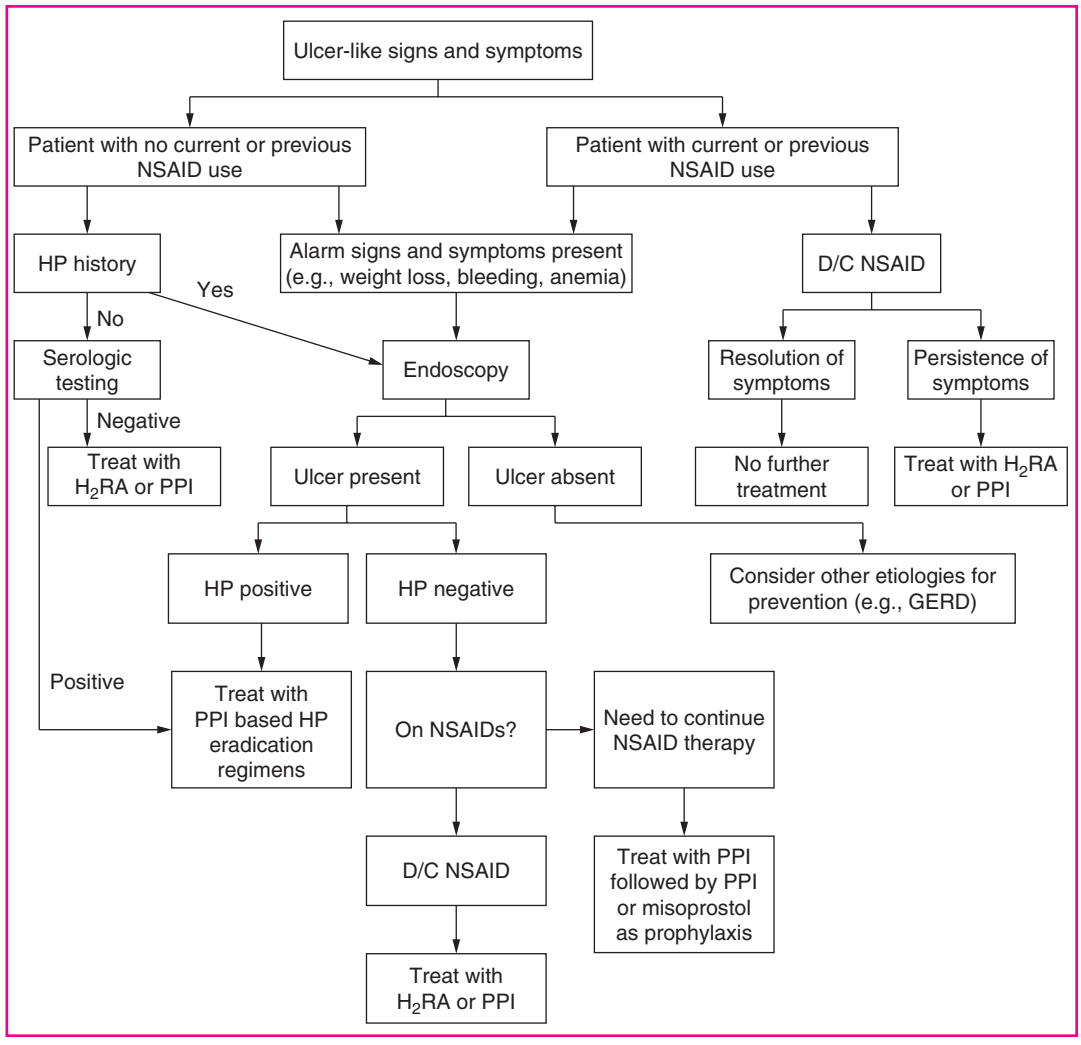


FIGURE 15–2. Approach to the patient presenting with ulcer-like symptoms. GERD, gastroesophageal reflux disease; HP *Helicobacter pylori*; H_2RA, histamine$_2$-receptor antagonist; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor. (Adapted from Berardi RR, Welage LS. Peptic ulcer disease. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 637, with permission.)

stress and avoid cigarette smoking, alcohol consumption, foods or beverages that exacerbate ulcer symptoms, and NSAID or aspirin use.[10,11]

The high success rates of medical therapies have reduced the number of surgical procedures performed and relegated surgery primarily to elective situations. For this reason, surgical interventions are generally reserved for complicated or refractory PUD. Some surgical procedures include: (1) **vagotomy** and **pyloroplasty**; (2) highly-selective vagotomy; or (3) vagotomy combined with **antrectomy**. Vagotomy is the central component of most procedures because of its targeted effects on blocking further acid secretion. These procedures are associated with a high success rate. Complications are rare but can include dumping syndrome, bile reflux, diarrhea, malabsorption and gastric atony.[12]

Pharmacologic Therapy

Treatment of *Helicobacter pylori*–Associated Ulcers

The primary goal of HP therapy is to completely eradicate the organism using an effective antibiotic-containing regimen. ❷ *Reliance on conventional acid-suppressive drug therapy alone as an alternative to HP eradication is discouraged because it is associated with a higher incidence of ulcer recurrence and side effects*. Reinfection rates are generally low after the initial course of therapy as long as the patient has received a regimen with proven efficacy and is compliant with it. The HP regimen that is chosen should have a per-protocol cure rate of greater than or equal to 90% or a cure rate based on intention-to-treat analysis of greater than or equal to 80%.[9] In addition to proven efficacy, the optimal treatment regimen should cause minimal adverse events, have low risk for the development of bacterial resistance, and be cost effective.[9]

Helicobacter pylori treatment regimens are presented in Table 15–3. ❸ *Eradication therapy with a PPI-based three-drug regimen should be considered for all patients who test positive for HP and have an active ulcer or a documented history of either an ulcer or ulcer-related complication. Different antibiotics should be used if a second course of HP eradication therapy is required.*

The first-line regimen should contain a PPI plus clarithromycin and either amoxicillin or metronidazole. The combination of two antimicrobials and a PPI leads to cure rates greater than 80% (by intention-to-treat basis) and reduces the

TABLE 15–3. Drug Regimens to Eradicate *Helicobacter pylori*[a]

Treatment Regimen	Cure Rates[b]
Two Drugs	
Amoxicillin 1 g three times a day + omeprazole 20 mg twice a day	Poor
Clarithromycin 500 mg three times a day + omeprazole 40 mg every day	Poor
Clarithromycin 500 mg three times a day + RBC 400 mg twice a day	Fair
Three Drugs	
Clarithromycin 500 mg twice a day + metronidazole 500 mg twice a day + omeprazole 20 mg twice a day	Good–excellent
Clarithromycin 500 mg twice a day + amoxicillin 1 g twice a day + lansoprazole 30 mg twice a day	Good–excellent
Clarithromycin 500 mg twice a day + metronidazole 500 mg twice a day + RBC 400 mg twice a day	Good
Amoxicillin 1 g twice a day + clarithromycin 500 mg twice a day + RBC 400 mg twice a day	Good
Four Drugs	
BSS 525 mg four times a day + metronidazole 250 mg four times a day + tetracycline 500 mg four times a day + H_2RA (conventional ulcer-healing dose)[c]	Good–excellent
BSS 525 mg four times a day + metronidazole 250 mg four times a day + amoxicillin 500 mg four times a day + H_2RA (conventional ulcer-healing doses)[c]	Good
BSS 525 mg four times a day + metronidazole + amoxicillin + PPI[d]	Good
Rescue Therapy[e]	
BSS 525 mg four times a day + metronidazole 500 mg four times a day + tetracycline 500 mg four times a day + omeprazole 20 mg twice a day[d]	Good–excellent
Furazolidone 200 mg twice a day + amoxicillin 1 g twice a day + omeprazole 20 mg twice a day[f]	Good
Amoxicillin 1 g twice a day + rifabutin 300 mg every day + pantoprazole 40 mg twice a day[g]	Good–excellent

[a]These regimens based on efficacy for a 14-day treatment duration unless otherwise noted.
[b]Cure rates based on intention-to-treat analysis from references 3, 12, 14, and 35, where: poor = less than 70% eradication, fair = 70–80%, good = 80–90%, and excellent = greater than 90%.
[c]H_2RA therapy should be continued for an additional 2 weeks.
[d]Duration of therapy is 7–10 days.
[e]Data based on refractory treatment data.
[f]Given for 7 days.
[g]Given for 10 days.
BSS, bismuth subsalicylate; H_2RA, H_2-receptor antagonist; PPI, proton pump inhibitor; RBC, ranitidine bismuth citrate (not available in the United States).

risk of selecting out resistant organisms.[13] Monotherapy with a single antibiotic or antiulcer agent is not recommended due to high failure rates. In the United States, two-drug regimens consisting of a PPI and an antibiotic are also not recommended.

The duration of therapy is controversial and varies by continent. Europeans routinely treat patients for 7 days whereas Americans usually rely on a 14-day regimen. While this seven additional days of therapy improves the absolute cure rate by approximately 9%,[14] longer courses decrease compliance and increase drug cost.

Bismuth-based four-drug regimens have clinical cure rates similar to three-drug, PPI-based regimens. Bismuth-based regimens usually include tetracycline, metronidazole, and an antisecretory agent (e.g., PPI or histamine$_2$-receptor antagonist [H_2RA]). Bismuth salts promote ulcer healing through antibacterial and mucosal protective effects. Bismuth subsalicylate is the only bismuth product available in the United States. While cheaper than most other regimens, drawbacks of bismuth-based regimens include the frequency of administration (four times a day), risk for salicylate toxicity in patients with renal impairment, and propensity for bothersome side effects (e.g., stool and tongue discoloration, constipation, nausea, and vomiting).

Patients may remain infected with HP after the initial course of therapy because of reinfection, non-compliance with the initial regimen, or antimicrobial resistance. Factors associated with decreased compliance include use of a large number of medications, a need for frequent drug administration or a long treatment duration, and the use of drugs that may cause intolerable side effects. Potential adverse drug events include taste disturbances (clarithromycin and metronidazole), nausea, vomiting, abdominal pain, and diarrhea. Superinfections with oral thrush or vaginal candidiasis can occur.

Preexisting antimicrobial resistance is an increasing cause of treatment failure and is estimated to account for up to 70% of all treatment failures. Geography is the most important factor in HP resistance. Metronidazole-resistant strains are more prevalent in Asia (85%) than North America (30%).[15] Primary resistance to amoxicillin and tetracycline remains low in both the United States and Europe. Clarithromycin resistance rates are estimated to be approximately 10% in the United States. Another confounding factor when evaluating potential antibiotic resistance is that culture and sensitivity studies are not routinely performed with HP infection.

Initiation of a second HP treatment regimen after failure of the initial treatment regimen is usually associated with a lower success rate. Reasons for failure are often the same as those reported with failure of the initial regimen: patient non-compliance and/or

antimicrobial resistance. In these situations, quadruple therapy is generally required, and metronidazole or clarithromycin should be replaced by another antibiotic if either one of these agents was used in the initial regimen. If both clarithromycin and metronidazole were used as initial therapy, a regimen consisting of furazolidone 100 mg four times a day with tetracycline, bismuth, and a PPI can be used. Another second-line regimen consisting of a PPI, amoxicillin 1 g twice daily and rifabutin 300 mg once daily for 10 days resulted in eradication rates greater than 80%.[16,17]

Treatment of NSAID-Induced Ulcers

Treatment and dosing recommendations to heal peptic ulcers or provide maintenance therapy are shown in Table 15–4. Choice of regimen in a patient with PUD related to NSAID use depends on whether NSAID use is to be continued. NSAIDs should be discontinued if possible and replaced with alternatives (such as acetaminophen) although this may not be desirable or feasible in some patients. For patients discontinuing NSAID therapy, PPIs, H_2RAs, or sucralfate are all effective for ulcer healing. PPI therapy heals NSAID ulcers faster than H_2RAs.[16,17] For patients continuing NSAID therapy, PPIs are preferred over H_2RAs or sucralfate.[18–21] If the decision is made to continue NSAID therapy, adjunctive strategies may be required to promote ulcer healing and prevent future recurrences.

Prevention of NSAID-Induced Ulcers

Prophylactic regimens against PUD are often required in patients who require long-term NSAID or aspirin therapy for osteoarthritis, rheumatoid arthritis, or cardioprotection. Misoprostol, H_2RAs, PPIs, and COX-2 selective inhibitors have been evaluated in controlled trials to reduce the risk of NSAID-induced PUD. ❹ *In patients at risk for NSAID-induced ulcers, PPIs at standard doses reduce the risk of both gastric and duodenal ulcers as effectively as misoprostol and are generally better tolerated.*

Although acute gastrointestinal bleeding is the most serious adverse outcome of NSAID therapy and is ultimately what clinicians are trying to prevent with prophylactic therapy, few studies have compared PUD prophylaxis strategies using this outcome measure. Acute gastrointestinal bleeding is not usually evaluated in studies because of the low frequency with which bleeding occurs in NSAID users, the small size of most prophylaxis studies, and their short duration. Instead, studies usually rely on secondary outcome variables to evaluate efficacy such as the incidence of ulcers during screening endoscopy or the incidence of patient-reported ulcer symptoms. Correlation between these secondary outcomes and PUD-related bleeding events is poor and thus, clinicians must be cautious when extrapolating the results of these studies to patient care.

Misoprostol

Misoprostol is a synthetic prostaglandin E_1 analog that exogenously replaces prostaglandin stores. The minimum effective dose shown to inhibit acid secretion and promote mucosal defense is 400 mcg/day. Misoprostol use is limited by a high frequency of bothersome gastrointestinal effects such as abdominal pain, flatulence, and diarrhea. In placebo-controlled studies diarrhea occurred with twice the frequency in the

TABLE 15–4. Oral Drug Regimens to Heal Peptic Ulcers or Maintain Ulcer Healing

Drug	Duodenal Ulcer or Gastric Ulcer Healing (mg/day)	Maintenance of DU or GU Healing (mg/day)
Mucosal Protectant		
Sucralfate	1 g four times daily 2 g twice daily	1 g four times daily 1–2 g twice daily
H_2-Receptor Antagonists		
Cimetidine	300 mg four times daily 400 mg twice daily 800 mg at bedtime	400–800 mg daily
Famotidine	20 mg twice daily 40 mg at bedtime	20–40 mg daily
Nizatidine	150 mg twice daily 300 mg at bedtime	150–300 mg daily
Ranitidine	150 mg twice daily 300 mg at bedtime	150–300 mg daily
Proton Pump Inhibitors		
Esomeprazole	20–40 mg daily	20–40 mg daily
Lansoprazole	15–30 mg daily	15–30 mg daily
Omeprazole	20–40 mg daily	20–40 mg daily
Pantoprazole	40 mg daily	40 mg daily
Rabeprazole	20 mg daily	20 mg daily

DU, duodenal ulcer; GU, gastric ulcer.

misoprostol-treated groups and led to drug discontinuation in a substantial number of patients.

In two large multicenter, placebo-controlled trials, misoprostol 200 mcg orally four times daily was effective in reducing the incidence of both GU and DU in patients taking NSAIDs.[22,23] Misoprostol is superior to H_2RAs in preventing NSAID-associated ulcers. One large randomized study found a significantly lower incidence of GU in patients receiving misoprostol 200 mcg four times daily compared to those receiving ranitidine 150 mg orally twice daily (1% versus 6%; *p* less than 0.01). However, the incidence of GI side effects such as diarrhea was substantially higher in the misoprostol-treated group.[24]

H_2-Receptor Antagonists

Refer to Chapter 14 on gastroesophageal reflux disease for more information on the H_2RAs. When given in standard doses, H_2RAs are not effective in preventing NSAID-related ulceration, but they do reduce symptoms and are generally well tolerated.[11] One randomized study demonstrated that high-dose therapy may be effective for preventing NSAID complications. When famotidine 20 mg twice daily, famotidine 40 mg twice daily, and placebo were compared in patients taking NSAIDs who required GI prophylaxis, the incidence of GU was significantly lower in patients taking 40 mg twice daily than in those taking either 20 mg twice daily or placebo.[25] The incidence of duodenal ulceration was similar between both famotidine groups and was significantly reduced with H_2RA therapy. In summary, although standard-dose H_2RA therapy reduces the risk of NSAID-related duodenal ulcers, higher doses are needed to reduce the risk of gastric ulcers.

Proton Pump Inhibitors

Refer to Chapter 14 on gastroesophageal reflux disease for more information on the PPIs. The PPI omeprazole is superior to both ranitidine and misoprostol for preventing recurrence of NSAID-associated PUD. In one study, omeprazole 20 mg daily was compared to misoprostol 200 mcg twice daily for NSAID-associated PUD prevention. At 6 months, the omeprazole-treated group had significantly fewer ulcers than those taking misoprostol. Furthermore, more patients discontinued ulcer prophylaxis in the misoprostol group due to adverse events.[26]

Another study randomized patients requiring NSAID prophylaxis to either omeprazole 20 mg daily or ranitidine 150 mg twice daily.[19] At 6 months, more patients who received omeprazole (72%) than ranitidine (59%) were in ulcer-free remission ($p = 0.004$). Omeprazole was also more efficacious in preventing GU recurrence than ranitidine (5.2% versus 16.3%; p less than 0.01). Adverse drug events were similar in the two groups.

In patients who experience a PUD-related bleeding event while taking aspirin but who require continued aspirin therapy, the addition of a PPI reduces the incidence of recurrent GI bleeding.[27]

COX-2 Selective Inhibitors

With the availability of NSAIDs with COX-2 selectivity, clinicians postulated that these agents would avoid the need to add an additional prophylactic agent to therapy in patients with PUD risk factors. ❺ *However, selective COX-2 inhibitors have not been shown to be any more effective than the combination of a PPI and a non-selective NSAID in reducing the incidence of ulcers, and questions remain regarding their long-term cardiovascular safety.*

Two large trials, the Vioxx Gastrointestinal Outcomes Research (VIGOR) study and the Celecoxib Long-term Arthritis Safety Study (CLASS), compared selective COX-2 inhibitors and traditional, non-selective NSAID therapy in terms of their ability to prevent clinical PUD (i.e., symptomatic ulcers and ulcer complications). VIGOR (9-month median follow-up) demonstrated that rofecoxib (50 mg daily) therapy was significantly more efficacious than naproxen.[28] The CLASS study (6-month median follow-up) found that high-dose celecoxib (400 mg twice daily) was superior to non-selective NSAID therapy (either ibuprofen 800 mg three times daily or diclofenac 75 mg twice daily).[29]

A number of methodologic factors may account in part for the lower incidence of clinical PUD observed with COX-2 therapy in these studies, including the short duration of clinical follow-up and the high doses of both celecoxib and rofecoxib used.[30] An important difference between these two studies is that patients taking low-dose aspirin were excluded from VIGOR but not from CLASS. In CLASS, patients in the celecoxib group who were taking low-dose aspirin had the same incidence of clinical PUD as those receiving a traditional NSAID therapy. This is an important issue, as many patients with arthritis also have coronary artery disease and are prescribed low-dose aspirin therapy because of its cardioprotective effects.[31] Low-dose aspirin is associated with PUD bleeding itself, and its use with a COX-2 inhibitor appears to largely negate the gastrointestinal-sparing effects of these agents.

Selective COX-2 inhibitors are not superior to PPIs in preventing NSAID-related PUD. One randomized, placebo-controlled trial that included 267 patients at high risk for ulceration (arthritic patients with a previously healed bleeding ulcer) compared celecoxib 200 mg twice daily to the combination of diclofenac 75 mg twice daily plus omeprazole 20 mg daily.[32] After 6 months, the risk for recurrent bleeding was found to be similar between groups (celecoxib, 4.9% and diclofenac/omeprazole, 6.4%); the authors concluded that neither of these therapies can completely prevent recurrent ulcer complications.

Longer-term studies evaluating the cardiovascular risks associated with the use of COX-2 inhibitors have found a higher incidence of cardiovascular mortality with the use of these agents compared to traditional NSAIDs.[29,33,34] This prompted the withdrawal of both rofecoxib and valdecoxib from the market and the inclusion of a black box warning in

the celecoxib package insert.[34–36] Given the cardiovascular risk of the COX-2 inhibitors, it has been suggested that an older non-selective NSAID and a PPI can be used as an alternative to COX-2 therapy in patients at high risk for NSAID-related PUD.[5,37]

Sucralfate

Sucralfate is a negatively-charged, non-absorbable agent that forms a complex by binding with positively-charged proteins in exudates, forming a viscous, paste-like, adhesive substance. This forms a coating that protects the ulcerated area of the gastric mucosa against gastric acid, pepsin, and bile salts. Limitations of sucralfate include the need for multiple daily dosing, large tablet size, and interaction with a number of other medications. Adverse effects include constipation, nausea, metallic taste, and the possibility for aluminum toxicity in patients with renal failure. While sucralfate may be used for the treatment of an NSAID-related ulcer when NSAID therapy is being stopped, it is not recommended for use as prophylaxis against NSAID-induced ulcers.

Conventional Treatment of Active Duodenal and Gastric Ulcers and Long-Term Maintenance of Ulcer Healing

Conventional therapy prior to the advent of HP eradication therapy consisted of standard doses of sucralfate or an H_2RA for 6 to 8 weeks. A PPI provides equivalent efficacy with a treatment duration of only 4 weeks. Long-term antiulcer therapy is ineffective for treating HP infections.

❻ *Low-dose maintenance therapy with a PPI or H_2RA is only indicated for patients who fail HP eradication, have HP-negative ulcers, or develop severe complications related to ulcer disease.* Drug regimens and doses are presented in Table 15–4.

Treatment of Refractory Ulcers

The presence of refractory ulcers [ulcers that persist beyond 8 weeks (DU) or 12 weeks (GU)] requires thorough assessment, including evaluation of medication compliance. The patient should be questioned regarding recent NSAID ingestion. Tolerance has been reported with as few as 4 weeks of H_2RA therapy, and thus a change to PPI therapy should be considered in this situation.[38] Other assessments that may be considered include an ulcer biopsy to exclude malignancy, HP testing (if not done initially), a serum gastrin measurement to exclude ZES, and gastric acid studies. In one study, increasing the starting dose of PPI therapy healed 90% of refractory ulcers after 8 weeks.[39]

OUTCOME EVALUATION

- Obtain a baseline complete blood cell count (CBC). Recheck the CBC if the patient exhibits alarm signs or symptoms.
- Obtain a baseline serum creatinine measurement. Calculate the estimated creatinine clearance and adjust the dose of H_2RAs and sucralfate according to package insert recommendations.
- Obtain a history of symptoms from the patient. Monitor for improvements in pain symptoms (e.g., epigastric or abdominal pain) daily.
- Monitor the patient for the development of any alarm signs and symptoms.
- Recommend a follow-up visit if signs and symptoms worsen at any time or do not improve within the defined treatment period.
- Assess for potential drug interactions whenever there is a change in the patient's medications, particularly for patients taking cimetidine, omeprazole, or sucralfate.
- Educate the patient on the importance of adhering to the HP-eradication regimen.
- Monitor the patient for complications related to antibiotic therapy (e.g., diarrhea or oral thrush) during and after completion of HP eradication therapy.
- Recommend follow-up care if the patient's signs and symptoms do not improve after completion of HP-eradication therapy.



Patient Care and Monitoring

General Recommendations: HP-Associated and NSAID-Induced Ulcers

1. Assess the severity of signs and symptoms. Identify the presence of any alarm signs and symptoms.
2. Educate the patient on monitoring for alarm signs and symptoms.
3. Obtain a history of prescription medication, over-the-counter medication, and dietary supplement use.
4. Encourage lifestyle modifications such as reducing tobacco use and ethanol ingestion and decreasing psychological stress.
5. Determine the appropriate duration of therapy for acid-suppressive therapy.
6. Define the current impact of PUD on the patient's quality of life and the improvement in these outcomes sought with drug therapy.
7. Evaluate current drug therapy for potential adverse drug reactions and drug interactions.

Helicobacter pylori–Associated Ulcers

1. Recommend an appropriate drug regimen that will eradicate the organism.
2. Identify the patient's drug allergies and avoid drug classes a patient is allergic to.
3. Avoid regimens with tetracycline in children.

(Continued)

4. Educate patients on specific adverse drug effects, particularly with metronidazole (avoidance of alcohol) and bismuth (change in stool color).
5. Assess the potential for drug interactions, particularly in patients taking regimens containing metronidazole, clarithromycin, and/or cimetidine.
6. Recommend different antibiotics if this treatment regimen is a result of failure of a prior HP regimen.
7. Educate the patient on the importance of adherence to eradication therapy.

NSAID-Associated Ulcers

1. Assess for risk factors for NSAID ulcers and recommend an appropriate strategy to reduce ulcer risk.
2. Monitor for signs and symptoms of complications associated with NSAID-related ulceration.
3. Recommend an appropriate treatment regimen to achieve the desired outcomes.
4. Assess and counsel patients on potential adverse drug events and drug interactions.
5. Inform patients who are receiving prophylactic therapy on the importance of its use, potential adverse drug events, and the possible alarm symptoms associated with PUD.

ABBREVIATIONS

BAO: basal acid output
cag-PAI: cag pathogenicity island
CBC: complete blood cell count
CLASS: Celecoxib Long-term Arthritis Safety Study
COX: cyclooxygenase
DU: duodenal ulcer
GU: gastric ulcer
HP: *Helicobacter pylori*
H_2RA: histamine$_2$-receptor antagonist
MALT: mucosa-associated lymphoid tissue
MAO: maximal acid output
NSAID: non-steroidal anti-inflammatory drug
PG: prostaglandin
PPI: proton pump inhibitor
PUD: peptic ulcer disease
SRMD: stress-related mucosal damage
VIGOR: Vioxx Gastrointestinal Outcomes Research (study)
ZES: Zollinger-Ellison syndrome

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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16 Inflammatory Bowel Disease

Brian A. Hemstreet



Learning Objectives

Upon completion of the chapter the reader will be able to:

1. Characterize the pathophysiologic mechanisms underlying inflammatory bowel disease (IBD).
2. Recognize the signs and symptoms of IBD, including major differences between ulcerative colitis and Crohn's disease.
3. Identify appropriate therapeutic outcomes for patients with IBD.
4. Describe pharmacologic treatment options for patients with acute or chronic symptoms of ulcerative colitis and Crohn's disease.
5. Create a patient-specific drug treatment plan based on symptoms, severity, and location of ulcerative colitis or Crohn's disease.
6. Recommend appropriate monitoring parameters and patient education for selected drug regimens for treating symptoms of IBD.

Key Concepts

❶ Inflammatory bowel disease includes both ulcerative colitis and Crohn's disease and is associated with inflammation of various areas of the gastrointestinal tract.

❷ Differentiation of ulcerative colitis and Crohn's disease is based on signs and symptoms as well as characteristic endoscopic findings including the extent, pattern, and depth of inflammation.

❸ Patients may manifest extraintestinal symptoms of IBD, such as arthritis, primary sclerosing cholangitis, erythema nodosum, and pyoderma gangrenosum, among others.

❹ Major treatment goals for patients with IBD include alleviation of signs and symptoms and suppression of inflammation during acute episodes and maintenance of remission thereafter.

❺ When designing a drug regimen for treatment of IBD, several factors should be considered, including the patient's symptoms, medical history, current medication use, drug allergies, and location and severity of disease.

❻ Antidiarrheal medications that reduce GI motility, such as loperamide, diphenoxylate/atropine, or codeine should be avoided in patients with active IBD due to the risk of precipitating acute colonic dilation (toxic megacolon).

❼ Treatment of acute episodes of ulcerative colitis is dictated by the severity and extent of disease, and first-line therapy of mild to moderate disease involves oral or topical aminosalicylate derivatives.

❽ Maintenance of remission of ulcerative colitis may be achieved with oral or topical aminosalicylates. Immunosuppressants such as azathioprine or 6-mercaptopurine can be used for unresponsive patients or those who develop corticosteroid dependency.

❾ Treatment of active mild to moderate Crohn's disease involves use of oral or topical aminosalicylate derivatives, whereas moderate to severe disease may require systemic corticosteroid therapy.

❿ Maintenance of remission of Crohn's disease may be achieved with oral or topical aminosalicylate derivatives, immunosuppressants (such as azathioprine, 6-mercaptopurine, and methotrexate), or infliximab.

❶ *Inflammatory bowel disease (IBD) encompasses both Crohn's disease (CD) and ulcerative colitis (UC). Both disorders are associated with inflammation of various regions within the gastrointestinal (GI) tract.* Differences exist between UC and CD with regard to the regions of the GI tract that may be affected as well as in the distribution and depth of inflammation. Some

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patients with IBD may also have inflammation involving organs other than the GI tract, known as "extraintestinal" manifestations. Symptoms of IBD are associated with significant morbidity, reduction in quality of life, and substantial costs to the health care system. For purposes of this chapter, references made to IBD will include both UC and CD. Significant differences between UC and CD will be discussed separately when applicable.

EPIDEMIOLOGY

Inflammatory bowel disease is most common in westernized countries such as the United States. Ulcerative colitis affects up to 500,000 people and Crohn's disease affects up to 480,000 people in the United States.[2–4] The age of initial presentation of IBD is bimodal, with patients typically diagnosed between the age ranges of 20 to 40 years or 60 to 80 years.[5] The peak incidence of CD occurs in the second and third decades of life, with a smaller peak in the fifth decade.[2,5] Peak incidence of UC occurs between the ages of 15 and 25 years.[6]

Men and women are approximately equally affected by IBD. In general, whites are affected more often than blacks, and persons of Jewish descent also have higher reported incidences of IBD. One of the greatest risk factors for development of IBD is a positive family history of the disease. The incidence of IBD is 10 to 40 times greater in patients with a first-degree relative who has IBD compared to the general population.[4,5,7] A positive family history may be more of a contributing factor for development of CD than UC.[7–9]

ETIOLOGY

The exact cause of IBD is not fully understood. Processes thought to be involved in its development include genetic predisposition, dysregulation of the inflammatory response within the GI tract, or perhaps environmental or antigenic factors.[3] The fact that a positive family history is a strong predictor of IBD supports the theory that genetic predisposition may be responsible in many cases. Many potential candidate genes have been identified. An example is a gene found on chromosome 16 that encodes for nucleotide oligomerization domain 2 (NOD2). NOD2 is a cytoplasmic protein expressed in macrophages, monocytes, and gut epithelial cells thought to be involved in recognition and degradation of bacterial products by the gut wall. Presence of NOD2 mutations has been shown to predispose patients to development of CD.[9,10] Less is known about genetic alterations that may predispose patients to UC, but UC may share common genetic features with CD.

An alteration in the inflammatory response regulated by intestinal epithelial cells may also contribute to development of IBD. This may involve inappropriate processing of antigens presented to the GI epithelial cells.[3] The inflammatory response in IBD may actually be directed at bacteria that normally colonize the GI tract. Products derived from these bacteria may translocate across the mucosal layer of the GI tract and interact with various cells involved in immunologic recognition. The result is T-cell stimulation, excess production of proinflammatory cytokines, and persistent inflammation within the GI tract.

The intestinal mucosa of patients with CD has a preponderance of CD4+ type 1 helper T cells, while patients with UC have more CD4+ lymphocytes with atypical type 2 helper T cells.[9] Likewise, drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) that disrupt the integrity of the GI mucosa may facilitate mucosal entry of intestinal antigens and lead to disease flares in patients with IBD.[11]

The role of antigens derived from dietary intake in the development of IBD is less well defined. There is some speculation that ingestion of large quantities of refined carbohydrates or margarine leads to higher rates of CD. Use of oral contraceptives has been associated with increased development of IBD in some cohort studies, but a strong causal relationship has not been proven.[7]

Lastly, positive smoking status has been shown to have protective effects in UC, leading to reductions in disease severity. The opposite is true in CD, as smoking may lead to increases in symptoms or worsening of the disease.[9]

PATHOPHYSIOLOGY

Ulcerative Colitis

The inflammatory response in UC is propagated by atypical type 2 helper T cells that produce proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF).[7] As discussed previously, a genetic predisposition to UC may partially explain the development of excessive colonic and rectal inflammation. The finding of positive perinuclear antineutrophil cytoplasmic antibodies (pANCA) in association with the human leukocyte antigen (HLA)-DR2 allele in a large percentage of patients with UC supports this theory.[4,12]

The role of an immune response to intestinal bacteria in the development of UC may not be as strong a contributing factor as it is in CD. The potential role of environmental factors in the development of UC implies that the immune response is directed against an unknown antigen. The findings that development and severity of UC are reduced in patients who smoke, or in those with appendectomies, may support the theory that these factors may somehow modify either the genetic component or phenotypic response to immunologic stimuli.[11,13]

NSAID use is also implicated in disease flares in patients with UC. NSAIDs may affect production of both nuclear factor κβ and peroxisome proliferator activated receptors (e.g., PPAR-γ), both of which are involved in regulating the intestinal responses.[11]

The inflammatory process within the GI tract is limited to the colon and rectum in patients with UC (Fig. 16–1). Most patients with UC have involvement of the rectum (**proctitis**) or both the

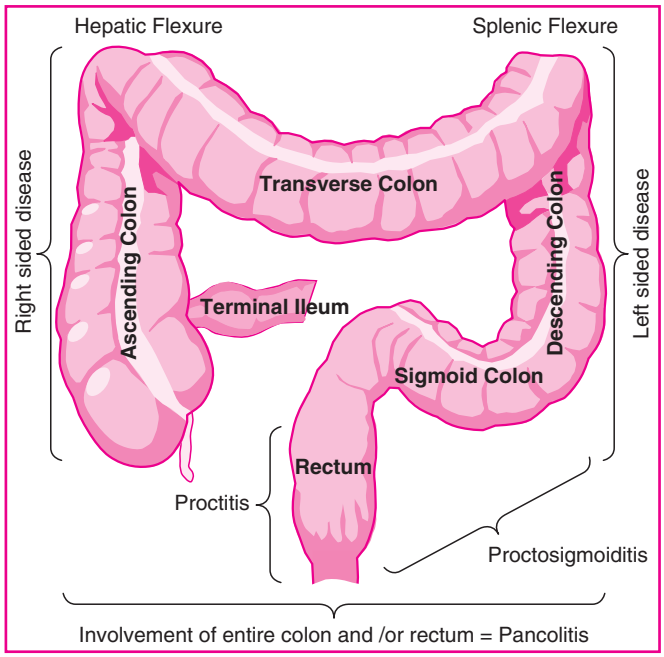


FIGURE 16–1. Major gastrointestinal landmarks and disease distribution in inflammatory bowel disease.

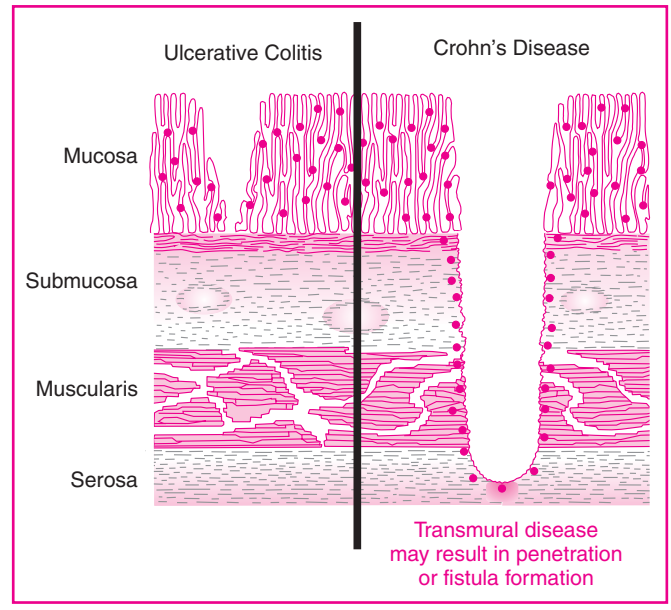


FIGURE 16–2. Depth of disease penetration in ulcerative colitis and Crohn's disease.

rectum and sigmoid colon (proctosigmoiditis). Inflammation involving the majority of the colon is referred to as **pancolitis**. Left-sided disease, defined as inflammation extending from the rectum to the splenic flexure, occurs in 30% to 40% of patients.[4] A small number of cases of UC involve mild inflammation of the terminal ileum, referred to as "backwash ileitis."

The pattern of inflammation in UC is continuous and confluent throughout the affected areas of the GI tract. The inflammation is also superficial and does not typically extend below the submucosal layer of the GI tract (Fig. 16–2). Ulceration or erosion of the GI mucosa may be present and varies with disease severity. The formation of **crypt abscesses** within the mucosal layers of the GI tract is characteristic of UC and may help to distinguish it from CD. Severe inflammation may also result in areas of hypertrophied GI mucosa, which may manifest as **pseudopolyps** within the colon.[12] The inflammatory response may progress in severity, leading to mucosal friability and significant GI bleeding.

Crohn's Disease

As with UC, the immune activation seen in CD involves the release of many proinflammatory cytokines. Cytokines thought to play major roles in CD are derived from T-helper type 1 cells and include interferon-γ, TNF-α, and IL-1, IL-6, and IL-12. TNF-α is a major contributor to the inflammatory process seen in CD. Its physiologic effects include activation of macrophages, procoagulant effects in the vascular endothelium, and increases in production of matrix metalloproteinases in mucosal cells.[9,15] Excessive production of both interferon-γ and TNF-α may account for the excessive clinical evidence of granulomatous disease in patients with CD.[10] TNF-α is also thought to induce production of nuclear factor κβ, which stimulates further production of TNF-α and other proinflammatory cytokines.[3,14]

The role of an immune response directed against endogenous bacteria as the initiating factor is more evident in CD, as evidenced by the apparent strong T-helper 1 activation against bacteria seen in animal models of this disease. Likewise, bacteria are often found deep in the intestinal mucosal layer of patients with CD. As mentioned previously, the finding of genetic mutations in NOD2 may result in excessive production of IL-12 and inhibition of intestinal phagocytes to break down bacterial antigens.[10]

Dysregulation of cytokines that normally downregulate inflammatory responses, such as transforming growth factor-β, may also be involved in the excessive inflammatory response seen in CD. As in UC, patients with CD may have disease flares due to ingestion of NSAIDs. The role of dietary antigens in the development of CD compared to UC is also another potential initiating factor. Excess ingestion of refined sugars or margarine may be higher in patients who develop CD.[7]

The distribution of inflammation in CD differs from that seen in UC, as any part of the entire GI tract may be affected in CD. The small intestine is the site most commonly involved. Within the small intestine, the terminal ileum and cecum are almost always affected. Approximately 20% of patients have isolated colonic involvement, whereas inflammation proximal to the small intestine is almost never seen without the presence of small or large intestinal disease.[12]

In contrast to UC, the pattern of inflammation in CD is described as discontinuous. Areas of inflammation are intermixed with areas of normal GI mucosa, resulting in characteristic "skip lesions." Superficial **aphthous ulcers** may also develop in the GI mucosa. These ulcers may coalesce into larger linear ulcers, resulting in fissure formation as they increase in depth, giving rise to the characteristic "cobblestone" pattern observed upon examination of the mucosa.

Furthermore, the inflammation may be **transmural**, penetrating to the muscularis or serosal layers of the GI tract (Fig. 16–2). The propensity for transmural involvement may lead to serious complications of CD, such as **strictures**, **fistulae**, and abscesses.[4,12] While rectal inflammation is typically less common in CD than UC, several types of perianal lesions may be observed in patients with CD. These include skin tags, hemorrhoids, fissures, anal ulcers, abscesses, and fistulae.[15]

CLINICAL PRESENTATION AND DIAGNOSIS

❷ *Differentiation of ulcerative colitis and Crohn's disease is based on signs and symptoms as well as characteristic endoscopic findings, including the extent, pattern, and depth of inflammation (see Presentation Box in second column).*

Extraintestinal Manifestations and Complications of IBD

❸ *Patients may manifest signs and symptoms of disease in areas outside the GI tract. These extraintestinal manifestations may occur in various body regions.*[5,8] Painful joint complications associated with IBD include sacroiliitis and ankylosing spondylitis. Ocular involvement with episcleritis, uveitis, or iritis may manifest as blurred vision, eye pain, and photophobia. Associated skin findings include pyoderma gangrenosum (involving papules and vesicles that develop into painful ulcerations) and erythema nodosum (red nodules of varying size typically found on the lower extremities). Nephrolithiasis may also develop at a higher rate in patients with IBD. Oxalate stones are more common in CD, and uric acid–containing stones are more common in UC.

Liver and biliary manifestations of IBD include an increased incidence of gallstone formation in patients with CD and development of sclerosing cholangitis or cholangiocarcinoma in patients with UC. Patients with UC are also at increased risk for development of colorectal cancer. Ongoing inflammation due to active IBD may induce a hypercoagulable state, resulting in higher rates of both arterial and venous thromboembolism. Likewise, inflammation and recurrent blood loss may result in the development of chronic anemia. Patients with IBD also have higher rates of osteopenia, osteoporosis, and fractures.[16]

A serious complication of UC is toxic megacolon, defined as dilation of the transverse colon of greater than 6 cm. Patients with toxic megacolon typically manifest systemic signs of severe inflammation such as fever, tachycardia, and abdominal distention.[3] Surgical intervention, including colonic resection, may be necessary to acutely manage toxic megacolon.

Formation of strictures, abscesses, fistulae, and obstructions in patients with CD is possible. Patients with CD may develop significant weight loss or nutritional deficiencies secondary to malabsorption of nutrients in the small intestine, or as a consequence of multiple small- or large-bowel resections. Common nutritional deficiencies encountered in IBD include vitamin B_{12}, fat-soluble vitamins, zinc, folate, and iron. Malabsorption in children with CD may contribute to significant reductions in growth and development.



Presentation of Inflammatory Bowel Disease

General
- Patients with CD or UC may present with similar symptoms.
- The onset may be insidious and subacute.
- Some patients present with extraintestinal manifestations before GI symptoms occur.
- In approximately 10% of cases it may not be possible to distinguish between UC and CD. These patients are described as having "indeterminate colitis."

Symptoms
- *Ulcerative colitis*: Diarrhea (bloody, watery, or mucopurulent), rectal bleeding, abdominal pain/cramping, weight loss and malnutrition, tenesmus, constipation (with proctitis)
- *Crohn's disease*: Diarrhea (less bloody than UC), rectal bleeding (less than UC), abdominal pain/cramping, weight loss and malnutrition (more common than UC), fatigue/malaise

Signs
- *Ulcerative colitis*: Fever, tachycardia (with severe disease), dehydration, arthritis, hemorrhoids, anal fissures, perirectal abscesses
- *Crohn's disease*: Fever, tachycardia (with severe disease), dehydration, arthritis, abdominal mass and tenderness, perianal fissure or fistula

Laboratory Tests
- *Ulcerative colitis*: Leukocytosis, decreased hematocrit/hemoglobin, elevated erythrocyte sedimentation rate (ESR), guaiac-positive stool, (+) perinuclear antineutrophil cytoplasmic antibodies (pANCA; up to 70% of patients)
- *Crohn's disease*: Leukocytosis, decreased hematocrit/hemoglobin, elevated ESR, guaiac-positive stool, (+) anti–*Saccharomyces cerevisiae* antibodies (up to 50% of patients), hypoalbuminemia with severe disease

Diagnosis

Because patients often present with nonspecific GI symptoms, initial diagnostic evaluation includes methods to characterize the disease and rule out other potential etiologies. This may include stool cultures to examine for infectious causes of diarrhea.

Endoscopic approaches are typically used and may include colonoscopy, proctosigmoidoscopy, or possibly upper GI endoscopy in patients with suspected CD. Endoscopy is useful for determining the disease distribution, pattern and depth of inflammation, and to obtain mucosal biopsy specimens. Supplemental information from imaging procedures, such as computed tomography (CT), abdominal x-ray, abdominal ultrasound, or intestinal barium studies may provide evidence of complications such as obstruction, abscess, perforation, or colonic dilation.[3]

After the diagnosis is made, the information derived from diagnostic testing and the patient's medical history and symptoms are used to gauge disease severity. The severity of active UC is generally classified as mild, moderate, severe, or fulminant.[1] Mild UC typically involves up to four bloody or watery stools per day without systemic signs of toxicity or elevation of ESR. Moderate disease is classified as more than four stools per day with evidence of systemic toxicity. Severe disease is considered more than six stools per day and evidence of anemia, tachycardia, or an elevated ESR. Lastly, fulminant UC may present as more than 10 stools per day with continuous bleeding, signs of systemic toxicity, abdominal distention or tenderness, colonic dilation, or a requirement for blood transfusion.

A similar classification scheme is used to gauge the severity of active CD.[2] Patients with mild to moderate CD are typically ambulatory and have no evidence of dehydration, systemic toxicity, loss of body weight, or abdominal tenderness, mass, or obstruction. Moderate to severe disease is considered in patients who fail to respond to treatment for mild to moderate disease, or those with fever, weight loss, abdominal pain or tenderness, vomiting, intestinal obstruction, or significant anemia. Severe to fulminant CD is classified as the presence of persistent symptoms or evidence of systemic toxicity despite outpatient corticosteroid treatment, or presence of cachexia, rebound tenderness, intestinal obstruction, or abscess.



Patient Encounter 1, Part 1

A 25-year-old Caucasian woman presents to the university student clinic with complaints of intermittent crampy abdominal pain and four to five loose stools per day. She describes some visible mucus and blood in the stool and states that these symptoms have been present for 6 to 8 weeks. She also has intermittent lower back pain, fatigue, fever, and a 10-lb (4.5 kg) weight loss. The back pain started about the same time as her gastrointestinal symptoms. She denies any sick contacts and has not eaten any take-out or restaurant food over the last 2 months. She takes nonprescription naproxen as needed for aches and pains. She has been using more naproxen recently because of the back pain. She also takes an oral contraceptive pill once daily. She consumes alcohol socially and currently smokes $^1/_2$ to 1 pack of cigarettes per day.

- What symptoms are suggestive of IBD in this patient?
- Are these symptoms more suggestive of UC or CD?
- What factors may be contributing to her IBD symptoms?
- What additional information would you acquire prior to recommending drug therapy?

TREATMENT

Desired Outcomes

Pharmacologic interventions for IBD are designed to target the underlying inflammatory response. Treatment goals involve both management of active disease and prevention of disease relapse. ❹ *Major treatment goals include alleviation of signs and symptoms and suppression of inflammation during acute episodes and maintenance of remission thereafter.* Addressing active IBD in a timely and appropriate manner may prevent major complications such as perforation and may reduce the need for hospitalization or surgical intervention. Once control of active disease is obtained, treatment regimens are designed to achieve the following long-term goals: (1) maintenance of remission and prevention of disease relapse; (2) improvement in the patient's quality of life; (3) prevention of surgical intervention or hospitalization; (4) management of extraintestinal manifestations; (5) prevention of malnutrition; and (6) prevention of treatment-associated adverse effects.

General Approach to Treatment

❺ *When designing a drug regimen for treatment of IBD, several factors should be considered, including the patient's symptoms, medical history, current medication use, drug allergies, and location and severity of disease.* A thorough patient history may also help to identify a family history of IBD or potential exacerbating factors, such as tobacco or NSAID use.

Nonpharmacologic Therapy

No specific dietary restrictions are recommended for patients with IBD, but avoidance of high-residue foods in patients with strictures may help to prevent obstruction. Nutritional strategies in patients with long-standing IBD may include use of vitamin and mineral supplementation. Administration of vitamin B_{12}, folic acid, fat-soluble vitamins, and iron may be needed to prevent or treat deficiencies. In severe cases, enteral or parenteral nutrition may be needed to achieve adequate caloric intake.

Patients with IBD, particularly those with CD, are also at risk for bone loss. This may be a function of malabsorption or an effect of repeated courses of corticosteroids. Patients with IBD should receive a baseline bone density measurement prior to receiving corticosteroids. Vitamin D and calcium supplementation should be used in all patients receiving long-term corticosteroids. Oral bisphosphonate therapy may also be considered in patients receiving prolonged courses of corticosteroids or in those with osteopenia or osteoporosis.

Surgical intervention is a potential treatment option in patients with complications such as fistulae or abscesses, or in patients with medically refractory disease. Ulcerative colitis is curable with performance of a total colectomy. Patients with UC may opt to have a colectomy to reduce the chance of developing colorectal cancer. Patients with CD may have affected areas of intestine resected. Unfortunately, CD may recur following surgical resection. Repeated surgeries may lead to significant malabsorption of nutrients and drugs consistent with development of short-bowel syndrome.

Pharmacologic Therapy

Several pharmacologic classes are available for the treatment and maintenance of IBD. Because there may be differences in the underlying disease process, distribution, and severity between CD and UC, response rates to drugs in the same pharmacologic class may differ between these two diseases. Therefore, initial selection of an appropriate agent for patients with active IBD should be designed to deliver maximum efficacy while minimizing toxicity. Response rates to individual classes of medications for both UC and CD will be discussed within the specific treatment section for each disease.

Symptomatic Interventions

Patients with active IBD often have severe abdominal pain and diarrhea. Medications used to manage these types of symptoms may have adverse consequences in patients with active IBD. ❻ *Antidiarrheal medications that reduce GI motility, such as loperamide, diphenoxylate/atropine, and codeine should be avoided in patients with active IBD due to the risk of precipitating acute colonic dilation (toxic megacolon).*[8] Drugs with anticholinergic properties, such as hyoscyamine and dicyclomine, are often used to treat intestinal spasm and pain, but these drugs may also reduce GI motility and should generally be avoided in active IBD. Once active disease is under control, antidiarrheal agents may be used with caution as adjunctive treatment.

Patients who have had multiple intestinal resections due to CD may have diarrhea related to the inability to reabsorb bile salts. Cholestyramine has been demonstrated to improve diarrheal symptoms in this population.[8,15] NSAIDs should be avoided for pain management due to their ability to worsen IBD symptoms. Narcotic analgesics should be used with caution, as they may significantly reduce GI motility.

Aminosalicylates

The aminosalicylates are among the most commonly used drugs for inducing and maintaining remission in patients with IBD (Table 16–1). These drugs are designed to deliver 5-aminosalicylate (5-ASA, mesalamine) to areas of inflammation within the GI tract. While the mechanism of mesalamine is not fully understood, it appears to have favorable anti-inflammatory effects. These effects may include reducing prostaglandin and leukotriene production, inhibiting bacteria-induced chemotaxis, scavenging of free radicals, and inhibiting nuclear factor κβ.[9] The delivery of mesalamine to the affected sites is accomplished by either linking mesalamine to a carrier molecule or altering the formulation to release drug in response to changes in intestinal pH. Topical suppositories and enemas are designed to deliver mesalamine directly to the distal colon and rectum.[17,18]

The prototypical aminosalicylate is sulfasalazine, which is comprised of mesalamine linked by a diazo bond to the carrier molecule sulfapyridine. This linkage prevents premature absorption of mesalamine in the small intestine. Once sulfasalazine is delivered to the colon, bacterial degradation of

TABLE 16–1. Aminosalicylates for Treatment of Inflammatory Bowel Disease

Drug	Trade Names	Formulation	Strengths	Daily Dosage Range	Site of Action
Sulfasalazine	Azulfidine®	Immediate-release or enteric-coated tablets	500 mg	2–6 g	Colon
	Azulfidine Entabs®				
	Sulfazine®				
	Sulfazine EC®				
Mesalamine	Rowasa®	Enema	4 g/60 mL	4 g	Distal left colon and rectum
	Asacol®	Delayed-release resin tablet	400 mg	1.6–4.8 g	Distal ileum and colon
	Canasa®	Suppository	500 and 1000 mg	1 g	Rectum
	Pentasa®	Microgranule controlled-release capsule	250 mg	2–4 g	Small bowel
			500 mg	2–4 g	Colon
Olsalazine	Dipentum®	Capsule	250 mg	1–3 g	Colon
Balsalazide	Colazal®	Capsule	750 mg	2–6.75 g	Colon

the diazo bond frees mesalamine from sulfapyridine. Sulfapyridine is then absorbed and excreted renally, while mesalamine acts locally within the GI tract.

Newer mesalamine products utilize non-sulfapyridine methods for drug delivery. Olsalazine uses two mesalamine molecules linked together, while balsalazide uses the inert carrier molecule 4-aminobenzoyl-β-alanine. Both drugs use a diazo bond similar to sulfasalazine. Other mesalamine formulations are pH-dependent formulations that release mesalamine at various points throughout the GI tract.

Sulfasalazine is associated with various adverse effects, most of which are thought to be due to the sulfapyridine component. Common adverse effects that may be dose related include headache, dyspepsia, nausea, vomiting, and fatigue.[19] Idiosyncratic effects include bone marrow suppression, reduction in sperm counts in males, hepatitis, and pulmonitis. Hypersensitivity reactions may occur in patients allergic to sulfonamide-containing medications.

The use of non-sulfapyridine–based aminosalicylates has led to greater tolerability. Although the adverse effects are similar to those of sulfasalazine, they occur at a much lower rate. Olsalazine, in particular, is associated with a higher incidence of secretory diarrhea. These agents can also be used safely in patients with a reported sulfonamide allergy.

Corticosteroids

Corticosteroids have potent anti-inflammatory properties and are used in active IBD to rapidly suppress inflammation. Corticosteroids have favorable effects in modulating several cell types involved in the inflammatory process.[20,21] They may be administered systemically or delivered locally to the site of action by altering the drug formulation (Table 16–2). Because these drugs usually improve symptoms and disease severity rapidly, they should be restricted to short-term management of active disease. Long-term use of systemic corticosteroids is associated with significant adverse effects, including cataracts, skin atrophy, hypertension, hyperglycemia, adrenal suppression, osteoporosis, and increased risk of infection, among others.[19,22]

Budesonide is a high-potency glucocorticoid used in CD that has low systemic bioavailability when administered orally.[23] The formulation releases budesonide in the terminal ileum for treatment of disease involving the ileum or ascending colon. Due to its reduced bioavailability, budesonide may prevent some long-term adverse effects in patients who have steroid-dependent IBD.[23,24]

TABLE 16–2. Corticosteroids for Treatment of Inflammatory Bowel Disease

Drug	Trade Names	Daily Dose
Prednisone	Generic	20–60 mg orally
Prednisolone	Generic	20–60 mg orally
Budesonide	Entocort EC®	Induction: 9 mg orally Maintenance: 6 mg orally
Methylprednisolone	Medrol® (PO) Solu-Medrol® (IV)	15–60 mg orally or IV
Hydrocortisone	Solu-Cortef®	300 mg IV in three divided doses
	Cortenema®	100 mg rectally at bedtime
	Cortifoam®	90 mg rectally once or twice daily
	Anucort® 25 mg	25–50 mg rectally twice daily
	Proctocort® 30 mg	25–50 mg rectally twice daily

Immunosuppressants

Agents targeting the excessive immune response or cytokines involved in IBD are potential treatment options (Table 16–3). Azathioprine and its active metabolite 6-mercaptopurine (6-MP) are inhibitors of purine biosynthesis and reduce IBD-associated GI inflammation. They are most useful for maintaining remission of IBD or reducing the need for long-term use of corticosteroids. Use in active disease is limited by their slow onset of action, which may be as long as 3 to 12 months. Adverse effects associated with azathioprine and 6-MP include hypersensitivity reactions resulting in pancreatitis, fever, rash, hepatitis, and leukopenia.[25,26]

Methotrexate is a folate antagonist used primarily for maintaining remission of CD. It may be administered orally, subcutaneously, or intravenously and may result in a steroid-sparing effect in patients with steroid-dependent disease.[26,27] Long-term methotrexate use may result in serious adverse effects, including hepatotoxicity, pulmonary fibrosis, and bone marrow suppression. Methotrexate is teratogenic and should not be used in pregnant women or those who plan to become pregnant.

Cyclosporine is a cyclic polypeptide immunosuppressant typically used to prevent organ rejection in transplant patients. Its use is restricted to patients with fulminant or refractory symptoms in patients with active IBD. Significant toxicities associated with cyclosporine are nephrotoxicity, risk of infection, seizures, hypertension, and liver function test abnormalities.[1,13,14]

TABLE 16–3. Immunosuppressant and Biologic Agents for Treatment of Inflammatory Bowel Disease

Drug	Trade Names	Dose
Azathioprine	Imuran®, Azasan®	1.5–2.5 mg/kg per day orally
6-Mercaptopurine	Purinethol®	1.5–2.5 mg/kg per day orally
Methotrexate	Rheumatrex®, Trexall®	15–25 mg weekly (IM/SC/orally)
Cyclosporine	Sandimmune®	4 mg/kg per day IV continuous infusion
Infliximab	Remicade®	Induction: 5 mg/kg IV at 0, 2, and 6 weeks; 10 mg/kg per dose IV for non-responders Maintenance: 5 mg/kg IV every 8 weeks

IM, intramuscular; IV, intravenous; SC, subcutaneous.

Biologic Agents

Infliximab is the only biologic agent routinely used for managing IBD. It is a murine-human IgG_1 antibody directed against TNF-α.[14] Reduction in TNF-α activity in patients with IBD is associated with improvement in the underlying inflammatory process. Disadvantages of infliximab include need for intravenous administration, significant drug cost, and potential for adverse effects. Adverse effects include infusion-related reactions such as fever, chest pain, hypotension, and dyspnea.[29] Infliximab has also been associated with reactivation of serious infections, particularly intracellular pathogens such as tuberculosis.[19,30] For this reason, infliximab should not be used in patients with current infections, and patients should be screened for tuberculosis prior to initiating therapy. Infliximab may also lead to the development or exacerbation of heart failure; it should be avoided in patients with advanced or decompensated heart failure.[31]

Other Agents

Antibiotics have been studied based on the rationale that they may interrupt the inflammatory response directed against endogenous bacterial flora. Metronidazole and ciprofloxacin have been the two most widely-studied agents.[32] Metronidazole may benefit some patients with pouchitis (inflammation of surgically-created intestinal pouches) and patients with CD who have had ileal resection or have perianal fistulas. Ciprofloxacin has shown some efficacy in refractory active CD. Both drugs may cause diarrhea, and long-term use of metronidazole is associated with the development of peripheral neuropathy.

Because smoking is associated with reduced symptoms of UC, nicotine has been studied as a potential treatment option. Transdermal nicotine may result in some improvement in mild to moderate UC symptoms. Daily doses between 15 and 25 mg appear to be most effective, but the role of nicotine therapy is not well defined.[1]

Probiotics, such as *Lactobacillus acidophilus* or *Bifidobacterium*, may offer possible benefit, based on the rationale that modification of the host flora may alter the inflammatory response. Some evidence exists for improvement in disease symptoms, but further well-controlled trials are needed.[26]

Treatment of Ulcerative Colitis

Drug and dosing guidelines based on disease severity and location are presented in Table 16–4.

Mild to Moderate Active UC

❼ *Treatment of acute episodes of ulcerative colitis is dictated by the severity and extent of disease, and first-line therapy of mild to moderate disease involves oral or topical aminosalicylate derivatives.* Topical suppositories and enemas are preferred for active distal UC (left-sided disease and proctitis), as they deliver mesalamine directly to the site of inflammation. Topical mesalamine is superior to both topical corticosteroids and oral aminosalicylates for inducing remission in active mild to moderate UC.[1,33,34] Enemas are appropriate for patients with



Patient Encounter 1, Part 2: The Medical History and Physical Examination

PMH
Tonsillectomy at age 5, fractured right clavicle (sports related)

FH
Both parents alive; father has history of hypertension, type 2 DM, and dyslipidemia; mother has a history of colon cancer with subtotal colectomy; brother with history of "indeterminate colitis"

SH
College student, social alcohol use and $^1/_2$ to 1 pack per day tobacco use for 6 years

Meds
Naproxen 220 mg PO as needed, Lo-Ovral PO once daily

ROS
(+) Diarrhea, abdominal pain, fatigue, back pain, fever, weight loss

PE
VS: blood pressure 118/65 mm Hg, pulse 92 beats per minute, respiratory rate 13/minutes, temperature 37.9°C (100.2°F)
CV: Tachycardia with normal rhythm, no murmurs, rubs, or gallops
HEENT: Dry mucous membranes
Abd: Soft, non-distended, mild diffuse tenderness, (+) bowel sounds, (–) hepatosplenomegaly, (–) masses, heme (+) stool
MS: Point tenderness over sacral area, (–) erythema, reduced lower back ROM

Labs
Sodium 139 mEq/L (139 mmol/L), potassium 3.2 mEq/L (3.2 mmol/L), chloride 100 mEq/L (100 mmol/L), bicarbonate 27 mEq/L (27 mmol/L), blood urea nitrogen 12 mg/dL (4.3 mmol/L urea), serum creatinine 1.0 mg/dL (88.4 μmol/L), albumin 4.2 g/dL (42 g/L), hemoglobin 11 g/dL (110 g/L or 6.82 mmol/L), hematocrit 33%, white blood cell count 11.0 x 10^3/mm^3 (11 × 10^9/L), platelets 300 × 10^3/mm^3 (300 × 10^9/L), ESR 120 mm/hour
Imaging: Abdominal x-ray: (–) obstruction, perforation, or colonic dilation
Colonoscopy: patchy "cobblestone" inflammation in the terminal ileum and ascending colon with evidence of recent bleeding, (–) polyps or strictures, biopsy taken
Path: Evidence of disease extension to muscularis with non-caseating granulomas

- How is this additional information helpful in determining disease type and severity?
- What are your treatment goals for this patient?
- What factors should you consider in choosing appropriate therapy for this patient?

TABLE 16–4. Treatment Recommendations for Ulcerative Colitis

Disease Severity and Location	Active Disease	Maintenance of Remission
Mild Disease		
Proctitis	Mesalamine suppository 1 g rectally daily	May reduce suppository frequency to 1 g 3 times/week
Left-sided disease	Mesalamine enema 1 g rectally daily, *or* Mesalamine 2.4–4.8 g/day or sulfasalazine 4–6 g/day orally	May reduce enema frequency to 1 g every other day, *or* Taper to mesalamine 1.6–2.4 g/day or sulfasalazine 2–4 g/day orally
Colitis	Mesalamine 2.4–4.8 g/day or sulfasalazine 4–6 g/day orally	Taper to mesalamine 1.6–2.4 g/day or sulfasalazine 2–4 g/day orally
Moderate Disease		
Proctitis	Mesalamine suppository 1 g rectally daily; If no response to mesalamine: • Prednisone 40–60 mg/day orally	May reduce suppository frequency to 1 g 3 times/week; taper prednisone as soon as possible; Consider adding azathioprine or 6-MP 1.5–2.5 mg/kg per day orally
Left-sided disease	Mesalamine enema 1 g rectally at bedtime daily, *or* Mesalamine 2.4–4.8 g/day or sulfasalazine 4–6 g/day orally	May reduce enema frequency to 1 g 3 times/week if symptoms permit; May reduce dose of oral agents if symptoms permit; Consider adding azathioprine or 6-MP 1.5–2.5 mg/kg per day orally
Colitis	Mesalamine 2.4–4.8 g/day or sulfasalazine 4–6 g/day orally; If no response to mesalamine or sulfasalazine: • Prednisone 40–60 mg/day orally; *or* • Infliximab 5 mg/kg IV at weeks 0, 2, and 6	Taper mesalamine to 1.6–2.4 g/day or sulfasalazine 2–4 g/day orally; If prednisone or infliximab were required: • Taper prednisone as soon as possible; • Give infliximab 5 mg/kg IV every 8 weeks Consider adding azathioprine or 6-MP 1.5–2.5 mg/kg per day orally
Severe or Fulminant Disease	Hydrocortisone 300 mg IV daily (or equivalent) × 7 days, *or* Infliximab 5 mg/kg IV at weeks 0, 2, and 6 If no response to IV corticosteroids or infliximab: • Cyclosporine 4 mg/kg per day IV	Change to oral corticosteroid and taper as soon as possible; Restart oral mesalamine or sulfasalazine May continue infliximab at maintenance doses of 5 mg/kg every 8 weeks

IV, intravenous; 6-MP, 6-mercaptopurine.

left-sided disease, as the medication will reach the splenic flexure. Suppositories deliver mesalamine up to approximately 20 cm and are most appropriate for treating proctitis.[6]

Topical mesalamine products provide a more rapid response than oral preparations. Improvement in symptoms may be seen in as little as 2 days, but 2 to 4 weeks of treatment may be necessary for maximal response. Response rates of up to 90% after 4 weeks of topical therapy have been reported, compared to 45% to 62% response rates with oral therapy.[6,18] Oral and topical mesalamine preparations may be used together to provide maximal effect. Oral mesalamine may also be used for patients who are unwilling to use topical preparations.

Topical corticosteroids are typically reserved for patients who do not respond to topical mesalamine. Patients should be properly educated regarding appropriate use of topical products. This includes proper administration and adequate retention of topical mesalamine products in order to maximize efficacy.

For patients with more extensive disease extending proximal to the splenic flexure, oral sulfasalazine or any of the newer oral mesalamine products is considered first-line therapy.[1] Doses should provide 4 to 6 g of sulfasalazine or 4.8 g of mesalamine. While little differences in efficacy exist between mesalamine products, sulfasalazine and olsalazine have a higher incidence of adverse effects.[18] Induction of remission may require 4 to 8 weeks of therapy at appropriate treatment doses.

Oral corticosteroids may be used for patients who are unresponsive to sulfasalazine or mesalamine. Prednisone doses of 40 to 60 mg per day (or equivalent) are recommended.[1] Azathioprine or 6-MP is used for patients unresponsive to corticosteroids or those who become steroid-dependent. Over a 12-month period, these agents have been shown to reduce the relapse rate to 36% versus 59% seen with placebo.[1] Infliximab 5 mg/kg may also be used for patients who are unresponsive to conventional oral therapies and may reduce the need for colectomy after 3 months of treatment.[35]

Severe or Fulminant UC

Patients with severe UC symptoms require hospitalization for management of their disease. If the patient is unresponsive to oral or topical mesalamine and oral corticosteroids, then a course of intravenous corticosteroids should be initiated.[1] Hydrocortisone 300 mg/day given in three divided doses or methylprednisolone 60 mg daily for 7 to 10 days are the preferred therapies.

Infliximab 5 mg/kg is also an option for severe UC. Cyclosporine 2 to 4 mg/kg per day given as a continuous intravenous infusion should be reserved for patients unresponsive to 7 to 10 days of intravenous corticosteroid therapy.

Patients with fulminant disease are treated similarly, although infliximab is not indicated for this population. Patients with fulminant UC should be assessed for signs of significant systemic toxicity or colonic dilation, which may require earlier surgical intervention.

Maintenance of Remission

Unfortunately, up to 50% of patients receiving oral therapies and up to 70% of untreated patients relapse within 1 year after achieving remission.[26] For this reason, patients may require maintenance drug therapy indefinitely to preserve remission.

❽ *Maintenance of remission of ulcerative colitis may be achieved with oral or topical aminosalicylates.* Mesalamine suppositories 1 g daily may prevent relapse in up to 90% of patients with proctitis.[1] Mesalamine enemas are appropriate for left-sided disease and may often be dosed three times weekly. Oral mesalamine at lower doses (e.g., 1.6 g per day) may be combined with topical therapies to maintain remission. Topical or oral corticosteroids are not effective for maintaining remission of distal UC and should be avoided.

Oral sulfasalazine or mesalamine is effective in maintaining remission in patients with more extensive disease.[1,26] Lower daily doses (e.g., 2 to 4 g sulfasalazine or 1.6 to 2.4 g mesalamine) may be used for disease maintenance. As with distal UC, oral corticosteroids are not effective for maintaining remission and should be avoided due to the high incidence of adverse effects.

❽ *Immunosuppressants such as azathioprine or 6-mercaptopurine can be used for unresponsive patients or those who develop corticosteroid dependency.* Remission may be maintained in up to 58% of patients after 5 years of treatment.[1,25] Intermittent infliximab dosing (5 mg/kg IV every 8 weeks) may be used to maintain disease remission and reduce the need for corticosteroids in patients with moderate to severe UC. Colectomy is an option for patients with progressive disease who cannot be maintained on drug therapy alone.

Treatment of Crohn's Disease

Drug and dosing guidelines based on disease severity and location are presented in Table 16–5.

Mild to Moderate Active CD

❾ *Induction of remission of mild to moderate active CD is accomplished with oral aminosalicylates.* Sulfasalazine 4 to 6 g per day is most effective for patients with colonic involvement, with response rates of 50%.[2,5] Mesalamine products have

TABLE 16–5. Treatment Recommendations for Crohn's Disease

Disease Location and Severity	Active Disease	Maintenance of Remission
Mild Disease		
Ileal or ileocolonic	Mesalamine 2.4–4.8 g/day or sulfasalazine 4–6 g/day orally	Taper mesalamine 1.6–2.4 g/day or sulfasalazine 2–4 g/day orally
Ileal +/– ascending colon	Budesonide 9 mg daily orally for up to 8 weeks	Taper budesonide to 6 mg daily for up to 3 months
Perianal	Mesalamine 2.4–4.8 g/day or sulfasalazine 4–6 g/day orally; May add metronidazole 10–20 mg/kg per day or ciprofloxacin 1 g daily	Taper mesalamine to 1.6–2.4 g/day or sulfasalazine 2–4 g/day orally
Moderate Disease	Same treatment as for mild disease; If inadequate response to aminosalicylate, consider; • Infliximab 5 mg/kg IV at 0, 2, and 6 weeks, *or* • Prednisone 40–60 mg/day orally, *or* • Budesonide 9 mg/day orally for up to 8 weeks; If fistulizing disease, consider: • Infliximab 5 mg/kg IV at 0, 2, and 6 weeks	Continue aminosalicylate at maintenance dose; May continue infliximab at maintenance doses of 5 mg/kg every 8 weeks; Taper prednisone as soon as possible; Taper budesonide to 6 mg daily for 3 months; Consider adding azathioprine or 6-MP 1.5–2.5 mg/kg per day orally or methotrexate 12.5–25 mg orally or IM/SC once weekly
Severe or Fulminant Disease	Hydrocortisone 300 mg IV daily (or equivalent) × 7 days, *or* Infliximab (severe or fistulizing disease) 5 mg/kg IV at 0, 2, and 6 weeks; Consider cyclosporine 4 mg/kg per day for refractory disease	Taper corticosteroid as soon as possible; May continue infliximab 5 mg/kg IV every 8 weeks; Consider adding azathioprine or 6-MP 1.5–2.5 mg/kg per day orally or methotrexate 12.5–25 mg orally or IM/SC weekly

IM; intramuscular; IV, intravenous; 6-MP, 6-mercaptopurine; SC, subcutaneous



Patient Encounter 2

A 57-year-old African-American man presents to the clinic for follow-up management of UC. He has had left-sided disease for 3 years and has been maintained in remission on maximal doses of oral mesalamine and prednisone 35 mg orally once daily. His provider has attempted several times to taper the prednisone dose, but the patient experiences a reappearance of symptoms if the dose is lowered below this level. Medical history is also significant for hypertension and heart failure. He has no known drug allergies.

- What are the risks of long-term corticosteroid use in this patient?
- What treatment options are available for reducing corticosteroid dependency in this patient?
- What other information is needed before recommending a pharmacologic intervention?

shown more variable results but may be used for patients with ileal, ileocolonic, or colonic CD.[2,36] These drugs are typically better tolerated than sulfasalazine at full treatment doses. Induction of remission may require up to 16 weeks of treatment at full doses.[36]

Budesonide 9 mg orally once daily for up to 8 weeks may be used for mild to moderate active CD in patients with involvement of the terminal ileum or ascending colon, with success expected in 50% to 60% of patients.[23] Because the formulation releases budesonide in the terminal ileum, it is not effective in reaching sites distal to the ascending colon.[23,36] Conventional oral corticosteroids such as prednisone and methylprednisolone may be used for patients who are unresponsive to aminosalicylates or budesonide.

Metronidazole or ciprofloxacin can be used in patients who do not respond to oral aminosalicylates. Response rates of up to 50% are reported, but the data are conflicting and these agents should generally not be considered first-line therapy.[2,36]

Moderate to Severe Active CD

❾ *Patients with moderate to severe active CD may be treated with oral corticosteroids, such as prednisone 40 to 60 mg daily.*[2] Budesonide 9 mg orally once daily may be used for moderate active CD involving the terminal ileum or ascending colon. Infliximab is an effective alternative to corticosteroid therapy for patients with moderate to severe CD, including patients with fistulizing or perianal disease.[15,37–39] The recommended regimen for induction of remission is infliximab 5 mg/kg at weeks 0, 2, and 6; it is effective in inducing remission in approximately 80% of patients at 8 weeks. Complete closure of existing enterocutaneous fistulae occurs in approximately 50% of patients. For patients with simple perianal fistulae, antibiotics and infliximab are appropriate treatment options. Complex perianal fistulae are those associated with multiple openings, abscess, stricture, or penetration into the vaginal wall. These types of perianal fistulae may require surgical intervention but may also be amenable to treatment with antibiotics, infliximab, azathioprine, or 6-MP.[2,15]

Severe to Fulminant Active CD

Most patients with severe to fulminant CD require hospitalization for appropriate treatment. Patients should be assessed for possible surgical intervention if abdominal distention, masses, abscess, or obstruction are present. Intravenous daily doses of corticosteroids equivalent to prednisone 40 to 60 mg are recommended as initial therapy to rapidly suppress severe inflammation.

If there are no contraindications, infliximab 5 mg/kg followed by 5 mg/kg at weeks 2 and 6 may be used for severe active CD. There is no evidence that infliximab is either safe or effective for fulminant disease.

Adjunctive therapy with fluid and electrolyte replacement should be initiated. Nutritional support with enteral or parenteral nutrition may be indicated for patients unable to eat for more than 5 to 7 days.[2] Some evidence suggests that enteral nutrition provides anti-inflammatory effects in patients with active CD.[40,41]

Limited evidence indicates that cyclosporine, or possibly tacrolimus, may be effective as salvage therapy for patients who fail intravenous corticosteroid therapy.[2] Surgical intervention may ultimately be necessary for medically refractory disease.

Maintenance of Remission in CD

Patients with CD are at high risk for disease relapse after induction of remission. Within 2 years, up to 80% of patients suffer a relapse; therefore, most patients should be evaluated for indefinite maintenance therapy. ❿ *Maintenance of remission of CD may be achieved with oral or topical aminosalicylate derivatives, immunosuppressants (such as azathioprine, 6-mercaptopurine, and methotrexate), or infliximab.*

In contrast to their use in UC, sulfasalazine and the newer aminosalicylates are marginally effective in preventing CD relapse in patients with medically-induced remission, with success rates of only 10% to 20% at 1 year.[26] Nevertheless, aminosalicylates are routinely used to maintain remission of CD. Some evidence does exist that the aminosalicylates may prevent or delay disease recurrence in patients with surgically-induced remisson.[2,26]

Several other treatment options exist for maintaining remission that may also reduce the need for corticosteroids.

Infliximab has been shown to maintain remission in 46% of patients compared to 23% of those treated with placebo over a 54-week period.[39] The dose used to maintain remission is 5 mg/kg IV given every 8 weeks. The dose may be increased to 10 mg/kg if patients lose response over time.

Azathioprine and 6-MP in oral doses up to 2.5 mg/kg per day have been shown to maintain remission in 45% of patients for up to 5 years.[2,25,26] These drugs may be used to prevent disease recurrence after surgically-induced remission. Methotrexate in doses ranging from 12.5 to 25 mg per week given orally, intramuscularly, or subcutaneously has resulted in remission rates of up to 52% at 3 years.[26,27]

Corticosteroids, while effective for rapidly inducing remission, are not effective for maintenance therapy and are associated with significant adverse effects with long-term use. Therefore, systemic or topical corticosteroids should not be used for maintaining remission in patients with IBD. Unfortunately up to 50% of patients treated acutely with corticosteroids become dependent on them to prevent symptoms.[2]

In place of conventional corticosteroids, budesonide 6 mg orally once daily may be used for up to 3 months after remission induction for mild to moderate CD. Remission rates decline significantly after this period.[23,24] The lower systemic bioavailability of budesonide results in a lower incidence of adverse effects than seen with conventional corticosteroids.

Treatment of IBD in Special Populations

Elderly Patients

Approximately 8% to 20% of patients with UC and 7% to 26% of patients with CD are elderly at initial diagnosis.[42] In general, IBD presents similarly in elderly patients compared to younger individuals. Elderly patients may have more comorbid diseases, some of which may make the diagnosis of IBD more difficult. Such conditions include ischemic colitis, diverticular disease, and microscopic colitis. Increased age is also associated with a higher incidence of adenomatous polyps, but the onset of IBD at an advanced age does not appear to increase the risk of developing colorectal cancer. Elderly patients may also use more medications, particularly NSAIDs, which may induce or exacerbate colitis.

Treatment of elderly patients with IBD is similar to that for younger patients, but special consideration should be given to some of the medications used. Corticosteroids may worsen diabetes, hypertension, heart failure, or osteoporosis. Infliximab should be used cautiously in patients with heart failure and should be avoided in New York Heart Association Class III or IV disease. Lastly, elderly patients requiring major surgical interventions may be at higher risk for surgical complications or may not meet eligibility criteria for surgery because of comorbid conditions, age-related organ dysfunction, or reduced functional status.

Children and Adolescents

CD occurs in approximately 4.56 per 100,000 pediatric patients, and UC occurs in about 2.14 cases per 100,000.[43] A major issue in children with IBD is the risk of growth failure secondary to inadequate nutritional intake. Failure to thrive may be an initial presentation of IBD in this population. Aggressive nutritional interventions may be required to facilitate adequate caloric intake. Chronic corticosteroid therapy may also be associated with reductions in growth.

Pediatric patients are also at higher risk for IBD-associated bone demineralization, which is accelerated by the use of systemic corticosteroids.

The aminosalicylates, azathioprine, 6-MP, and infliximab are all viable options for treatment and maintenance of IBD in pediatric patients. Use of immunosuppressive therapy or infliximab may help reduce overall corticosteroid exposure.

Pregnant Women

Inducing and maintaining remission of IBD prior to conception is the optimal approach in women planning to become pregnant. Active IBD may result in prematurity and low birth weight. Thus, pregnant women with IBD should be monitored closely, particularly during the third trimester.[44]

Patients do not need to discontinue drug therapy for IBD once they become pregnant, but certain adjustments may be required.[44,45] The aminosalicylates are considered safe to use in pregnancy, but sulfasalazine is associated with folate malabsorption. Because pregnancy results in a higher folate requirement, pregnant patients treated with sulfasalazine should be supplemented with folic acid 1 mg orally twice daily.[44] As with non-pregnant patients, corticosteroids may be used for treatment of active disease but not for maintenance of remission. Generally, corticosteroids confer no additional risk on the mother or fetus and are generally well tolerated. Both azathioprine and 6-MP have been used successfully in pregnant patients and do not appear to be associated with an increased risk, despite carrying a Food and Drug Administration (FDA) pregnancy category D rating. Cyclosporine has been used successfully for severe disease in pregnant patients and appears to be relatively safe; however, it should be reserved for fulminant disease unresponsive to conventional medical therapy.

Infliximab is FDA category B and also appears to carry minimal risk in pregnant patients. Little is known about excretion of infliximab in breast milk, so benefit versus risk should be considered if it is used during nursing.

Methotrexate is a known abortifacient and carries an FDA category X pregnancy rating. Thus, it is contraindicated during pregnancy. Metronidazole carries a theoretical risk of mutagenicity in humans, but short courses are safe during pregnancy. Prolonged use of metronidazole should be avoided in pregnant patients due to lack of safety data supporting its use.[45] First-trimester use of the antidiarrheal diphenoxylate has been associated with fetal malformations and should be avoided.

OUTCOME EVALUATION

- Monitor for improvement of symptoms in patients with active IBD, such as reduction in the number of daily stools, abdominal pain, fever, and heart rate.
- For patients in remission, assure that proper maintenance doses of medications are used and educate the patient to seek medical attention if symptoms recur or worsen.
- Evaluate patients receiving systemic corticosteroid therapy for improvement in symptoms and opportunities to taper or discontinue steroid therapy. For patients using more than 5 mg daily of prednisone for more than 2 months or for steroid-dependent patients consider the following:
  - Central bone mineral density testing to evaluate the need for preventive or therapeutic bisphosphonate therapy;
  - Periodic monitoring of blood glucose, lipids, and blood pressure;
  - Evaluation for evidence of cushingoid features or signs or symptoms of infection.
- When considering treatment with azathioprine or 6-MP, obtain baseline complete blood counts and liver function tests. These tests should be monitored closely (every 2 to 4 weeks) at the start of therapy and then approximately every 3 months during maintenance therapy.
- With azathioprine and 6-MP, monitor for hypersensitivity reactions, including severe skin rashes and pancreatitis. Educate the patient regarding signs and symptoms of pancreatitis (nausea, vomiting, and abdominal pain).
- Prior to initiating methotrexate therapy, obtain complete blood count, serum creatinine, liver function tests, chest x-ray, and pregnancy test (if female). Monitor blood counts weekly for 1 month, then monthly thereafter.
- Prior to initiating infliximab, obtain a tuberculin skin test to rule out latent tuberculosis. Assure that patients do not have a clinically significant systemic infection or New York Heart Association Class III or IV heart failure.
- In patients receiving infliximab, monitor for infusion-related reactions such as hypotension, dyspnea, fever, chills, or chest pain when administering intravenous doses.
- In patients with fistulae, monitor at every infliximab dosing interval for evidence of fistula closure and overall reduction in the number of fistulae.



Patient Care and Monitoring

1. Evaluate the patient's symptoms to determine if they are consistent with UC or CD. Determine whether the patient has evidence of extraintestinal manifestations or GI complications related to IBD. Identify any psychosocial problems related to the presence of IBD.
2. If the patient is presenting with an exacerbation of preexisting IBD, determine if the symptoms are similar in type and severity to the patient's previous episodes.
3. Assess the patient's medical history for pertinent drug allergies, tobacco use, and current prescription and nonprescription drug therapies. Determine if any of the medications could exacerbate IBD. If applicable, inquire about adherence or recent changes to the patient's current IBD drug regimen.
4. Use available diagnostic laboratory, endoscopic, and imaging data to gauge the extent and severity of the patient's disease.
5. Construct a drug treatment plan based on the disease severity and location. Identify potential contraindications or financial barriers to drug therapy. Inquire if the patient has an aversion to or inability to properly use certain drug formulations that you may wish to recommend, such as topical (rectal) products.
6. Assess whether the patient will require maintenance therapy after remission induction. If so, identify the treatment duration. Decide when the patient should receive follow-up care.
7. Outline parameters to evaluate the efficacy and toxicity of the drug regimen you are recommending. Determine whether the patient will need preventive drug therapy or diagnostic testing to prevent or screen for potential drug-related toxicities.
8. Educate the patient on proper use of drug therapy, including when to expect symptom improvement after initiation of treatment and which signs or symptoms to report that might be related to adverse drug effects.
9. Provide patient education on the proper use of aminosalicylate medications and assess regularly for adherence. Include the following:
   - Proper use of suppositories and enemas
   - The appropriate number of tablets or capsules to take per day
   - Appropriate dose titration, particularly with oral sulfasalazine
   - The time frame the patient can expect improvement based on drug dose and disease severity
   - Signs or symptoms of potential adverse effects
10. Once remission is achieved, evaluate the patient's drug regimen to determine if dose reductions or changes in frequency of administration are required. Reinforce the need for adherence to drug therapy in order to maximize effectiveness.
11. Educate patients about their disease state. Refer the patient to available support groups or IBD organizational resources if they are having difficulty in coping with their disease.

ABBREVIATIONS

5-ASA:	5-aminosalicylate
CD:	Crohn's disease
CT:	computed tomography
ESR:	erythrocyte sedimentation rate
FDA:	Food and Drug Administration
GI:	gastrointestinal
HLA:	human leukocyte antigen
IBD:	inflammatory bowel disease
IL:	interleukin
IM:	intramuscular
IV:	intravenous
6-MP:	6-mercaptopurine
NOD2:	nucleotide oligomerization domain 2
NSAID:	non-steroidal anti-inflammatory drug
pANCA:	perinuclear antineutrophil cytoplasmic antibodies
PO:	orally
PPAR-γ:	peroxisome proliferator activated receptor-γ
PR:	per rectum
SC:	subcutaneous
TNF-α:	tumor necrosis factor-α
UC:	ulcerative colitis

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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17 Nausea and Vomiting

Sheila Wilhelm



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Identify several causes of nausea and vomiting.
2. Describe the pathophysiologic mechanisms of nausea and vomiting.
3. Describe the three stages of nausea and vomiting.
4. Distinguish between simple and complex nausea and vomiting.
5. Identify the goals of treating nausea and vomiting.
6. Recommend a treatment regimen for a patient with nausea and vomiting associated with cancer chemotherapy, surgery, pregnancy, or motion sickness.
7. Outline a monitoring plan to evaluate the treatment outcomes for nausea and vomiting.

Key Concepts

❶ Nausea and vomiting are symptoms that can be due to a number of different causes.
❷ To treat nausea and vomiting most effectively, it is important to first identify the underlying cause of the symptoms.
❸ Nonpharmacologic approaches to treating nausea and vomiting include dietary, physical, and psychological changes.
❹ For prophylaxis of acute chemotherapy-induced nausea and vomiting, the combination of a 5-HT_3 antagonist and a corticosteroid is recommended for patients receiving highly emetogenic cisplatin or non–cisplatin-based chemotherapy.
❺ Droperidol or a 5-HT_3 receptor antagonist should be administered at the end of surgery to patients at high risk for developing postoperative nausea and vomiting.
❻ Nausea and vomiting of pregnancy affects the majority of pregnant women; the teratogenic potential of the therapy is the primary therapeutic consideration.
❼ Because the vestibular system is replete with muscarinic-type cholinergic and histaminic (H_1) receptors, anticholinergics and antihistamines are the most commonly used pharmacologic agents to prevent and treat motion sickness.

Nausea and vomiting are due to complex interactions of the gastrointestinal system, the vestibular system, and various portions of the brain. Nausea and vomiting have a variety of causes that can be simple or complex. Preventing and treating nausea and vomiting require pharmacologic and nonpharmacologic measures tailored to individual patients and situations.

ETIOLOGY AND EPIDEMIOLOGY

❶ *Nausea and vomiting are symptoms that can be due to a number of different causes.* Various disorders of the gastrointestinal, cardiac, neurologic, and endocrine systems can lead to nausea and vomiting (Table 17–1).[1–4] Cancer chemotherapy agents are rated according to their emetogenic potential, and antiemetic therapy is prescribed based on these ratings. Due to potentially severe nausea and vomiting, some patients are unable to complete their chemotherapy treatment regimen. Radiation therapy can induce nausea and vomiting, especially when it is used to treat abdominal malignancies.[5]

Oral contraceptives, hormone therapy, oral hypoglycemic agents, anticonvulsants, and opiates are other common therapies that can cause nausea and vomiting.[1] Some medications, such as digoxin and theophylline, cause nausea and vomiting in a dose-related fashion. Nausea and vomiting may indicate higher-than-desired drug concentrations. Ethanol and other toxins also cause nausea and vomiting.

Postoperative nausea and vomiting (PONV) occurs in 30% of surgical patients overall, and in up to 70% of high-risk patients.[6,7] This can be due to severing or disturbing the vagus nerve leading to gastric motility abnormalities. Additional risk

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TABLE 17–1. Causes of Nausea and Vomiting

Gastrointestinal or Intraperitoneal	**Cardiac**	**Therapy-Induced**
Obstructing disorders	Cardiopulmonary disease	Cancer chemotherapy
Pyloric obstruction	Cardiomyopathy	Antibiotics
Small bowel obstruction	Myocardial infarction	Cardiac anti-arrhythmics
Colonic obstruction	Congestive heart failure	Digoxin
Achalasia	**Neurologic**	Oral hypoglycemics
Superior mesenteric artery syndrome	Vestibular disease	Oral contraceptives
Enteric infections	Motion sickness	Theophylline
Inflammatory bowel diseases	Labyrinthitis	Opiates
Pancreatitis	Head trauma	Anticonvulsants
Appendicitis	Migraine headache	Radiation therapy
Cholecystitis	Increased intracranial pressure	Ethanol
Biliary colic	Intracranial hemorrhage	Toxins
Gastroparesis	Meningitis	Operative procedures
Postvagotomy syndrome	Hydrocephalus	**Endocrine/Metabolic**
Intestinal pseudo-obstruction	Psychogenic causes	Pregnancy (morning sickness and hyper-emesis gravidarum)
Functional dyspepsia	Psychogenic vomiting	Renal disease (uremia)
Gastroesophageal reflux	Depression	Diabetes (ketoacidosis)
Peptic ulcer disease	Psychiatric illness	Thyroid and parathyroid disease
Hepatitis	Self-induced	Adrenal insufficiency
Peritonitis	Anticipatory	Electrolyte abnormalities (hyponatremia, hypercalcemia)
Gastric malignancy	Rumination	
Liver failure	**Other Causes**	
	Bulimia and anorexia nervosa	
	Cyclic vomiting syndrome	

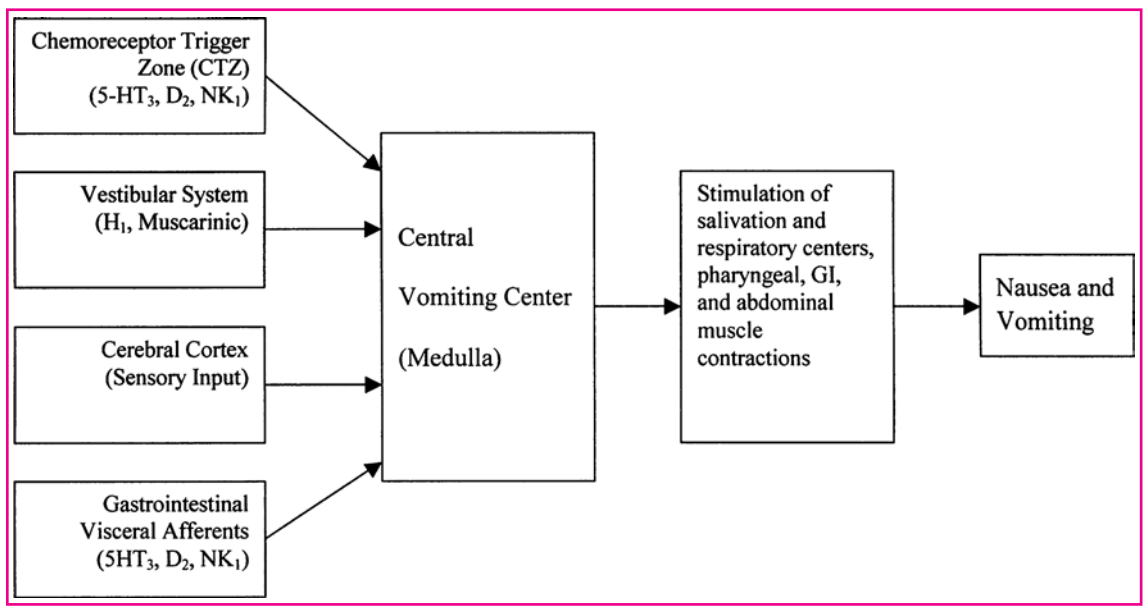


FIGURE 17–1. Physiologic pathways that result in nausea and vomiting. 5-HT_3, serotonin type 3 receptor; D_2, dopamine type 2 receptor; GI, gastrointestinal; H_1, histamine type 1 receptor, NK_1, neurokinin-1. (Adapted from American Society of Health-System Pharmacists. ASHP therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. Am J Health Syst Pharm 1999;56:729–764, with permission.)

factors for PONV include female gender, history of motion sickness or PONV, non-smoking status, and use of opioids in the postoperative period.[8] The choice of anesthetic agents and the duration of surgery may also contribute to PONV.[6]

Pregnancy-associated nausea and vomiting is common, affecting 70% to 85% of pregnant women, especially early in pregnancy.[9] Approximately one-half of pregnant women experience nausea and vomiting of pregnancy (NVP), one-quarter experience nausea alone, and one-quarter are not affected.[9] In 0.5% to 2% of pregnancies, this can lead to **hyperemesis gravidarum**, a potentially life-threatening condition of prolonged nausea, vomiting, and consequently, malnutrition.[9]

PATHOPHYSIOLOGY

Nausea and vomiting consist of three stages: (1) **nausea**, (2) **retching**, and (3) **vomiting**. Nausea is the subjective feeling of a need to vomit.[1] It is often accompanied by autonomic symptoms such as pallor, tachycardia, diaphoresis, and salivation. Retching, which follows nausea, consists of diaphragm, abdominal wall, and chest wall contractions and spasmodic breathing against a closed glottis.[1] Retching can occur without vomiting, but this stage produces the pressure gradient needed for vomiting, although no gastric contents are expelled. Vomiting, or emesis, is a reflexive, rapid, and forceful oral expulsion of upper gastrointestinal contents due to powerful and sustained contractions in the abdominal and thoracic musculature.[1] Vomiting, like nausea, can be accompanied by autonomic symptoms.

Regurgitation, unlike vomiting, is a passive process without involvement of the abdominal wall and diaphragm wherein gastric or esophageal contents move into the mouth.[1] In patients with gastroesophageal reflux disease (GERD), one hallmark symptom is acid regurgitation.

Various areas in the brain and the gastrointestinal (GI) tract are stimulated when the body is exposed to noxious stimuli (e.g., toxins), gastrointestinal irritants (e.g., infectious agents), or chemotherapy. These areas include the **chemoreceptor trigger zone** (CTZ) in the area postrema of the fourth ventricle of the brain, the vestibular system, visceral afferents from the GI tract, and the cerebral cortex.[2,3] These in turn stimulate regions of the reticular areas of the medulla within the brain stem. This area is the central vomiting center, the area of the brain stem that coordinates the impulses sent to the salivation center, respiratory center, and the pharyngeal, GI, and abdominal muscles that lead to vomiting (Fig. 17–1).[10]

The CTZ, located outside the blood–brain barrier (BBB), is exposed to cerebrospinal fluid and blood.[2,3] Therefore it is easily stimulated by uremia, acidosis, and the circulation of toxins such as chemotherapeutic agents. The CTZ has many serotonin type 3 (5-HT_3), neurokinin-1 (NK_1), and dopamine (D_2) receptors.[2] Visceral vagal nerve fibers are rich in 5-HT_3 receptors. They respond to gastrointestinal distention, mucosal irritation, and infection.

Motion sickness is caused by stimulation of the vestibular system. This area contains many histaminic (H_1) and muscarinic cholinergic receptors. The higher brain (i.e., cerebral cortex) is affected by sensory input such as sights, smells, or emotions that can lead to vomiting. This area is involved in anticipatory nausea and vomiting associated with chemotherapy.

Nausea and vomiting can be classified as either simple or complex.[4] Simple nausea and vomiting occurs occasionally and is either self-limiting or relieved by minimal therapy. It does not have detrimental effects on hydration status, electrolyte balance, or weight because it is short-lived. Alternatively, complex nausea and vomiting requires more aggressive therapy because electrolyte imbalances, dehydration, and weight loss may occur. Unlike simple nausea and vomiting, complex nausea and vomiting can be caused by exposure to noxious agents.

CLINICAL PRESENTATION AND DIAGNOSIS



Clinical Presentation of Nausea and Vomiting

Symptoms

- Patients with nausea often complain of autonomic symptoms such as diaphoresis, general disinterest in surroundings, pallor or faintness, and salivation.

Signs

- With complex and prolonged nausea and vomiting, patients may show signs of malnourishment, weight loss, and dehydration (dry mucous membranes, skin tenting, tachycardia, and lack of axillary sweat).

Laboratory Tests

- Dehydration, electrolyte imbalances, and acid-base disturbances may be evident in complex and prolonged nausea and vomiting.
- Elevated blood urea nitrogen (BUN) and serum creatinine (SCr) concentrations, especially with a BUN to SCr ratio of 20:1 or greater, suggest dehydration.
- Calculated fractional excreted sodium (FeNa) less than 1% in patients with compromised baseline renal function, and less than 0.2% in patients with normal baseline renal function indicates dehydration and reduced renal perfusion.
- Low serum chloride and elevated serum bicarbonate levels indicate metabolic alkalosis.
- Arterial blood gases with a normal or elevated pH indicates metabolic alkalosis that may or may not be compensated.
- Hypokalemia may occur from gastrointestinal potassium losses and intracellular potassium shifts to compensate for alkalosis.

TREATMENT

Desired Outcomes

The primary goal of treatment is to relieve the symptoms of nausea and vomiting, which should increase the patient's quality of life. Drug therapy for nausea and vomiting should be safe, effective, and economical.

General Approach to Treatment

❷ *To treat nausea and vomiting most effectively, it is important to first identify the underlying cause of the symptoms.* Treating the cause (if possible) will in turn eliminate the nausea and vomiting.

Profuse or prolonged vomiting can lead to complications of dehydration and metabolic abnormalities. Patients must have adequate hydration and electrolyte replacement orally (if tolerated) or intravenously to prevent and correct these problems. Some pharmacologic treatments work locally in the GI tract (e.g., antacids and prokinetic agents), whereas others work in the central nervous system (e.g., antihistamines and antiemetics).[1]

Nonpharmacologic Therapy

A variety of effective pharmacologic treatments exist for nausea and vomiting, but they all have unwanted adverse treatment effects. For this reason, nonpharmacologic treatment options may be considered in selected patients.

Nonpharmacologic options are desirable for treating NVP due to concern for teratogenic effects with drug therapies. When treating PONV, the nonpharmacologic approach is appealing to minimize additive CNS depression with antiemetics and anesthetic agents. ❸ *Nonpharmacologic approaches to treating nausea and vomiting include dietary, physical, and psychological changes.*

Dietary approaches are the cornerstone of treatment for NVP.[11] They are included in treatment guidelines even though there is little evidence to support their effectiveness.[9] Recommendations include eating frequent, small meals; avoiding spicy or fatty foods; eating high-protein snacks; and eating bland or dry foods the first thing in the morning.[9,11] In addition to dietary changes, there is some evidence that women taking a multivitamin at the time of conception are less likely to seek medical attention for NVP.[9]

Acupressure and acupuncture have been investigated based on the theory that certain points on the body control specific bodily functions.[11] The P6 (Neiguan) point on the inside of the wrist has been used historically by acupuncturists to treat nausea and vomiting. While this approach seems safe and cost effective, efficacy data in the treatment of NVP are conflicting. The majority of studies showed a benefit to this approach, but the studies had methodologic flaws.[9,11,12]

Acupressure has also been investigated as a preventative tool for PONV and motion sickness.[13,14] Acupressure wrist bands may be effective in preventing PONV after short surgical procedures when applied prior to exposure to emetic stimuli such as anesthetic agents.[13] In contrast, the bands were not effective for preventing nausea and vomiting due to motion sickness in one study.[14]

Hypnosis may be effective for severe NVP.[11] Psychotherapy is another non-invasive treatment approach that is safe during pregnancy or in situations in which adverse treatment effects and drug interactions are a concern. One small study suggested that patients with hyperemesis gravidarum may benefit from the combination of psychotherapy and antiemetics.

Pharmacologic Therapy

Table 17–2 contains the names, usual adult dosages, and common adverse effects of the pharmacologic treatments for nausea and vomiting.[1,4,10]

Antacids and Antisecretory Agents

Antacids act locally in the stomach by neutralizing gastric acid and can be used to relieve nausea and vomiting related to gastric acid or heartburn.[4] Common antacids include magnesium hydroxide, aluminum hydroxide, and calcium carbonate. Antacids are generally safe when used infrequently but can cause diarrhea or constipation, which is product dependent (see Chapter 14 on gastroesophageal reflux disease for more detailed information on antacids). Because these agents are available over the counter (OTC), they are often used as first-line therapy.

The histamine$_2$-receptor antagonists or H_2RAs (cimetidine, famotidine, nizatidine, and ranitidine) and proton pump inhibitors (omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole) reduce the amount of acid secreted into the stomach by gastric parietal cells. These agents are also helpful for nausea and vomiting related to gastric acid secretion.

Anticholinergics (Scopolamine)

The anticholinergic agent scopolamine blocks muscarinic receptors in the vestibular system, thereby halting signaling to the central nervous system (CNS). It is effective for preventing and treating motion sickness and perhaps for preventing PONV as well.[15,16] Scopolamine is available as an adhesive transdermal patch that is effective for up to 72 hours after application. This may be beneficial for patients unable to tolerate oral medications or those requiring continuous prevention of motion sickness (e.g., passengers on cruise ships). Scopolamine is associated with adverse anticholinergic effects such as sedation, visual disturbances, dry mouth, and dizziness.

Antihistamines

Antihistamines are commonly used to prevent and treat nausea and vomiting due to motion sickness, vertigo, or migraine headache.[1,17] Their efficacy is presumably due to the high concentration of histamine (H_1) and muscarinic cholinergic receptors within the vestibular system. Similarly to scopolamine, antihistamines such as diphenhydramine and

TABLE 17–2. Antiemetic Agents: Adult Doses and Adverse Effects

Drug	Adult Dosing	Adverse Effects[a]
Antacids		
Magnesium hydroxide, aluminum hydroxide, calcium carbonate, others	15–30 mL every 2–4 hours as needed	Diarrhea, constipation
H_2-Receptor Antagonists		
Cimetidine (Tagamet HB)	200 mg twice daily as needed	Most common: Headache, diarrhea
Famotidine (Pepcid AC)	10 mg twice daily as needed	Less common: Constipation
Nizatidine (Axid AR)	75 mg twice daily as needed	Rare: Anemia, elevated hepatic transaminases
Ranitidine (Zantac 75)	75 mg twice daily as needed	
Proton Pump Inhibitors		
Esomeprazole (Nexium)	20 mg once daily as needed	Most common: Headache
Lansoprazole (Prevacid)	15 mg once daily as needed	Less common: Diarrhea, abdominal pain, nausea, vomiting
Omeprazole (Prilosec)	20 mg once daily as needed	Rare: Elevated hepatic transaminases, hyperglycemia
Pantoprazole (Protonix)	40 mg once daily as needed	
Rabeprazole (Aciphex)	20 mg once daily as needed	
Anticholinergics		
Scopolamine (Transderm Scop)	0.5 mg every 72 hours as needed	Most common: Dry mouth, drowsiness, impaired eye accommodation Rare: Disorientation, memory disturbances, dizziness, hallucinations
Antihistamines		
Cyclizine (Marezine)	50 mg every 4–6 hours as needed	Most common: Sedation, dry mouth, constipation
Dimenhydrinate (Dramamine)	50–100 mg every 4–6 hours as needed	Less common: Confusion, blurred vision, urinary retention
Diphenhydramine (Benadryl)	10–150 mg every 4–6 hours as needed	
Hydoxyzine (Atarax, Vistaril)	25–100 mg every 6 hours as needed	
Meclizine (Bonine, Antivert)	25–50 mg every 24 hours as needed	
Phenothiazines		
Chlorpromazine (Thorazine)	10–25 mg every 4–6 hours as needed	Most common: Sedation, lethargy, skin sensitization
Chlorpromazine suppository	50–100 mg every 6–8 hours as needed	Less common: Cardiovascular effects, extrapyramidal effects, cholestatic jaundice, hyperprolactinemia
Prochlorperazine (Compazine)	5–10 mg 3–4 times daily as needed	Rare: Neuroleptic malignant syndrome, hematologic abnormalities
Prochlorperazine suppository	25 mg twice daily as needed	
Promethazine (Phenergan)	12.5–25 mg every 4–6 hours as needed	
Thiethylperazine (Torecan)	10 mg 3 times daily	
Butyrophenones		
Droperidol (Inapsine)	2.5–5 mg every 4–6 hours as needed	Most common: Sedation, hypotension, tachycardia
Haloperidol (Haldol)	1–5 mg every 12 hours as needed	Less common: Extrapyramidal effects, dizziness, increase in blood pressure, chills, hallucinations
Benzamides		
Domperidone (Motilium)[b]	10–20 mg 3 times daily as needed	Most common: Sedation, restlessness, diarrhea (metoclopramide), agitation, central nervous system depression
Metoclopramide (Reglan)	PONV: 10–20 mg 10 minutes prior to anesthesia; CINV: 1–2 mg/kg every 2 hours × 2, then every 3 hours × 3; Delayed CINV: 0.5 mg/kg *or* 20 mg every 6 hours as needed, days 2–4	Less common: Extrapyramidal effects (more frequent with higher doses), hypotension, neuroleptic syndrome, supraventricular tachycardia (with intravenous administration)
Trimethobenzamide (Tigan)	200–250 mg 3 to 4 times daily as needed	
Corticosteroids		
Dexamethasone (Decadron)	10 mg prior to chemotherapy, repeat with 4–8 mg every 6 hours for a total of 4 doses	Most common: Gastrointestinal upset, anxiety, insomnia Less common: Hyperglycemia, facial flushing,euphoria, perineal itching or burning (with dexamethasone, probably secondary to vehicle and rate of injection)
Methylprednisolone (Solu-Medrol)	125–500 mg every 6 hours for total of 4 doses	
Cannabinoids		
Dronabinol (Marinol)	5–7.5 mg/m^2 every 2–4 hours as needed	Most common: Drowsiness, euphoria, somnolence, vasodilation, vision difficulties, abnormal thinking, dysphoria
Nabilone (Cesamet)	1–2 mg 2–3 times daily as needed	Less common: Diarrhea, flushing, tremor, myalgia

(*Continued*)

TABLE 17-2. Antiemetic Agents: Adult Doses and Adverse Effects *(Continued)*

Drug	Adult Dosing	Adverse Effects[a]
Benzodiazepines		
Lorazepam (Ativan)	0.5–2 mg prior to chemotherapy	Most common: Sedation, amnesia Rare: Respiratory depression, ataxia, blurred vision, hallucinations, paradoxical reactions (weeping, emotional reactions)
Serotonin Antagonists		
Dolasetron (Anzemet)	1.8 mg/kg intravenously 30 minutes prior to chemotherapy *or* 100 mg orally within 1 hour before chemotherapy	Most common: Headache, asymptomatic prolongation of electrocardiographic interval Less common: Constipation, asthenia, somnolence, diarrhea, fever, tremor or twitching, ataxia, lightheadedness, dizziness, nervousness, thirst, muscle pain, warm or flushing sensation on intravenous administration Rare: Transient elevations in hepatic transaminases
Granisetron (Kytril)	10 mcg/kg intravenously prior to chemotherapy *or* 1 mg orally up to 1 hour prior to chemotherapy and 1 mg 12 hours after the first dose, or 2 mg up to 1 hour prior to chemotherapy	
Ondansetron (Zofran)	32 mg intravenously prior to chemotherapy as a single dose, or 0.15 mg/kg prior to chemotherapy, repeat at 4 and 8 hours *or* 8 mg orally 30 minutes prior to chemotherapy, repeat at 4 and 8 hours and every 12 hours for 1–2 days after chemotherapy completion	
Palonosetron (Aloxi)	0.25 mg intravenously 30 minutes prior to chemotherapy	
Neurokinin-1 Antagonist		
Aprepitant (Emend)	125 mg on day 1, 1 hour prior to chemotherapy; 80 mg on days 2 and 3	Most common: Fatigue, hiccups Less common: Dizziness, headache, insomnia Rare: Transient elevations in hepatic transaminases

[a]Most common, greater than 10%, less common, 1–10%, rare, less than 1%. Based on FDA-approved labeling and generalized to the drug class.
[b]Not available in the United States.
CINV, chemotherapy-induced nausea and vomiting; PONV, postoperative nausea and vomiting.

meclizine cause undesired effects including drowsiness and blurred vision. Cetirizine and fexofenadine, two second-generation antihistamines without CNS depressant properties, were found to be ineffective for treating motion sickness, perhaps because they lack CNS effects.[17]

Some antihistamines such as diphenhydramine, dimenhydrinate, and meclizine are available without a prescription, making self-treatment convenient for patients. Antihistamines are available in a variety of dosage forms, including oral capsules, tablets and liquids. Liquid formulations are convenient for children or adults who are unable to swallow solid dosage forms.

Dopamine Antagonists

Stimulation of dopamine (D_2) receptors in the CTZ leads to nausea and vomiting (Fig. 17–1). Phenothiazine antiemetics act primarily via a central antidopaminergic mechanism in the CTZ.[1] Common phenothiazines that have long been used for treating nausea and vomiting include promethazine, prochlorperazine, chlorpromazine, and thiethylperazine. They are available as oral solids and liquids, rectal suppositories, and parenteral formulations. This permits effective use of phenothiazines in a variety of settings including treatment of severe motion sickness or vertigo, gastritis or gastroenteritis, NVP, PONV, or CINV.[5,6,9,18–20]

Phenothiazines may cause sedation, orthostatic hypotension, and **extrapyramidal symptoms** (EPS) such as dystonia (involuntary muscle contractions), tardive dyskinesia (irreversible and permanent involuntary movements), and akathisia (motor restlessness or anxiety).[1,21,22] Chronic phenothiazine use has been associated with EPS, but single doses have also caused these effects.[23]

Akathisia is disturbing for patients and can be disruptive to patient care. Giving diphenhydramine with prochlorperazine may reduce the incidence of akathisia, but the combination increases the risk of sedation.[24] Slowing the intravenous infusion rate of prochlorperazine does not decrease akathisia.[22,23]

Droperidol, a butyrophenone derivative, is another centrally-acting anti-dopaminergic agent effective for preventing PONV and treating opioid-induced nausea and vomiting.[1,6] It is also used for treating CINV for patients who are intolerant to serotonin receptor antagonists and corticosteroids.[5]

Adverse effects of droperidol include sedation, agitation, and restlessness. In addition, droperidol carries a United States Food and Drug Administration (FDA) black box warning regarding the potential for QT interval prolongation and cardiac arrhythmias that may result in torsades de pointes and sudden cardiac death.[25] Droperidol should not be used in patients with a prolonged QT interval or in those who are at risk for developing a prolonged QT interval (e.g., heart failure, electrolyte abnormalities, or concurrently taking other medications that may prolong the QT interval).[25] A 12-lead electrocardiogram (ECG) is recommended prior to treatment with droperidol.

The substituted benzamides metoclopramide and domperidone (not available in the United States) act as dopamine (D_2) antagonists both centrally in the CTZ and peripherally in the GI tract.[1,26] They also display cholinergic activity, which increases lower esophageal sphincter tone and promotes gastric motility. Metoclopramide at high doses has antiserotonergic properties as well. Because metoclopramide and domperidone have both antiemetic and prokinetic effects, both are used for a variety of disorders including PONV, CINV, NVP, gastroparesis, GERD, and migraine headaches.[1,5,6,9,27–29] Metoclopramide is available in injectable, oral solid, and oral liquid dosage forms, allowing for its use in both hospitalized and ambulatory patients. Other substituted benzamides include trimethobenzamide and benzquinamide.

Metoclopramide crosses the BBB and has centrally-mediated adverse effects. Young children and the elderly are especially susceptible to these effects, which include somnolence, reduced mental acuity, anxiety, depression, and EPS (akathisia, dystonia, and tardive dyskinesia).[30] The overall incidence of adverse effects is estimated to be 10% to 20%.[1]

Domperidone minimally crosses the BBB; it acts in the CTZ which lies outside of the BBB. As such, domperidone is less likely to cause the centrally-mediated adverse effects seen with metoclopramide and has an estimated overall incidence of 5% to 10%.[1,30] However, domperidone has been associated with prolonged QT intervals, cardiac arrhythmias, and sudden death.[31] It should not be used for patients with underlying long QT interval or for those on other medications that prolong the QT interval. Both metoclopramide and domperidone can cause hyperprolactinemia, galactorrhea, and gynecomastia.

Corticosteroids

Corticosteroids, especially dexamethasone and methylprednisolone, are used alone or in combination with other antiemetics for preventing and treating CINV or radiation-induced nausea and vomiting.[5,10] They are administered either orally or intravenously. Their efficacy is thought to be due to release of 5-HT, reduction in the permeability of the BBB, and reduction of inflammation.[32] Common adverse effects with short-term use include gastrointestinal upset, anxiety, insomnia, and hyperglycemia.[10] Because treatment for CINV is generally of short duration, long-term adverse effects (e.g., reduction in bone mineral density, corticosteroid-related diabetes, and cataracts) are not usually seen.

Cannabinoids

Cannabinoids have antiemetic activity when used alone or in combination with other antiemetics.[5] Dronabinol and nabilone are commercially available oral formulations used for preventing and treating refractory CINV.[5,10] Dronabinol is also used to treat anorexia and weight loss associated with human immunodeficiency virus (HIV) infection. Cannabinoids are thought to exert their antiemetic effect centrally, although the exact mechanism of action is unknown.[1,10] Sedation, euphoria, hypotension, ataxia, dizziness, and vision difficulties can occur with cannabinoids.

Benzodiazepines

Benzodiazepines, especially lorazepam, are used to prevent and treat CINV.[5,10] Lorazepam is thought to prevent input from the cerebral cortex and limbic system from reaching the central vomiting center in the brain stem.[10] Sedation and amnesia are common side effects. Respiratory depression can occur with high doses or when other central depressants such as alcohol are combined with benzodiazepines.

Serotonin Antagonists

Chemotherapeutic agents cause release of 5-hydroxytryptamine (5-HT, serotonin) from enterochromaffin cells in the intestinal mucosa.[32] This increase in 5-HT concentrations leads to stimulation of the visceral vagal nerve fibers and CTZ, thereby triggering nausea and vomiting. Both the CTZ and the vagal visceral nerve fibers are rich in 5-HT_3 receptors.[2] Selective 5-HT_3 receptor antagonists (ondansetron, granisetron, dolasetron, and palonosetron) are available to prevent and treat nausea and vomiting due to stimulation of these receptors, especially for prevention and treatment of CINV.[5,10,32] They are also used to treat PONV.[6] These agents are well tolerated; the most common adverse effects are headache, somnolence, diarrhea, and constipation.[10] Asymptomatic electrocardiograph changes have also been reported.

Neurokinin-1 Receptor Antagonists

Aprepitant is the first NK_1 receptor antagonist antiemetic drug.[33] NK_1 receptors are present in the CTZ and GI tract and are involved

in the nausea and vomiting response, especially CINV.[10,32] Aprepitant is effective for preventing acute and delayed CINV when used with a 5-HT_3 antagonist and a corticosteroid.[33,34]

Chemotherapy-Induced Nausea and Vomiting

CINV is classified as: (1) acute (occurring within 24 hours after receiving chemotherapy); (2) delayed (occurring more than 24 hours after receiving chemotherapy); or (3) anticipatory (occurring prior to chemotherapy in patients who experienced acute or delayed nausea and vomiting with previous courses).[10] Risk factors for CINV include poor emetic control with prior chemotherapy, female gender, low chronic alcohol intake, and younger age.[5] Chemotherapeutic agents are classified according to their emetogenic potential (Table 17–3), which aids in predicting CINV.[35] Risk factors that are useful in predicting anticipatory nausea and vomiting include poor prior control of CINV and a history of motion sickness or NVP.[5,10]



Patient Encounter 1

A 28-year-old healthy woman seeks your advice. She is about to leave on a 7-day Caribbean cruise and is concerned about motion sickness. She recently experienced nausea and one episode of vomiting while on a sailboat on Lake Michigan for an afternoon. She is not allergic to any medications. She does not smoke and only occasionally drinks alcohol. She takes an oral contraceptive (ethinyl estradiol and norgestimate) and occasional ibuprofen for headaches.

- What nonpharmacologic and pharmacologic options are available for this woman?
- How would you instruct her to use the recommended modalities?
- What adverse effects would you discuss with her?

TABLE 17–3. Emetogenicity of Chemotherapeutic Agents

Lowest Emetogenic Potential
Androgens
Bleomycin
Busulfan (oral less than 4 mg/kg per day)
Capecitabine (oral)
Chlorambucil (oral)
Cladribine
Corticosteroids
Doxorubicin (liposomal)
Fludarabine
Hydroxyurea
Interferon
Melphalan (oral)
Mercaptopurine
Methotrexate (less than or equal to 50 mg/m^2)
Thioguanine (oral)
Tretinoin
Vinblastine
Vincristine
Vinorelbine
Low Emetogenic Potential
Asparaginase
Cytarabine (less than 1 g/m^2)
Docetaxel
Doxorubicin HCl (less than 20 mg/m^2)
Etoposide
Fluorouracil (less than 1 g/m^2)
Gemcitabine
Methotrexate (greater than 50 mg/m^2; less than 250 mg/m^2)
Mitomycin
Paclitaxel
Teniposide
Thiotepa
Topotecan
Moderate Emetogenic Potential
Aldesleukin
Cyclophosphamide (IV, less than or equal to 750 mg/m^2)
Dactinomycin (less than or equal to 1.5 mg/m^2)
Doxorubicin HCl (20–60 mg/m^2)
Epirubicin HCl (less than or equal to 90 mg/m^2)
Idarubicin
Ifosfamide
Methotrexate (250–1000 mg/m^2)
Mitoxantrone (less than or equal to 15 mg/m^2)
High Emetogenic Potential
Carboplatin
Carmustine (less than 250 mg/m^2)
Cisplatin (50 mg/m^2)
Cyclophosphamide (greater than 750 mg/m^2 to less than or equal to 1500 mg/m^2)
Cytarabine (greater than or equal to 1g/m^2)
Dactinomycin (greater than 1.5 mg/m^2)
Doxorubicin HCl (greater than 60 mg/m^2)
Irinotecan
Melphalan (IV)
Methotrexate (greater than 1 g/m^2)
Mitoxantrone (greater than 15 mg/m^2)
Oxaliplatin
Highest Emetogenic Potential
Carmustine (greater than 250 mg/m^2)
Cisplatin (greater than 50 mg/m^2)
Cyclophosphamide (greater than 1500 mg/m^2)
Dacarbazine (greater than or equal to 500 mg/m^2)
Lomustine (greater than 60 mg/m^2)
Mechlorethamine
Pentostatin
Streptozocin

Data from DiPiro CV, Taylor AT. Nausea and vomiting. In: DiPiro JT, Talbert RL, Yee GC, et al., (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 665–676, and Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997; 15:103–109.

❹ *For prophylaxis of acute CINV, the combination of a 5-HT$_3$ antagonist and corticosteroid is recommended for patients receiving highly emetogenic cisplatin or non–cisplatin-based chemotherapy.*[5,10] Patients receiving moderately emetogenic chemotherapy should receive a corticosteroid such as dexamethasone or methylprednisolone alone, whereas patients receiving chemotherapy unlikely to cause CINV should not require prophylaxis.[5,10]

Antiemetics can be administered either intravenously or orally in this situation, depending on patient characteristics such as ability to take oral medications, dosage form availability, and cost considerations.[5,10] The intravenous and oral routes are equally effective. When used at equipotent doses, the 5-HT$_3$ antagonists have similar efficacy in preventing acute CINV, despite pharmacokinetic and receptor binding affinity differences.[5,10,36]

Patients undergoing chemotherapy should have antiemetics available to treat breakthrough nausea and vomiting even if prophylactic antiemetics were given.[10] A variety of antiemetics may be used, including lorazepam, dexamethasone, methylprednisolone, prochlorperazine, promethazine, metoclopramide, and dronabinol. The 5-HT$_3$ antagonists are effective for treating breakthrough nausea and vomiting, but they have not been shown to be superior to more traditional and less expensive antiemetics.

Delayed nausea and vomiting is more difficult to prevent and treat. It occurs most often with cisplatin- and cyclophosphamide-based regimens, especially if delayed nausea and vomiting occurred with previous courses of chemotherapy.[10] Patients at greatest risk are those who previously had poorly-controlled acute CINV.[5] Patients receiving highly emetogenic chemotherapy should receive a corticosteroid plus metoclopramide or a 5-HT$_3$ antagonist to prevent delayed nausea and vomiting.[5,10] Intermediate or low emetogenic chemotherapy regimens do not require prophylactic regimens for delayed nausea and vomiting.

The NK$_1$ receptor antagonist aprepitant has shown promise for preventing delayed nausea and vomiting.[33,34,37,38] When aprepitant was added to a standard antiemetic regimen for patients receiving cisplatin-based highly emetogenic chemotherapy, complete response rates (no emesis and no rescue therapy) were significantly improved for both acute and delayed nausea and vomiting.[34,37] Aprepitant may also benefit patients receiving moderately emetogenic chemotherapy, but more data are needed.[33,39]

The 5-HT$_3$ antagonist palonosetron is the first 5-HT$_3$ antagonist to be approved for prevention of both acute and delayed CINV.[40] Compared to the other 5-HT$_3$ antagonists, palonosetron has a longer serum half-life (40 hours compared to 4 to 9 hours) and a higher receptor binding affinity, which may contribute to its efficacy in preventing delayed CINV.[41]

The best strategy for preventing anticipatory nausea and vomiting is to prevent acute and delayed CINV by using the most effective antiemetic regimens recommended based on the emetogenic potential of the chemotherapy and patient factors. CINV should be aggressively prevented with the first cycle of therapy rather than waiting to assess patient response to less effective regimens. If anticipatory nausea and vomiting occurs, benzodiazepines and behavioral therapy such as relaxation techniques are the suggested approaches.[1,5]

Postoperative Nausea and Vomiting

PONV is a common complication of surgery and can lead to delayed discharge and unanticipated hospitalization.[6] The overall incidence of PONV for all surgeries and patient populations is 25% to 30%, but PONV can occur in 70% to 80% of high-risk patients.[6,26] Risk factors for PONV include patient factors (female gender, non-smoking status, and history of PONV or motion sickness), anesthetic factors (use of volatile anesthetics, nitrous oxide, or intraoperative or postoperative opioids), and surgical factors (duration and type of surgery).[6,8,26]

The first step in preventing PONV is reducing baseline risk factors when appropriate.[6] Regional anesthesia rather than general anesthesia should be used. Opioids should be replaced



Patient Encounter 2

A 57-year-old woman is scheduled for an abdominal hysterectomy due to uterine fibroids. She is very anxious about her surgery.

PMH
Uterine fibroids
Hypertension × 6 years
Hypercholesterolemia × 6 years

FH
Father died of lung cancer; mother is still alive with a history of hypertension and cerebrovascular accident

SH
Works as a high school teacher; drinks one glass of wine with dinner three times per week; does not use tobacco

Med
Hydrochlorothiazide 25 mg PO once daily
Lisinopril 20 mg PO once daily
Simvastatin 40 mg PO once daily at bedtime
Aspirin 81 mg PO once daily
Acetaminophen as needed for headache or body aches

Labs
Within normal limits

ECG: Normal sinus rhythm
Anesthesia for the surgery will be thiopental 4.5 mg/kg, atracurium 0.5 mg/kg, and fentanyl 0.05 mg followed by tracheal intubation, 70% nitrous oxide, and 0.5% to 2% isoflurane in oxygen.

- What risk factors for PONV does this patient have?
- Identify your treatment goals for this patient.
- What nonpharmacologic and pharmacologic measures can be taken to prevent PONV?
- Discuss any contraindications or adverse effects associated with your recommended treatments.

with other analgesics such as non-steroidal anti-inflammatory drugs. Nitrous oxide and volatile inhaled anesthetics should be avoided.

❺ *Droperidol or a 5-HT_3 receptor antagonist should be administered at the end of surgery to patients at high risk for developing postoperative nausea and vomiting.*[1,6,7,26,42] Dexamethasone is also effective when given as a single dose prior to induction of anesthesia.[6,42,43] Anticholinergics and antihistamines are also effective for preventing PONV.[6]

Combinations of antiemetics may be the most effective method of preventing PONV for high-risk patients.[7,42] Droperidol plus a 5-HT_3 antagonist or dexamethasone plus a 5-HT_3 antagonist are effective combinations.[43,44] Three-drug combinations such as dexamethasone, droperidol, and a 5-HT_3 antagonist have not been formally studied but may be a reasonable approach.[42]

Nausea and Vomiting of Pregnancy

❻ *Nausea and vomiting of pregnancy affect the majority of pregnant women; the* ***teratogenic potential*** *of the therapy is the primary therapeutic consideration.*[9] Risks and benefits of any therapy must be weighed by the health care professional and the patient.

Nonpharmacologic therapy such as dietary, physical, and behavioral approaches should be considered first. Pyridoxine (vitamin B_6) 10 to 25 mg three to four times daily alone or in combination with an antihistamine such as doxylamine is often used for NVP.[9,11,12] This combination was previously marketed as Bendectin or Debendox but was withdrawn due to concerns over possible teratogenic effects, although the literature did not support this claim.[11,12] Pyridoxine is well tolerated, but doxylamine and other antihistamines commonly cause drowsiness. For more severe NVP, promethazine, metoclopramide, and trimethobenzamide may be effective and have not been associated with teratogenic effects.[9]

In rare instances (0.5% to 2% of pregnancies), NVP progresses to hyperemesis gravidarum.[9] Treatment may require the use of enteral or parenteral nutrition if weight loss is present. A corticosteroid such as methylprednisolone may be considered. Methylprednisolone is associated with oral clefts in the fetus when used during the first trimester; therefore, corticosteroids should be reserved as a last resort and should be avoided during the first 10 weeks of gestation.[9,11]

Motion Sickness and Vestibular Disturbances

Nausea and vomiting can be caused by disturbances of the vestibular system in the inner ear.[18] Vestibular disturbances can result from infection, traumatic injury, neoplasm, and motion. Patients may experience dizziness and vertigo in addition to nausea and vomiting. If a patient is susceptible to motion sickness, some general preventive measures include minimizing exposure to movement, restricting visual activity, ensuring adequate ventilation, reducing the magnitude of movement, and taking part in distracting activities.[45]



Patient Encounter 1, Part 2

Four months later, the patient returns to your practice. She is 8 weeks pregnant and complains of nausea and occasional vomiting. She is only taking prenatal vitamins. She does not smoke or drink alcohol. She was told at her last prenatal visit that she was appropriately gaining weight. She asks for your advice about preventing and treating nausea and vomiting.

- What general considerations about treating nausea and vomiting of pregnancy will you discuss with this patient?
- What nonpharmacologic and pharmacologic treatment options are available for her?

❼ *Because the vestibular system is replete with muscarinic-type cholinergic and histaminic (H_1) receptors, anticholinergics and antihistamines are the most commonly used pharmacologic agents to prevent and treat motion sickness.* Oral medications should be taken prior to motion exposure to allow time for adequate absorption. Once nausea and vomiting due to motion sickness occur, oral medication absorption may be unreliable, making the therapies ineffective. Scopolamine, the anticholinergic medication used for motion sickness, is available as a transdermal patch delivery system, which may be helpful for patients who cannot tolerate oral medications or who require treatment for a prolonged period. Drowsiness and reduced mental acuity are the most bothersome side effects of antihistamines and anticholinergics. Visual disturbances, dry mouth, and urinary retention can also occur.

OUTCOME EVALUATION

- The symptoms of simple nausea and vomiting are self-limited or can be relieved with minimal treatment. Monitor patients for adequate oral intake and alleviation of nausea and vomiting.
- Patients with complex nausea and vomiting may have malnourishment, dehydration, and electrolyte abnormalities.
  - Monitor patients for adequate oral intake. If the patient has weight loss, assess whether enteral or parenteral nutrition is needed.
  - Assess for dry mucous membranes, skin tenting, tachycardia, and lack of axillary sweat to determine if dehydration is present.
  - Obtain blood urea nitrogen (BUN), serum creatinine (SCr), calculated fractional excretion of sodium (FeNa), serum electrolytes, and arterial blood gases.
- Ask patients to rate the severity of nausea.
- Monitor the number and volume of vomiting episodes.
- Ask patients about adverse effects to the antiemetics used. Use this information to assess efficacy and tailor the patient's antiemetic regimen.



Patient Care and Monitoring

1. Identify the underlying cause of the nausea and vomiting and eliminate it if possible. Counsel the patient to avoid known triggers.
2. Assess the patient to determine whether the nausea and vomiting is simple or complex and whether patient-directed therapy is appropriate.
3. Obtain a thorough patient history including the prescription, non-prescription, and herbal medications being used. Identify any substances that may be causing or worsening nausea and vomiting. Determine which treatments for nausea and vomiting have been used in the past and their degree of efficacy.
4. Develop a treatment plan with the patient and other health care professionals if appropriate. Choose therapeutic options based on the underlying cause of nausea and vomiting, duration and severity of symptoms, comorbid conditions, medication allergies, presence of contraindications, risk of drug-drug interactions, and treatment adverse-effect profiles.
5. Use the oral route of administration if the patient has mild nausea with minimal or no vomiting. Seek an alternative route (e.g., transdermal, rectal suppository, or parenteral) if the patient is unable to retain oral medications due to vomiting.
6. Educate the patient about nonpharmacologic measures such as stimulus avoidance, dietary changes, acupressure or acupuncture, and psychotherapy.
7. To assess efficacy, ask the patient whether he or she is still experiencing nausea or vomiting while using the therapy. Assess whether treatment failure is due to inappropriate medication use or the need for additional or different treatments and proceed accordingly.
8. Assess for adverse effects by asking the patient what he or she has experienced. Also, patient observation or examination is useful for diagnosing adverse effects such as EPS.
9. Provide patient education regarding causes of nausea and vomiting, avoidance of triggers, potential complications, therapeutic options, medication adverse effects, and when to seek medical attention.

ABBREVIATIONS

BBB:	blood–brain barrier
BUN:	blood urea nitrogen
CINV:	chemotherapy-induced nausea and vomiting
CNS:	central nervous system
CTZ:	chemoreceptor trigger zone
D_2:	dopamine type 2 receptor
ECG:	electrocardiogram
EPS:	extrapyramidal symptom
FDA:	United States Food and Drug Administration
FeNa:	fractional excretion of sodium
GERD:	gastroesophageal reflux disease
GI:	gastrointestinal
H_1:	histamine type 1 receptor
HIV:	human immunodeficiency virus
H_2RA:	$histamine_2$-receptor antagonist
5-HT_3:	5-hydroxytryptamine (serotonin) type 3 receptors
NK_1:	neurokinin type 1 receptors
NVP:	nausea and vomiting of pregnancy
OTC:	over the counter
PONV:	postoperative nausea and vomiting
SCr:	serum creatinine

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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18 Constipation, Diarrhea, and Irritable Bowel Syndrome

Beverly C. Mims and Clarence E. Curry, Jr.



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Identify the causes of constipation.
2. Compare the features of chronic constipation with those of constipation-predominant irritable bowel syndrome (IBS).
3. Recommend lifestyle modifications and therapeutic interventions for the treatment of constipation.
4. Distinguish between acute and chronic diarrhea.
5. Compare and contrast diarrhea caused by different infectious agents.
6. Explain how medication use can lead to diarrhea.
7. Discuss nonpharmacologic strategies for treating diarrhea.
8. Identify the signs and symptoms of IBS.
9. Contrast diarrhea-predominant IBS and constipation-predominant IBS.
10. Discuss the goals of IBS treatment.
11. Evaluate the effectiveness of principal pharmaceutical therapies for IBS.

Key Concepts

❶ Constipation has been defined in many ways and it is important to know what is meant when the term is used.
❷ Chronic constipation exists when symptoms last for at least 3 months.
❸ Lifestyle modifications should be employed prior to the use of laxatives in most instances of constipation.
❹ Oral laxatives are the primary pharmacologic intervention for relief of constipation.
❺ When diarrhea is severe and oral intake is limited, dehydration can occur, particularly in the elderly and infants.
❻ The primary treatment of acute diarrhea includes fluid and electrolyte replacement, dietary modifications, and drug therapy.
❼ IBS is generally described as a functional disorder rather than a distinct disease entity.
❽ IBS symptoms typically cluster around two main types: diarrhea-predominant IBS and constipation-predominant IBS.
❾ Diagnosis of IBS is made by symptom-based criteria and the exclusion of organic disease.
❿ The principal goal of IBS treatment is to reduce or control symptoms.

CONSTIPATION

❶ *Constipation has been defined in many ways, and it is important to know what is meant when the term is used.* Constipation, when not associated with symptoms of irritable bowel syndrome (IBS), can be defined as a heterogeneous disorder characterized by disorganized passage of feces resulting in infrequent stools, difficult passage of stools or both.[1] It may be described as difficulty passing stool with too much effort, unproductive urges, too small amount of stool, too hard consistency of stool, painful elimination of stool, or a feeling of incomplete evacuation. The existence of some or all of these symptoms suggests the presence of constipation when the frequency of elimination of feces is limited to twice weekly or less or when more than 3 days have passed without elimination of stool. ❷ *Chronic constipation exists when symptoms last for at least 3 months.*

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EPIDEMIOLOGY AND ETIOLOGY

Constipation is a common complaint of patients seeking medical attention, and about one-third of patients with constipation seek medical treatment. Constipation occurs in approximately 20% of the population.[2] Approximately 2.5 million physician visits and 90,000 hospitalizations per year in the United States are due to constipation[3,4] Many medications and some disease states are associated with constipation. Constipation is associated with high socioeconomic costs and has considerable quality-of-life ramifications.[5]

Elderly patients, non-Caucasians, women, and those of lower educational and socioeconomic levels are more likely to report being constipated. Constipation in children can occur because of a change in the usual diet or fluid intake, a deviation from usual toileting routines such as during vacations, or avoidance of bowel movements because of pain associated with having a stool. Children who are diagnosed with severe constipation at a young age are likely to continue to suffer through puberty.

PATHOPHYSIOLOGY

Constipation can be due to primary and secondary causes (Table 18–1). Primary or idiopathic constipation is typified by normal-transit constipation, slow-transit constipation, and **dyssynergic defecation**. In the normal-transit type, colonic motility is unchanged and patients tend to experience hard stools despite normal movements. In the slow-transit type, motility is decreased leading to infrequent harder, drier stools. In dyssynergic defecation (also known as pelvic floor dysfunction), patients have lost the ability to relax the anal sphincter while coordinating muscle contractions of the pelvic floor. Some causes of secondary constipation are listed in Table 18–1.

TABLE 18–1. Causes of Constipation

Primary Causes
Normal-transit constipation (includes idiopathic or functional disorders)
Slow-transit constipation (includes motility disorders)
Defecatory or rectal evacuation disorders (e.g., Hirschsprung's disease, pelvic floor dyssynergia)
Secondary Causes (selected)
Endocrine/metabolic conditions (diabetes mellitus, hypothyroidism, hypercalcemia)
Gastrointestinal conditions (irritable bowel syndrome, diverticulitis, hemorrhoids)
Neurogenic conditions (brain trauma, spinal cord injury, cerebrovascular accident, Parkinson's disease)
Psychogenic (postponing the urge to defecate, psychiatric conditions)
Medications (analgesics, anticholinergerics, calcium channel blockers, clonidine, diuretics, phenothiazines, tricyclic antidepressants, iron supplements, calcium- and aluminum-containing antacids)
Miscellaneous (immobility, poor diet, laxative abuse, hormonal disturbances)

Constipation affects about 50% of pregnant women. Progesterone levels may be responsible in part for slowing digestion. Reabsorption mechanisms may affect colon water during pregnancy leading to harder stools and more difficult bowel movements. Intake of iron supplements may also contribute to constipation during pregnancy.

CLINICAL PRESENTATION AND DIAGNOSIS

Diagnosis

A complete history should be obtained so that the patient's symptoms can be evaluated and the diagnosis of constipation confirmed. The diagnosis of constipation is suggested by fewer than three bowel movements per week, consistency of hard lumpy stool, excessive straining, prolonged defecation time, or need to support the perineum or digitally manipulate the anorectum.

Dietary habits should be evaluated and attention paid to psychosocial issues. A complete family history should be obtained,



Clinical Presentation of Constipation

Symptoms

- Functional constipation (constipation occurring in the absence of a demonstrated pathologic condition) involves the presence of at least two of the following symptoms: straining, lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction or blockage, need for manual maneuvers to facilitate defecation and/or, infrequent (fewer than three) bowel movements per week.
- Other complaints may include painful or difficult defecation, bloating, and absence of loose stools.
- Alarm (or red flag) symptoms include worsening of constipation, blood in the stools, weight loss, fever, anorexia, nausea, and vomiting.
- The patient should seek medical attention when symptoms are severe, last longer than 3 weeks, are disabling, when alarm symptoms occur, or whenever a significant change in usual bowel habits occurs.

Laboratory Tests (to identify secondary causes)

- Thyroid function tests; abnormal thyroid hormone levels may suggest hypo- or hyperthyroidism, either of which may be associated with constipation.
- Serum calcium; either increased or decreased serum calcium levels may be associated with constipation.
- Glucose; increased blood glucose may indicate diabetes mellitus, which may be associated with constipation.
- Serum electrolytes; dehydration may be associated with constipation.
- Urinalysis may also indicate dehydration, if present.
- Complete blood count; anemia may be due to cancer or another systemic disorder accompanied by constipation.

particularly as it relates to inflammatory bowel disease and colon cancer. A full record of prescription and over-the-counter medications is mandatory to identify drug-related causes of constipation.

In most cases, there is no underlying cause of constipation, and the physical examination and rectal examination are normal. Sigmoidoscopy, barium enema, or colonoscopy alone or in combination are required in patients who have weight loss, rectal bleeding, or anemia with constipation. These examinations can be used to exclude the presence of cancer or strictures, especially in patients over the age of 50 years. **Sigmoidoscopy** alone is appropriate in patients without alarm symptoms and those younger than 50 years of age. However, all adults older than 50 years of age who present with new-onset constipation should undergo **colonoscopy** to rule out malignancy. When bleeding is present, a double-contrast **barium enema** may be ordered.

TREATMENT

Desired Outcomes

In patients with constipation, the principal goals are to: (1) identify and treat secondary causes, (2) relieve symptoms, and (3) restore normal bowel function.

Nonpharmacologic Therapy

❸ *Lifestyle modifications should be employed prior to the use of laxatives in most instances of constipation.* Constipation usually responds to dietary fiber supplementation, hydration, and exercise. Increasing fiber intake to 20 to 35 grams/day may help overcome constipation. Foods high in fiber include beans, whole grains, bran cereals, fresh fruits, and vegetables such as asparagus, brussels sprouts, cabbage, and carrots. Persons with constipation should avoid excessively processed low-fiber foods such as luncheon meats, hot dogs, certain cheeses, and ice cream.

Adequate fluid intake is also important; the recommended intake for people who do not require fluid restriction is 6 to 8 eight-ounce glasses of water daily.

Walking and other aerobic exercises help to tone the muscles of the lower abdominal area, which promotes propulsion in the bowel. Constipation is a frequent complaint of sedentary persons.

Each day most persons experience a strong peristaltic wave known as the gastrocolic reflex. A bowel movement usually follows. When the urge to have a bowel movement occurs, it should not be ignored. Some people put off having a stool for various reasons, which may lead to more difficulty in passing stool. Time should be planned daily to attempt having a stool. A busy lifestyle should not be allowed to interfere with normal bowel function.

Pharmacologic Therapy

❹ *Oral laxatives are the primary pharmacologic intervention for relief of constipation* (Table 18–2). There are several different drug classes, as described below.

Bulk-Forming Laxatives

These agents are either naturally derived (psyllium) or synthetic (methylcellulose). They act by swelling in intestinal fluid, forming a gel that aids in fecal elimination and promoting peristalsis. They may cause flatulence (which is less common with methylcellulose) and abdominal cramping. Bulk-forming laxatives must be taken with sufficient water to avoid becoming lodged in the esophagus and producing an obstruction. Bulk-forming laxatives must be taken with sufficient water to avoid becoming lodged in the esophagus and producing obstruction or worsening constipation.

Osmotic Laxatives

These products cause water to enter the lumen of the colon. Lactulose and sorbitol are osmolar, non-absorbable sugars. Magnesium containing products increase secretion of electrolytes

TABLE 18–2. Dosage Recommendations for Selected Laxatives and Cathartics

Agent	Recommended Adult Dose
Agents That Cause Softening of Feces in 1–3 Days	
Bulk-forming agents	
Methylcellulose	4–6 g/day
Polycarbophil	4–6 g/day
Psyllium	Varies with product
Emollients	
Docusate sodium	50–360 mg/day
Docusate calcium	50–360 mg/day
Docusate potassium	100–300 mg/day
Lactulose	15–30 mL orally
Sorbitol	30–50 g/day orally
Mineral oil	15–30 mL orally
Agents That Result in Soft or Semifluid Stool in 6–12 Hours	
Bisacodyl (oral)	5–15 mg orally
Phenolphthalein	30–270 mg orally
Cascara sagrada	Dose varies with formulation
Senna	Dose varies with formulation
Magnesium sulfate (low dose)	Less than 10 g orally
Agents That Cause Watery Evacuation in 1–6 Hours	
Magnesium citrate	18 g in 300 mL water
Magnesium hydroxide	2.4–4.8 g orally
Magnesium sulfate (high dose)	10–30 g orally
Sodium phosphates	Varies with salt used
Bisacodyl (suppository)	10 mg rectally
Polyethylene glycol-electrolyte preparations	4 L

From Spruill WJ, Wade WE. Diarrhea, constipation and irritable bowel syndrome. In DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill, Inc; 677–692, with permission.

and water into gut lumen. Products containing magnesium or sodium phosphate derivatives (saline laxatives) are most useful for acute bowel evacuation. A principal concern with these agents is that improper use can cause dehydration and electrolyte disturbances. Osmotic agents may cause flatulence, abdominal cramping, and bloating. Magnesium may accumulate inpatients with renal dysfunction.

Polyethylene glycol (PEG, MiraLax) is an osmotic laxative available only by prescription. It is useful in patients who are experiencing acute constipation and who have had inadequate response to more traditional agents. Principal adverse effects include upset stomach, bloating, cramping, and gas.

Lubricants

Lubricant laxatives work by coating the stool, which allows it to be expelled more easily. The oily film covering the stool also keeps the stool from losing its water to intestinal reabsorption processes. Mineral oil (liquid petrolatum) is a non-prescription heavy oil that should be used with caution, if at all, since it may be aspirated into the lungs and cause lipoid pneumonia. This is of particular concern in the young or the elderly.

Stimulant Laxatives

Diphenylmethane derivatives (e.g., bisacodyl) and anthraquinones (e.g., senna) have a selective action on the nerve plexus of intestinal smooth muscle leading to enhanced motility. The onset of effect is rapid but the effects can be harsh (cramping), depending on the dose taken. Castor oil is another member of this class that is used less frequently.

Emollients

Also known as surfactants and stool softeners, emollients (e.g., salts of docusate) act by increasing the surface wetting action on the stool leading to a softening effect. They reduce friction and make the stool easier to pass. These agents are not recommended for treating constipation of long duration.

Tegaserod Maleate

Tegaserod maleate (Zelnorm) is a partial serotonin (5-HT_4) receptor agonist that causes an increase in peristaltic activity and intestinal secretion and moderation of visceral sensitivity. It increases the frequency of bowel movements and reduces abdominal discomfort, bloating, and straining. It is indicated for the treatment of patients younger than 65 years of age who experience chronic idiopathic constipation. The most common adverse effects include headache, abdominal pain, diarrhea, and nausea.

Lubiprostone

Lubiprostone (Amitiza), a bicyclic acid oral agent, is approved for treatment of chronic idiopathic constipation in adults. It has not been studied in children. Lubiprostone acts locally on intestinal chloride channels and increases intestinal fluid secretion, resulting in increased intestinal motility and thereby increasing the passage of stool.[6]

Lubiprostone is contraindicated in patients with a history of mechanical gastrointestinal obstruction. Safety has not been established in pregnant women; animal studies indicated the potential to cause fetal loss. Women who could become pregnant should have a negative pregnancy test result prior to beginning therapy with lubiprostone.

Gastrointestinal adverse events reported with lubiprostone include nausea, diarrhea, abdominal distention, abdominal pain, flatulence, vomiting, loose stools, and dyspepsia. Nausea is a prominent adverse effect and may be minimized when lubiprostone is taken with food.

The recommended dose of lubiprostone is 24 mcg orally twice daily with food. Early studies evaluated lubiprostone use for no longer than 4 weeks. Patients should be assessed periodically for the need to continue therapy.

Treatment Recommendations

Slow-transit constipation can be treated with chronic administration of osmotic laxatives. Tegaserod maleate 6 mg orally twice daily is an acceptable treatment. Senna, bisacodyl, and other stimulants should be used only when the others fail to deliver the desired effect.

Laxatives may provide appropriate relief when constipation occurs during the postpartum period, when not breastfeeding and in immobile patients. Patients who are not constipated but who need to avoid straining (e.g., patients with hemorrhoids, hernia, or myocardial infarction) may benefit from stool softeners or mild laxatives.

Laxatives should not be given to children younger than 6 years of age unless prescribed by a physician. Because children may not be able to describe their symptoms well, they should be evaluated by a physician before being given a laxative. Treating secondary causes may resolve the constipation without the use of laxatives. As in adults, children benefit from a healthy balanced diet, adequate fluid, and regular exercise.

Because many elderly persons experience constipation, laxative use is sometimes viewed as a normal part of daily life. However, mineral oil can be a special hazard in bedridden elderly persons because it can lead to pneumonia through inhalation of oil droplets into the lungs. Lactulose may be a better choice in this situation. Regular use of any laxative that affects fluid and electrolytes may result in significant unwanted adverse effects.

Bulk-forming laxatives are commonly used during pregnancy. Stool softeners (Category C) should not be used during pregnancy. To avoid constipation pregnant women should be advised to eat regular meals that are balanced among fruit, vegetables and whole grains; maintain adequate water intake; and get appropriate exercise.

Patients with the following conditions should use laxatives only under the supervision of a health care provider: (1) colostomy; (2) diabetes mellitus (some laxatives contain large amounts of sugars such as dextrose, galactose, and/or sucrose; (3) heart disease (some products contain sodium; (4) kidney disease; and (5) swallowing difficulty (bulk-formers may produce esophageal obstruction).

OUTCOME EVALUATION

- Ask the patient about the absence or improvement in symptoms to determine whether laxative therapy is effective. Patients should have an increase in stool frequency to more than three well-formed stools per week. Patients should report the absence of prolonged defecation time or the absence of the need for excessive straining.
- When acute overuse or chronic misuse of saline or stimulant laxatives is suspected, it may be necessary to check for electrolyte disturbances (e.g., hypokalemia, hypernatremia, hyperphosphatemia, or hypocalcemia).
- Some laxatives (e.g., bulk-forming agents) contain significant amounts of sodium or sugar and may be unsuitable for salt-restricted or diabetic patients. When low-sodium or sugar-free products are not used, monitor serum concentrations of sodium and glucose as needed with chronic use.
- Saline laxatives containing magnesium, potassium, or phosphates should be used cautiously in persons with reduced kidney function. Monitor appropriate serum electrolyte concentrations in patients with unstable renal function evidenced by changing serum creatinine or creatinine clearance.
- All laxatives are contraindicated in patients with abdominal pain, nausea, vomiting, symptoms of appendicitis or undiagnosed abdominal pain. Patients should consult their physicians if sudden changes in bowel habits persist for more than fourteen days or if use of a laxative for seven days results in no effect.



Patient Care and Monitoring for Constipation

1. Assess the patient's symptoms to determine if patient-directed therapy is appropriate or whether the patient should be evaluated by a physician. Determine type and frequency of symptoms.
2. Review available diagnostic data to determine the cause or type of constipation.
3. Obtain a thorough history of prescription, non-prescription, and dietary supplement use. Determine what treatments have been helpful in the past. Is the patient taking any medications that may contribute to constipation?
4. Remember that no single therapy has proven effective for all patients who present with constipation.
5. Develop a plan to assess the effectiveness of laxative use in cases of chronic constipation.
6. Evaluate the patient for the presence of adverse drug reactions, drug allergies, and drug interactions.
7. Provide patient education about constipation, lifestyle modifications, and drug therapy.

DIARRHEA

Diarrhea is not a disease in itself but rather a symptom of some underlying problem. It is a condition marked by increased stool frequency (usually greater than 3 times daily), stool weight, liquidity, and decreased consistency of stools compared to a patient's usual pattern. Acute diarrhea is defined as diarrhea lasting for 14 days or less. Diarrhea lasting more than 30 days is called chronic diarrhea. Illness of 15 to 30 days is referred to as persistent diarrhea.[7]

EPIDEMIOLOGY AND ETIOLOGY

Most cases of diarrhea in adults are mild and resolve quickly. Infants and children (especially under 3 years of age) are highly susceptible to the dehydrating effect of diarrhea, and its occurrence in this age group should be taken seriously.

Acute Diarrhea

There are many possible causes of acute diarrhea, but infection is the most common cause. Infectious diarrhea occurs because of food and water contamination via the fecal-oral route. Viruses are the cause in a large proportion of cases. Likely viral suspects include Rotavirus, Norwalk, and adenovirus. Patients usually exhibit sudden low-grade fever, vomiting, and watery stools.

Bacteria are likely precipitants in many other cases including *Escherichia coli*, *Salmonella* species, *Shigella* species, *Vibrio cholerae*, and *Clostridium difficile*. The term dysentery has often been used to describe some of these bacterial infections when associated with serious occurrences of bloody diarrhea. Additionally, acute diarrheal conditions can be prompted by parasites–protozoa such as *Entamoeba histolytica*, *Microsporidium*, *Giardia lamblia*, and *Cryptosporidium parvum*. Most of these infectious agents can be causes of **traveler's diarrhea**, a common malady afflicting travelers worldwide. It usually occurs during or just after travel subsequent to the ingestion of fecally-contaminated food or water. It has an abrupt onset but usually subsides within 2 to 3 days.



Patient Encounter 1

A 70-year-old man complains of small, hard stools for the past 2 weeks. He also states that his bowel movements are less frequent than normal and that he has not had constipation previously. He has a history of hypertension, angina pectoris, and osteoarthritis and began a new medication 3 weeks ago. He asks for your recommendation of a laxative.

- What are the possible causes of his constipation?
- What are the special considerations in this older man?
- What nonpharmacologic and pharmacologic therapies would be appropriate for his condition?

TABLE 18–3. Selected Drugs and Substances That May Cause Acute Diarrhea

Drugs			
Antibiotics	Hydralazine	Metformin	Sorbitol
Colchicine	Laxatives	Misoprostol	Theophylline
Digitalis	Mannitol	Quinidine	
Dietary Supplements			
St. John's wort	Echinacea	Ginseng	Aloe vera
Poisons			
Arsenic	Cadmium	Mercury	

Noninfectious causes of acute diarrhea include drugs and toxins (Table 18–3), laxative abuse, food intolerance, irritable bowel syndrome (IBS), inflammatory bowel disease, ischemic bowel disease, lactase deficiency, Whipple's disease, pernicious anemia, diabetes mellitus, malabsorption, fecal impaction, diverticulosis, and celiac sprue.

Lactose intolerance is responsible for many cases of acute diarrhea, especially in patients of African descent, Asians, and Native Americans. Foods should be considered as possible causes, especially fat substitutes, dairy products, and products containing non-absorbable carbohydrates.

The diarrhea of IBS is sudden and perhaps watery but likely loose, usually accompanied by urgency, bloating, and abdominal pain occurring upon arising in the morning or immediately following a meal. Inflammatory bowel disease is typically associated with the sudden onset of bloody diarrhea accompanied by urgency, crampy abdominal pain, and fever. Patients who experience bowel ischemia may develop bloody diarrhea, particularly if they progress to shock.

Chronic Diarrhea

Chronic diarrhea lasts for longer than 4 weeks. Most cases result from functional or inflammatory bowel disorders, endocrine disorders, malabsorption syndromes and drugs (including laxative abuse). In chronic diarrhea, daily watery stools may not occur. Diarrhea may be either intermittent or persistent.

PATHOPHYSIOLOGY

During normal processes, approximately 9 liters of fluid traverse the gastrointestinal tract daily. Of this amount, 2 liters represent gastric juice, 1 liter is saliva, 1 liter is bile, 2 liters are pancreatic juice, 1 liter is intestinal secretions, and 2 liters are ingested. Of these 9 L of fluid presented to the intestine, only about 150 to 200 mL remain in the stool after reabsorptive processes occur.

Any event that leads to a significant increase in the amount of fluid retained in the stool may result in diarrhea. Large-stool diarrhea often signifies small intestinal involvement, whereas small-stool diarrhea usually originates in the colon. Diarrhea may be classified according to pathophysiologic mechanisms, which include osmotic, secretory, inflammatory, and altered motility.

Osmotic diarrhea results from the intake of unabsorbable but water-soluble solutes in the intestinal lumen leading to water retention. Common causes include lactose intolerance and ingestion of magnesium-containing antacids.

Secretory diarrhea results in an increase in the net movement (secretion) of ions into the intestinal lumen leading to an increase in intraluminal fluid. Medications, hormones, and toxins may be responsible for secretory activity.

Inflammatory (or exudative) diarrhea results from changes to the intestinal mucosa that damage absorption processes and lead to an increase in proteins and other products in the intestinal lumen with fluid retention. The presence of blood or fecal leukocytes in the stool is indicative of an inflammatory process. The diarrhea of inflammatory bowel disease (e.g., ulcerative colitis) is inflammatory in nature.

Increased motility results in decreased contact between ingested food and drink and the intestinal mucosa, leading to reduced reabsorption and increased fluid in the stool. Diarrhea resulting from altered motility is often established after other mechanisms have been excluded. IBS-related diarrhea is due to altered motility.

Although diarrhea can often be attributed to a specific mechanism, some patients develop diarrhea due to overlapping mechanisms. For example, malabsorption syndromes and traveler's diarrhea are associated with both secretory and osmotic diarrhea.

Drug-induced diarrhea can occur by several mechanisms. First, water can be drawn into the intestinal lumen osmotically. Second, the intestinal bacterial ecosystem can be upset leading to the emergence of invasive pathologic organisms triggering secretory and inflammatory processes. Saline laxatives are an example of the first mechanism and many antibiotics act by the second. A third way is through altered motility as may occur with tegaserod maleate. Other drugs such as procainamide or colchicine produce diarrhea through undetermined mechanisms. Discontinuation of the offending drug may be the only measure needed to ameliorate the diarrhea.

CLINICAL PRESENTATION AND DIAGNOSIS

Diagnosis

Patients with diarrhea should be questioned about the onset of symptoms, recent travel, diet, source of water, and medication use. Other important considerations include duration and severity of the diarrhea along with an accounting of the presence of associated abdominal pain or vomiting, blood in the stool, stool consistency, stool appearance, stool frequency, and weight loss. Although most cases of diarrhea are self-limited, infants, children, elderly persons, and immunocompromised patients are at risk for increased morbidity.

Findings on physical examination can assist in determining hydration status and disease severity. The presence of blood in



Clinical Presentation of Acute Diarrhea

Signs and Symptoms

- Patients with acute diarrhea have the abrupt onset of loose, watery, or semi-formed stools.
- Abdominal cramps and tenderness, rectal urgency, nausea, bloating, and fever may be present.
- The disorder is generally self-limited, lasting 3 to 4 days even without treatment.
- Patients with acute infectious diarrhea from invasive organisms also have bloody stools and severe abdominal pain.

Laboratory Tests in Acute Diarrhea

- Stool cultures can help identify infectious causes. Cultures are subject to time delay. New methodology using real-time polymerase chain reaction (PCR) shortens the reporting time.
- Stool may also be analyzed for mucus, fat, osmolality, fecal leukocytes, and pH. The presence of mucus suggests colonic involvement. Fat in the stool may be due to a malabsorption disorder. Fecal leukocytes can be found in inflammatory diarrheas including infections caused by invasive bacteria (e.g., *E. coli, Shigella,* and *Campylobacter* species). Stool pH (normally greater than 6) is decreased by bacterial fermentation processes.
- Stool volume and electrolytes can be assessed in large-volume watery stools to determine whether the diarrhea is osmotic or secretory.
- CBC and blood chemistries may be helpful in patients whose symptoms persist. The presence of anemia, leukocytosis, or neutropenia may provide further clues to the underlying cause.

Signs and Symptoms of Chronic Diarrhea

- In patients with chronic diarrhea, symptoms may be severe or mild. Weight loss can be demonstrated, and weakness may be present.
- Dehydration may be manifested by decreased urination, dark-colored urine, dry mucous membranes, increased thirst, and tachycardia.

Laboratory Tests in Chronic Diarrhea

- All of the tests described for acute diarrhea would be used to establish a diagnosis of chronic diarrhea because the differential diagnosis is more complicated. The data obtained can help categorize the diarrhea as watery, inflammatory, or fatty, narrowing the focus on a primary disorder.
- Colonoscopy allows visualization and biopsy of the colon and is preferred if blood has been found in the stool or if the patient has AIDS.

the stool suggests an invasive organism, an inflammatory process, or perhaps a neoplasm. Large-volume stools suggest a small-intestinal disorder, whereas small-volume stools suggest a colon or rectal disorder. Patients with prolonged or severe symptoms may require colonoscopic evaluation to identify the underlying cause.

TREATMENT

Most healthy adults with diarrhea do not develop dehydration or other complications and can be treated symptomatically by self medication. ❺ *When diarrhea is severe and oral intake is limited, dehydration can occur, particularly in the elderly and infants.* Other complications of diarrhea resulting from fluid loss include electrolyte disturbances, metabolic acidosis, and cardiovascular collapse.

Children are more susceptible to dehydration (particularly when vomiting occurs) and may require medical attention early in their course, especially if younger than the 3 years of age. Physician intervention is also necessary for elderly patients who are sensitive to fluid loss and electrolyte changes due to concurrent chronic illness.

Patients should undergo medical evaluation in the following circumstances: (1) moderate to severe abdominal tenderness, distention, or cramping; (2) bloody stools; (3) evidence of dehydration (e.g., thirst, dry mouth, fatigue, dark-colored urine, infrequent urination, reduced urine, dry skin, rapid pulse, rapid breathing, muscle cramps, muscle weakness, sunken eyes, or light-headedness); (4) high fever (greater than or equal to 101°F or 38°C); (5) evidence of weight loss greater than 5% of total body weight; and (6) diarrhea that lasts greater than 48 hours.

Desired Outcomes

The goals of treatment for diarrhea are to relieve symptoms, maintain hydration, treat the underlying cause(s), and maintain nutrition. ❻ *The primary treatment of acute diarrhea includes fluid and electrolyte replacement, dietary modifications, and drug therapy.*

Nonpharmacologic Therapy

Fluid and Electrolytes

Fluid replacement is not a treatment to relieve diarrhea but rather an attempt to restore fluid balance. In many parts of the world where diarrheal states are frequent and severe, fluid replacement is accomplished using oral rehydration solution (ORS), a measured mixture of water, salts, and glucose. The World Health Organization–recognized solution consists of 75 mEq/L sodium, 75 mmol/L glucose, 65 mEq/L chloride, 20 mEq/L potassium, and 10 mEq/L citrate, having a total osmolarity of 245 mOsm/L. A simple solution can be prepared from 1 L water mixed with 8 teaspoonfuls of sugar and 1 teaspoonful of table salt. Some commercial products include Pedialyte, Rehydralyte, and Ceralyte. Patients with diarrhea who are not dehydrated may replace fluid by drinking flat soft drinks such as ginger ale, tea, fruit juice, broth, or soup. Caution is advised in using sports drinks for dehydration, as they may not provide an appropriate amount of electrolytes. Severe diarrhea may require the use of parenteral solutions such as lactated Ringer's or normal saline solution to replace large and life-threatening fluid losses.[8]

Dietary Modifications

Once an acute diarrheal situation ensues, patients typically eat less as they become focused on the diarrhea. Both children and adults should attempt to maintain nutritional intake. Food provides not only nutrients but also fluid volume that helps replace what is lost. However, food-related fluid may not be enough to compensate for diarrheal losses. Some foods may be inappropriate if they irritate the gastrointestinal tract or if they are implicated as the cause of the diarrhea. Patients with chronic diarrhea may find that increasing bulk in the diet may help (e.g., rice, bananas, whole-wheat, and bran).

Pharmacologic Therapy

The goal of drug therapy is to control symptoms, enabling the patient to continue with as normal a routine as possible while avoiding complications (Table 18–4). Most infectious diarrheas are self-limited or curable with anti-infective agents.

Adsorbents and Bulk Agents

Attapulgite adsorbs excess fluid in the stool with few adverse effects. Calcium polycarbophil is a hydrophilic polyacrylic resin that also works as an adsorbent, binding about 60 times its weight in water and leading to the formation of a gel that enhances stool formation. Neither attapulgite nor polycarbophil is systemically absorbed. Both products are effective in reducing fluid in the stool but can also adsorb nutrients and other medications. Their administration should be separated from other oral medications by 2 to 3 hours. Psyllium and methylcellulose products may also be used to reduce fluid in the stool and relieve chronic diarrhea.

TABLE 18–4. Pharmacotherapy for Diarrhea

Drug	Usual Dose	Type of Diarrhea
Attapulgite	Adults: 1200–1500 mg after each loose stool Maximum 9000 mg in 24 hours Children ages 6–12: 750 mg after each loose stool Maximum 4500 mg in 24 hours	Acute and chronic Chronic
Calcium polycarbophil	Adults: 1000 mg 4 times daily or after each loose stool, not to exceed 12 tablets per day Children ages 6–12: 500 mg 3 times daily Children ages 3–6: 500 mg twice daily	
Loperamide	Adults: 4 mg initially, then 2 mg after each subsequent loose stool; maximum 16 mg in 24 hours Children's maximum doses: Ages 2–5: 3 mg Ages 6–8: 4 mg Ages 8–12: 6 mg	Acute and chronic
Diphenoxylate/atropine	Adults: Two tablets (5 mg) initially, then one tablet every 3–4 hours, not to exceed 20 mg in 24 hours Children 2–12 years old: Oral solution (avoid tablets) 0.3 to 0.4 mg/kg per day in divided doses Do not administer to children less than 2 years of age	Acute and chronic
Bismuth subsalicylate	Adults: 30 mL (regular strength) or 2 tablets, repeated every 30–60 minutes as needed Maximum 8 doses daily Children: Consumers should speak with a physician before giving to children under 12 years of age	Traveler's and nonspecific acute diarrhea

Antiperistaltic (Antimotility) Agents

Antiperistaltic drugs prolong intestinal transit time, thereby reducing the amount of fluid lost in the stool. The two drugs in this category are loperamide HCl (available over the counter as Imodium A-D and generically) and diphenoxylate HCl with atropine sulfate (available by prescription as Lomotil and generically). The atropine is included only as an abuse deterrent; when taken in large doses, the unpleasant anticholinergic effects of atropine negate the euphoric effect of diphenoxylate. Both loperamide and diphenoxylate are effective in relieving symptoms of acute non-infectious diarrhea and are safe for most patients experiencing chronic diarrhea. These products should be discontinued in patients whose diarrhea worsens despite therapy.

Antisecretory Agents

Bismuth subsalicylate is thought to have antisecretory and antimicrobial effects and is used to treat acute diarrhea. Although it passes largely unchanged through the gastrointestinal tract, the salicylate portion is absorbed in the stomach and small intestine. For this reason, bismuth subsalicylate should not be given to people who are allergic to salicylates, including aspirin. Caution should be exercised with regard to the total dose administered in patients who concurrently take salicylates for other reasons to avoid the possibility of salicylism. Patients taking bismuth subsalicylate should be informed that their stool will turn black.

Octreotide is an antisecretory agent that has been used for severe secretory diarrhea associated with cancer chemotherapy, HIV, diabetes, gastric resection, and gastrointestinal tumors. It is administered as a subcutaneous or intravenous bolus injection in an initial dose of 500 mcg three times daily to assess the patient's tolerance to gastrointestinal adverse effects. Biweekly serum levels of insulin-like growth factor-1 (IGF-1 or somatomedin C) can be used as a guide to dose titration. Possible adverse effects include nausea, bloating, pain at the injection site, and gallstones (with prolonged therapy).

Probiotics

Probiotics are dietary supplements containing bacteria that may promote health by enhancing the normal microflora of the gastrointestinal tract while resisting colonization by potential pathogens. Probiotics can stimulate the immune response and suppress the inflammatory response. Yogurt can provide relief from diarrhea due to lactose intolerance. It supports digestion of lactose because the bacteria used to make yogurt produce lactase and digest the lactose before it reaches the colon. The *Lactobacillus acidophilus* in yogurt, cottage cheese, and acidophilus milk improves digestion of lactose and may prevent or relieve diarrhea related to lactose deficiency and milk intake. Although lactase is not a probiotic, lactase tablets may also be used to prevent diarrhea in susceptible patients.



Patient Encounter 2

KW, a 31-year-old day care teacher, complains of nausea, vomiting, abdominal cramps, and frequent watery stools for the past 2 days. She also indicates that her heart has been "racing" and her mouth has been very dry. Although she looks ill, she does not have a fever.

- What is the likelihood that her diarrhea is due to an invasive microorganism?
- Which of her symptoms suggest the presence of dehydration?
- Discuss potential treatment measures for this woman.

Anti-Infectives

Empiric antibiotic therapy is an appropriate approach to traveler's diarrhea. Eradication of the causal microbe depends on the etiologic agent and its antibiotic sensitivity. Most cases of traveler's diarrhea and other community-acquired infections result from enterotoxigenic (ETEC) or enteropathogenic (EPEC) *Escherichia coli.* Routine stool cultures do not identify these strains; primary empiric antibiotic choices include fluoroquinolones such as ciprofloxacin or levofloxacin. Azithromycin may be a feasible option when fluoroquinolone resistance is encountered.

Although most cases of infectious diarrhea resolve with therapy, routine antibiotic use may contribute to antimicrobial resistance. Empiric treatment should be considered for other acute infectious diarrhea including those caused by non–hospital acquired invasive organisms such as Shiga toxin–producing *Escherichia coli* (STEC) O157, *Campylobacter, Salmonella,* and *Shigella* organisms producing moderate to severe fever, **tenesmus**, and bloody stools.[9]

OUTCOME EVALUATION

- Monitor the patient with diarrhea from the point of first contact until symptoms resolve, keeping in mind that most episodes are self-limiting.
- Question the patient to determine whether symptom resolution occurs within 48 to 72 hours in acute diarrhea.
- Monitor for the maintenance of hydration, particularly when symptoms continue for more than 48 hours. Look for increasing thirst, decreased urination, dark-colored urine, dry mucous membranes, and rapid heartbeat as suggestive of dehydration, especially when nausea and vomiting have been present.
- Monitor for symptom control in patients with chronic diarrhea.
- When antibiotics are used, monitor for completion of the course of therapy.



Patient Care and Monitoring for Diarrhea

1. Assess the patient's symptoms to determine if patient-directed therapy is appropriate or whether the patient should be evaluated by a physician. Determine the type of symptoms, severity, frequency, and exacerbating factors. Remember to inquire about recent foreign travel.
2. Determine if the patient is dehydrated.
3. Determine whether the patient has a history of disease that might be associated with diarrhea.
4. Obtain a thorough current history of prescription, nonprescription, and dietary supplement use. Remember to review the current therapy as a potential cause of diarrhea.
5. Determine if any diarrhea treatments have been attempted, including home remedies.
6. Medical referral is advised if the patient is pregnant, breast-feeding, younger than 3 or older than 70 years of age, or suffers from multiple medical conditions.
7. If home care is recommended, provide clear instructions about how to proceed if symptoms do not improve or new symptoms emerge.
8. Discuss the importance of maintaining nutrition by modifying the diet to include low-residue meals (low-fiber meals).
9. Educate the patient about: (1) the causes of acute and chronic diarrhea; (2) the possible complications of diarrhea; (3) the goals of treatment for diarrhea; (4) the antidiarrheal medication used to manage acute or chronic diarrhea; and (5) if appropriate, the circumstances when antibiotics are used to treat diarrhea.

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is a disorder of the gastrointestinal tract that interferes with the normal functions of the colon. At various points in the past, IBS has been referred to as **mucous colitis**, spastic colon, irritable colon, or nervous stomach. ❼ *IBS is generally described as a functional disorder rather than a disease per se. A functional disorder involves symptoms that cannot be attributed to a specific injury, infection, or other physical problem.* A functional disorder occurs because of altered physiologic processes rather than structural or biochemical defects and may be subject to nervous system influence. IBS is associated with frequent fluctuation in symptoms, loss of productivity, and decreased quality of life. Although IBS has been referred to as **functional bowel disease**, true functional bowel disease may be more indicative of widespread gastrointestinal involvement including (but not limited to) the colon.

EPIDEMIOLOGY AND ETIOLOGY

IBS is one of the most common disorders seen in primary care and the most common reason for referral to gastroenterologists. Although between 15% and 20% of Americans suffer from IBS, only about one-quarter of those affected seek medical attention. The associated costs to society are significant, and the recurrent nature of IBS contributes to these costs through missed workdays, inattention on the job, and high consumption of health services.[10]

In the United States, IBS affects women about twice as often as men. However, this may reflect a woman's tendency to seek medical care more often than a man may. Irritable bowel syndrome can occur at any age, but presentation is most common between the ages of 20 and 50 years. Onset beyond 60 years of age is rare. However, prevalence for older adults is the same as for young persons. Prevalence is similar in Caucasians and African-Americans but may be lower in people of Hispanic origin. A genetic link is unproven, but IBS seems more common in certain families.

There is strong association between emotional distress and IBS. Psychosocial trauma (e.g., a history of abuse, recent death of a close relative or friend, or divorce) is more likely to be found in patients presenting with IBS than in the general population. An increased prevalence of psychiatric disorders such as anxiety, depression, personality disorders, and somatization (psychological distress expressed as physical symptoms) occurs among adult patients with IBS. Alcohol consumption and smoking have not been shown to be risk factors for developing IBS.[11]

Some people show first evidence of IBS after contracting gastroenteritis, which has led to speculation about whether an infection makes the gastrointestinal tract susceptible to functional problems. Women with IBS may have symptoms triggered by menstrual periods.

PATHOPHYSIOLOGY

Enteric nerves control intestinal smooth muscle action and are connected to the brain by the autonomic nervous system. IBS is thought to result from dysregulation of this "brain-gut axis." The enteric nervous system is composed of two ganglionated plexuses that control gut innervation: the submucous plexus (Meissner's plexus) and the myenteric plexus (Auerbach's plexus). The enteric nervous system and the central nervous system (CNS) are interconnected and interdependent. A number of neurochemicals mediate their function, including serotonin (5-hydroxytryptamine or 5-HT), acetylcholine, substance P, and nitric oxide, among others.

Two 5-HT receptor sub-types, 5-HT_3 and 5-HT_4, are involved in gut motility, visceral sensitivity, and gut secretion. The 5-HT_3 receptors slow colonic transit and increase fluid absorption, whereas 5-HT_4 receptor stimulation results in accelerated colonic transit.

Although no single pathologic defect has been found to account for the pattern of exacerbations and remissions seen in IBS, CNS abnormalities, dysmotility, visceral hypersensitivity, and a number of other factors have been implicated.[12]

The passage of fluids into and out of the colon is regulated by epithelial cells. In IBS, the colonic lining (epithelium) appears to work properly. However, increased movement of the contents in the colon can overwhelm its absorptive capacity.

Disturbed intestinal motility appears to be a central feature of IBS, which leads to altered stool consistency. Studies suggest that the colon of IBS sufferers is abnormally sensitive to normal stimuli.[13] This enhanced visceral sensitivity manifests as pain, especially related to gut distention.

IBS activity may be affected by the immune system. Some IBS patients have been found to have antibodies, which may indicate food hypersensitivity that might be involved in symptom production.[14] Specifically, sensitivity has been demonstrated to common foods such as wheat, beef, pork, soy, and eggs.

CLINICAL PRESENTATION AND DIAGNOSIS

Diagnosis

❾ *The diagnosis of IBS is made by symptom-based criteria and the exclusion of organic disease.* IBS is diagnosed by obtaining a careful and thorough history to identify symptoms characteristic of the disorder. It is equally important to distinguish between IBS and conditions having similar symptoms. Patients should be questioned about the character of their stools. This should include questions about frequency, consistency, color, and size. Moreover, because of the functional nature of IBS, a patient may present with symptoms of upper gastrointestinal problems such as gastroesophageal reflux disease (GERD) or with excessive flatulence. Patients should also be questioned about diet to determine whether symptoms seem to occur in relationship to meals or specifically after consumption of certain dietary products.

Barium enema, sigmoidoscopy, or colonoscopy may be indicated in the presence of red flag symptoms (fever, weight loss, bleeding, and anemia, which may be accompanied by persistent severe pain), which often point to a potentially serious non-IBS problem. A barium enema may identify polyps, diverticulosis,



Clinical Presentation of Irritable Bowel Syndrome

Symptoms

- Patients report a history of abdominal pain or discomfort that is relieved with defecation. Symptom onset is associated with change in frequency or appearance of stool. Some persons experience hard, dry stools whereas others experience loose or watery stools. Some stools may be small and pellet-like in appearance while others may be narrow and pencil-like.
- ❽ *Symptoms can typically be categorized as either diarrhea-predominant IBS (IBS-D) or constipation-predominant IBS (IBS-C). Patients with IBS-D usually report more than three loose or watery stools daily. Those with IBS-C usually have fewer than three bowel movements per week; stools are typically hard and lumpy and accompanied by straining.*
- While many patients fit into one of these categories, some patients report alternating episodes of diarrhea and constipation.
- Other common symptoms include: (1) feelings of incomplete evacuation; (2) abdominal fullness; (3) bloating; (4) flatulence; (5) passage of clear or white mucus with a stool; and (6) occasional fecal incontinence.
- Periods of normal stools and bowel function are punctuated by episodes of sudden symptoms.
- Symptoms are often exacerbated by stress.
- Left lower quadrant abdominal pain is often brought on or made worse by eating. Passage of stool or flatus may provide some relief.
- IBS-C can often be distinguished from chronic constipation primarily by the presence of abdominal pain and discomfort. Although pain and discomfort may be present in some patients with chronic constipation, it is an expected feature of IBS.
- Patients with IBS may experience comorbidities outside the gastrointestinal tract such as fibromyalgia, sleep disturbances, headaches, dyspareunia, and temporomandibular joint syndrome.

Signs

- The physical examination is often normal in IBS.
- The patient may appear to be anxious.
- Palpation of the abdomen may reveal left lower quadrant tenderness, which may indicate a tender sigmoid colon.
- Abdominal distention may be present in some cases.
- The following "red flag" or alarm features are *not* associated with IBS and may indicate inflammatory bowel disease, cancer, or other disorders: fever, weight loss, bleeding, and anemia, which may be accompanied by persistent severe pain.

Laboratory Tests

- In most cases, laboratory testing reveals no abnormalities in IBS, but certain tests can be used to identify other causes for the patient's symptoms.
- Complete blood cell count (CBC) may identify anemia, which may suggest blood loss and an organic source for GI symptoms.
- Serum electrolytes and chemistries may indicate metabolic causes of symptoms.
- Thyroid-stimulating hormone (TSH) should be ordered when thyroid dysfunction is suspected. Hypothyroidism may be responsible for constipation and related symptoms.
- Stool testing for ova and parasites may identify *Clostridium difficile* and amoeba as possible causes of diarrhea rather than IBS.
- Fecal leukocytes can be found in inflammatory diarrhea, especially when due to invasive microorganisms.
- A positive stool guaiac test indicating blood in the gastrointestinal tract does not support a diagnosis of IBS.
- An elevated erythrocyte sedimentation rate (ESR) is consistent with a systemic inflammatory process such as inflammatory bowel disease rather than IBS.
- Testing for lactose deficiency can confirm the presence of lactose intolerance, which may explain the symptoms.



Patient Encounter 3, Part 1

A 38-year-old woman presents complaining of headache, abdominal pain, bloating, occasional nausea, and excessive belching. These symptoms have occurred with increasing frequency over the past 2 to 3 weeks. The abdominal pain is crampy in character and located in the left lower abdominal area. She has also had alternating episodes of diarrhea and constipation and the presence of white threadlike material in her stool during some of the past 3 weeks.

- Which of the patient's symptoms are characteristics of IBS?
- How well does this woman fit the typical epidemiologic profile of patients with IBS?

tumors, or other abnormalities that might be responsible for the symptoms. In addition, exaggerated haustral contractions may be noted with barium enema. Such contractions impede stool movement and contribute to constipation.

Flexible sigmoidoscopy can be performed to identify obstruction in the rectum and lower colon, whereas colonoscopy can evaluate the entire colon for organic disease.

The diagnostic basis for IBS has long been centered on the presence of symptoms, first defined by the Manning criteria: (1) abdominal pain relieved by defecation with either (a) looser stools with pain onset, or (b) frequent stools with pain onset; (2) abdominal distention; (3) mucus in the stool; and (4) sensation of incomplete evacuation.[15,16] These practical criteria have been used widely.

The Rome II criteria (preceded by Rome I) are the most current diagnostic criteria for establishing the presence of IBS. They presume the absence of a structural or biochemical explanation for the symptoms. These rather stringent criteria can be applied clinically, but not as easily as the older Manning criteria.[17] The Rome II criteria define IBS as occurring when symptoms of abdominal discomfort or pain exist at least 12 weeks (*which need not be consecutive*) in the preceding 12 months that have two of the three following features: (1) relieved with defecation; (2) onset associated with a change in the frequency of stool; and/or (3) onset associated with a change in the form of stool. IBS is unlikely if symptom onset occurs in old age, the disorder has a steady but aggressive course, or the patient experiences frequent awakening because of symptoms.

TREATMENT

General Approach to Treatment

⓾ *The principal goal of IBS treatment is to reduce or control symptoms.* The treatment strategy is based on: (1) the prevailing symptoms and their severity; (2) the degree of functional impairment; and (3) the presence of psychological components. A standard treatment regimen is not possible because of the heterogeneous nature of the IBS patient population. Patients suffering from IBS can benefit from clinician support and reassurance, since specific pathology is unlikely to be found.

Nonpharmacologic Therapy

Diet and Other Lifestyle Modifications

Dietary modification is a standard therapeutic modality. Food hypersensitivities and adverse effects are thought to occur widely in IBS patients, especially those with diarrhea-predominant type. Elimination diets are the most commonly used strategy, usually focusing on milk and dairy products, fructose and sorbitol, wheat, and beef. Flatulence may be controlled by reducing gas-causing foods such as beans, celery, onions, prunes, bananas, carrots, and raisins. Response to elimination diets varies widely but they may be useful in individual patients. Care must be taken to avoid creating nutritional deficits while attempting to eliminate an offending food.

Psychological Treatments

Psychotherapy focused on reducing the influence of the CNS on the gut has been studied. Cognitive behavioral therapy (CBT), dynamic psychotherapy, relaxation therapy, and hypnotherapy have been reported to be effective in some patients. However, CBT and relaxation therapy do not appear to be better than standard approaches.[18] Biofeedback may provide relief in cases of severe constipation, but definitive evidence is lacking.[16] Psychotherapy interventions provide relief from pain and diarrhea but not constipation.[19]

Pharmacologic Therapy

Botanicals

Peppermint oil is widely advocated; it acts as an antispasmodic agent due to its ability to relax gastrointestinal smooth muscle. However, it also relaxes the lower esophageal sphincter, which could allow reflux of gastric contents into the esophagus. The usual dose is 1 to 2 enteric-coated capsules containing 0.2 mL of peppermint oil two to three times daily.

Matricaria recutita, known as German chamomile, is also purported to have antispasmodic properties. It is taken most often as a tea up to four times a day. Benzodiazepine, alcohol, and warfarin users should be cautioned against taking this product because it can cause drowsiness, and it contains coumarin derivatives.[20]

Antispasmodics

Antispasmodic agents such as dicyclomine or hyoscyamine have been among the most frequently used medications for treating abdominal pain in patients with IBS (Table 18–5).

TABLE 18–5. Common Pharmacologic Treatments for Irritable Bowel Syndrome

Generic (Brand) Name	Dose
Antispasmodics	
Dicyclomine (Bentyl)	10–20 mg every 4–6 hours as needed
Hyoscyamine (Levsin)	0.125–0.25 mg orally or sublingually every 4 hours as needed
Propantheline bromide (Pro-Banthine)	15 mg three times a day (before meals) and 30 mg at bedtime
Clidinium bromide plus chlordiazepoxide HCl (Librax)	5–10 mg three to four times a day
Hyoscyamine, scopolamine, atropine, phenobarbital (Donnatal)	1–2 tablets three to four times daily
Tricyclic Antidepressants	In Diarrhea-Predominant IBS:
Amitriptyline	50–150 mg daily
Doxepin	10–150 mg daily
Selective Serotonin Reuptake Inhibitors	In Constipation-Predominant IBS:
Paroxetine (others can be used)	10–40 mg daily
Bulk-Forming Laxatives	
Psyllium (Metamucil)	2.5–4 g daily
Methylcellulose (Citrucel)	4–6 g daily
Antimotility Agents	
Loperamide (Imodium A-D)	4 mg; then 2 mg after each loose stool; daily maximum 16 mg
5-HT_3 Receptor Antagonist	
Alosetron (Lotronex)	1 mg daily
5-HT_4 Receptor Agonist	
Tegaserod maleate (Zelnorm)	6 mg twice daily

5-HT, serotonin.

Side effects include blurred vision, constipation, urinary retention, and (rarely) psychosis. Although their effectiveness remains unconfirmed, these drugs may deserve a trial in patients with intermittent postprandial pain.[16]

Antidepressants

Tricyclic antidepressants (TCAs) such as amitriptyline and doxepin have been used with some success in the treatment of IBS-related pain (Table 18–5). They modulate pain principally through their effect on neurotransmitter reuptake, especially norepinephrine and serotonin. Their helpfulness in functional gastrointestinal disorders seems independent of mood-altering effects normally associated with these agents. Low-dose TCAs (e.g., amitriptyline, desipramine, or doxepin 10 to 25 mg daily) may help patients with IBS who predominantly experience diarrhea or pain.

The selective serotonin reuptake inhibitors (SSRIs) paroxetine, fluoxetine, and sertraline are potentially useful due to the significant effect of serotonin in the gut. SSRIs principally act on 5-HT_1 or 5-HT_2 receptors, but they can also have some effect on gut-predominant 5-HT_3 and 5-HT_4 receptors, perhaps reducing visceral hypersensitivity. They may be beneficial for patients with IBS-C or when the patient presents with IBS complicated by a mood disorder.[19] SSRIs should be reserved for use when TCAs are not effective because evidence supporting their use solely in IBS is lacking.

Bulk-Forming Agents

Bulk-forming agents may improve stool passage in constipation-predominant patients but are unlikely to have a favorable effect on pain or global IBS symptoms.[21] Psyllium may increase flatulence, which may worsen discomfort in some patients. Methylcellulose products are less likely to increase gas production. Although fiber-based supplements are more likely to be useful in constipation-predominant IBS, these products may be dose-adjusted in diarrhea to increase stool consistency. Other laxative products might be used in constipation-predominant IBS, but most are less desirable than bulking agents due to the potential for unwanted effects.

Anti-Motility Agents

Loperamide stimulates enteric nervous system receptors, inhibiting peristalsis and fluid secretion. It improves stool consistency and reduces the number of stools.[21] Consequently, it is most useful in patients who have diarrhea as a prominent symptom. However, it can occasionally aggravate abdominal pain.

Alosetron

Stimulation of 5-HT_3 receptors triggers hypersensitivity and hyperactivity of the large intestine. Alosetron (Lotronex) is a selective 5-HT_3 antagonist that blocks these receptors and is used to treat women with severe diarrhea-predominant IBS. Eligible patients should have frequent and severe abdominal pain, frequent bowel urgency or incontinence, and restricted daily activities. Alosetron has been shown to improve overall symptoms and quality of life. Alosetron can cause constipation in some patients.

Because alosetron has been associated with ischemic colitis, it may be prescribed only under strict guidelines, including signing of a consent form by both patient and physician. Patients selected for therapy should exhibit chronic IBS symptoms and have failed to respond to conventional therapy.

Tegaserod Maleate

Tegaserod maleate (Zelnorm) stimulates 5-HT_4 receptors in the GI tract, thereby increasing intestinal secretion, peristalsis, and small bowel transit. It also reduces sensitivity related to abdominal distention. It has been shown to be more effective than placebo in improving global IBS symptoms and altered bowel habits in constipation-predominant IBS.[21] Diarrhea is a possible adverse effect.



Patient Encounter 3, Part 2

Upon further questioning, the patient states that she had similar symptoms near the end of graduate school 6 years ago. The symptoms gradually subsided after graduation, so she did not seek medical attention. She is an accountant and recently received a promotion at work. As a result, she has taken on considerably more responsibility.

PMH
Anxiety; muscle contractions; headaches

FH
Mother has migraine headaches

SH
Non-smoker; drinks a glass of wine occasionally

Meds
Naproxen 220 mg every 12 hours as needed for headaches and menstrual pain
Loperamide 2 mg as needed for diarrhea

Allergies
No known drug allergies

Physical Exam
Gen: Alert and oriented, well developed and well nourished, anxious black woman
VS: blood pressure 137/88 mm Hg, pulse 80 beats per minute, respiratory rate 21/minutes, temperature 98.7°F (37.1°C), Ht 5′7″, Wt 74 kg
Integ: Hair and nails unremarkable; scalp dry and flaky; skin otherwise unremarkable
HEENT: PERRLA, EOMI
Chest: Clear to A & P bilaterally
CV: RRR, normal S_1 and S_2; no S_3 or S_4
Abd: (+) BS, mildly tender LLQ
Rectal: No palpable masses; no hemorrhoids; stool negative for occult blood

- What information is consistent with the diagnosis of IBS?
- Outline an appropriate therapeutic plan for this patient.

Ischemic colitis has been observed in some patients taking tegaserod. The drug should be discontinued promptly if rectal bleeding, bloody diarrhea, or worsening abdominal pain occurs.

In March of 2007, the FDA announced that tegaserod maleate would be voluntarily withdrawn from the market because of information indicating an increased risk of serious cardiovascular events (myocardial infarction, unstable angina, and stroke).

OUTCOME EVALUATION

- Because symptoms vary in intensity and among patients, a specific drug therapy may not lead to equivalent symptom abatement in different patients.
- Monitor for adequate relief of symptoms. Patients whose pain does not respond to drug therapy may have a psychological comorbid condition and may require psychiatric intervention.
- Specifically, monitor for relief of pain if present initially. Monitor patients with symptoms of constipation or diarrhea for frequency, appearance, and size of stools in relationship to their normal characteristics. As stools normalize, associated symptoms such as bloating and abdominal distention should resolve.
- For patients taking bulk-forming agents, monitor for relief of constipation. Hard stools should become softer within 72 hours.
- Monitor antidepressant therapy for relief of lower abdominal pain.
- Assess 5-HT_4 receptor agonists (tegaserod) for relief of crampy abdominal pain and bloating.
- Evaluate 5-HT_3 receptor antagonists (alosetron) for relief of abdominal pain and fecal incontinence.
- Antispasmodics may provide limited relief of crampy abdominal pain.
- Antimotility agents should be expected to reduce stool frequency and control diarrhea.
- Monitor complete blood cell count, serum electrolytes and chemistries, stool guaiac, and erythrocyte sedimentation rate yearly for changes that might signal an overlapping organic problem.
- Refer any patient presenting with red flag signs for medical evaluation.



Patient Care and Monitoring

1. Assess symptoms to determine if patient-directed therapy is appropriate or whether physician evaluation is needed.
2. Determine the type, severity, and frequency of symptoms and possible exacerbating factors.
3. Listen attentively to the patient's complaints and reassure the patient to allay fears about invasive disease.
4. Obtain a thorough current history of prescription, nonprescription, and dietary supplement use.
5. Determine if any IBS treatments have been attempted and how effective they have been.
6. Determine whether the patient has received educational intervention about IBS, health promotion, and symptom prevention measures.
7. Provide patient education about IBS symptoms, lifestyle modifications, and drug therapy for IBS:
   - Explain how to use medications relative to symptom intensity.
   - If taking alosetron, determine compliance with special use requirements.
   - Describe potential adverse effects.
   - List drugs that may interact with the therapy.
   - Discuss what to do if red flag symptoms occur.

ABBREVIATIONS

CBC: complete blood cell count
CBT: cognitive behavioral therapy
CNS: central nervous system
EPEC: enteropathogenic *Escherichia coli*
ESR: erythrocyte sedimentation rate
ETEC: enterotoxigenic *Escherichia coli*
GERD: gastroesophageal reflux disease
GI: gastrointestinal
5-HT_4: serotonin
IBS: irritable bowel syndrome
IBS-C: constipation-predominant irritable bowel syndrome
IBS-D: diarrhea-predominant irritable bowel syndrome
IGF-1: insulin-like growth factor-1
ORS: oral rehydration solution
PCR: polymerase chain reaction
PEG: polyethylene glycol
SSRI: selective serotonin reuptake inhibitor
STEC: Shiga toxin–producing *Escherichia coli*
TCA: tricyclic antidepressant
TSH: thyroid-stimulating hormone

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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19 Portal Hypertension and Cirrhosis

Laurajo Ryan



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Describe the epidemiology and social impact of portal hypertension and cirrhosis.
2. Explain the pathophysiology of cirrhosis and portal hypertension.
3. Outline the progression of liver damage from excessive alcohol intake.
4. Identify the signs and symptoms of liver disease in a given patient.
5. Clarify the consequences associated with decreased hepatic function.
6. List the treatment goals for a patient with portal hypertension and its complications.
7. Evaluate patient history and physical exam findings and recommend a specific regimen including both pharmacologic and nonpharmacologic therapy.

Key Concepts

❶ Portal hypertension is the precipitating factor for the complications of cirrhotic liver disease—ascites, spontaneous bacterial peritonitis (SBP), variceal bleeding, and hepatic encephalopathy. Lowering portal pressure can reduce the complications of cirrhosis and decrease morbidity and mortality.

❷ Chronic excessive ingestion of ethanol causes progressive liver damage because both ethanol and its metabolic products are direct hepatotoxins.

❸ Cirrhosis is irreversible; treatments are directed at limiting disease progression and minimizing complications.

❹ Non-selective β-blockers are first-line treatment for preventing variceal bleeding; they vasoconstrict the splanchnic bed through multiple mechanisms.

❺ The goals of treating ascites are to minimize acute discomfort, re-equilibrate ascitic fluid, and prevent SBP. Treatment should modify the underlying disease pathology; without directed therapy, fluid will rapidly reaccumulate.

❻ Cirrhosis is a high aldosterone state; spironolactone is a direct aldosterone antagonist and a primary treatment for ascites.

❼ During acute variceal hemorrhage, crucial desired outcomes include controlling bleeding, preventing rebleeding, and avoiding acute complications such as SBP.

❽ Long-term antibiotic prophylaxis for SBP decreases mortality in patients with a history of SBP and low-protein ascites [ascitic fluid albumin less than 1 g/dL (less than 10 g/L)].

❾ Lactulose is the foundation of pharmacologic therapy to prevent and treat hepatic encephalopathy because its unique mechanism binds ammonia in the gut and facilitates its excretion.

Cirrhosis is the progressive replacement of normal hepatic cells by fibrous scar tissue. This scarring is accompanied by the loss of viable **hepatocytes**, which are the functional cells of the liver. ❶ *Progressive cirrhosis is irreversible and leads to* ***portal hypertension*** *that is in turn responsible for many of the complications of advanced liver disease. These consequences include (but are not limited to)* ***spontaneous bacterial peritonitis (SBP), hepatic encephalopathy,*** *and* ***variceal bleeding.***[1]

EPIDEMIOLOGY AND ETIOLOGY

Cirrhosis is the result of long-term insult to the liver, so damage is typically not evident clinically until the fourth decade of life. Chronic liver disease and cirrhosis combined were the 12th leading cause of death in the United States in 2002. In patients between the ages of 25 and 64, damage from excessive alcohol use accounted for over one-half of the deaths.[2] Alcoholic liver disease and viral hepatitis are the most common causes of cirrhosis in the United States and worldwide.

Variations occur, but cirrhosis typically develops after 10 or more years of daily ingestion of 80 g of ethyl alcohol; this is an average of 6 to 8 drinks per day (a drink is equivalent to 1 ounce

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of hard liquor, 4 ounces of wine, or a 12-ounce beer).[3] With equivalent alcohol intake, women tend to develop cirrhosis more quickly than men do. Differences in alcohol metabolism may account for this gender disparity; women metabolize less alcohol in the gastrointestinal (GI) tract, allowing delivery of higher levels of ethanol to the liver.[4] Genetic factors also play a role in development of alcoholic liver disease; some persons will progress to cirrhosis with much less cumulative alcohol use than is typical in a cirrhotic patient (either fewer drinks per day, or faster disease development) while others do not develop the disease with even more excessive intake.

Infection with one or more strains of viral hepatitis often causes acute inflammation of the liver, while chronic infection with hepatitis B or C can lead to cirrhosis. Hepatitis B and C are common in intravenous drug users and can also be transmitted through sexual contact, but many cases of hepatitis C are idiopathic.[5,6] Hepatitis C is a more common cause of cirrhosis than hepatitis B in the United States while hepatitis B is more common in the rest of the world.[7] See Chapter 21 on viral hepatitis for a complete discussion of infectious hepatitis.

Approximately 30% of patients with cirrhosis experience variceal bleeding at some point. Variceal bleeding carries a remarkably high mortality rate; up to 55% of patients with advanced disease die from their first bleeding episode. Mortality from variceal bleeding correlates with disease severity; risk factors for bleeding varices include poor liver function, large varices, and red signs (wales) on endoscopic examination.[8] In patients who survive the first incident of bleeding, more than two-thirds experience a repeat episode.

Development of ascites in cirrhotic patients is a particularly ominous marker; mortality 1 year after initial development of ascites is approximately 50%.[9]

In addition to the high mortality rate, cirrhosis carries an enormous social burden from hospitalizations, lost wages, and decreased productivity, not to mention the emotional strain of the disease on both patients and families.

Once cirrhosis is diagnosed, disease progression is relentless, regardless of the initial insult to the liver. Determining the specific cause of cirrhosis requires examination of both physical presentation and past medical history. An accurate social history is particularly important because few factors in the physical and laboratory examination aid in determining disease etiology. Understanding the cause of a patient's cirrhosis is imperative because it can affect therapeutic options and treatment decisions.

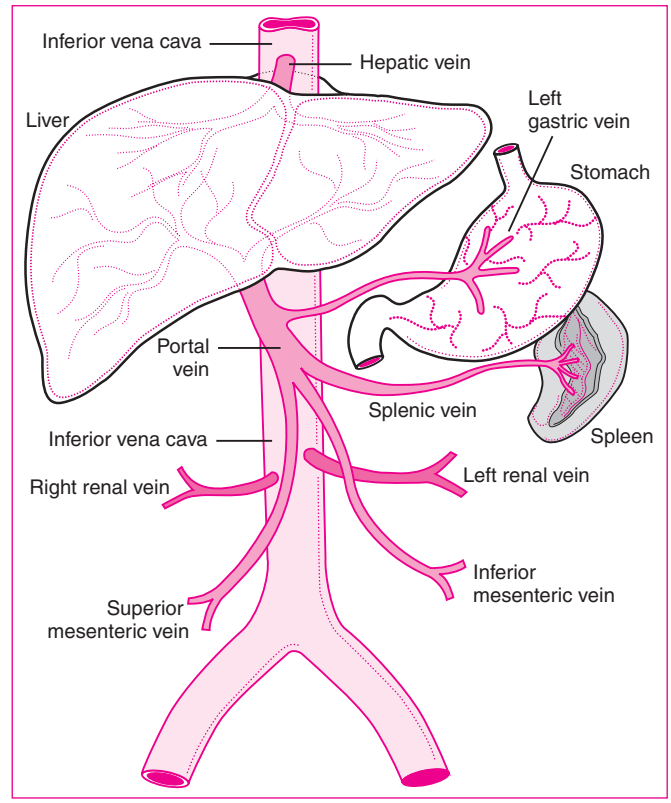


FIGURE 19–1. The portal venous system. (From Timm EJ, Stragand JJ. Portal hypertension and cirrhosis. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 694, with permission.)

PATHOPHYSIOLOGY

Portal Hypertension and Cirrhosis

The portal vein is the primary vessel leading into the liver; it receives deoxygenated venous blood flow from the small intestine, stomach, pancreas, and spleen (Fig. 19–1). The inflow from these organ systems accounts for approximately 75% of the blood delivered to the liver. The hepatic artery provides the remaining 25% of the blood supply in the form of oxygenated blood from the abdominal aorta. Normal portal vein pressure is between 5 and 10 mm Hg; this level maintains blood flow to the liver at approximately 1 L/minute. Portal hypertension occurs when portal vein pressure exceeds 10 to 12 mm Hg.[10,11]

Portal hypertension is a consequence of increased resistance to blood flow through the portal vein. Increased resistance is usually due to restructuring of intrahepatic tissue (sinusoidal damage) but may also be caused by presinusoidal damage such as portal vein occlusion from trauma, malignancy, or thrombosis. A third (and the least common) mechanism is outflow obstruction of the hepatic vein. This latter damage is posthepatic, and normal liver structure is maintained. This chapter will focus on portal hypertension caused by intrahepatic damage from cirrhosis.

Sinusoidal damage from cirrhosis is the most common cause of portal hypertension. The sinusoids are porous vessels within the liver that surround radiating rows of hepatocytes, the basic functional cells of the liver (Fig. 19–2). Progressive destruction of hepatocytes and an increase in fibroblasts and connective tissue surrounding the hepatocytes culminate in cirrhosis. Fibrosis and regenerative nodules of scar tissue

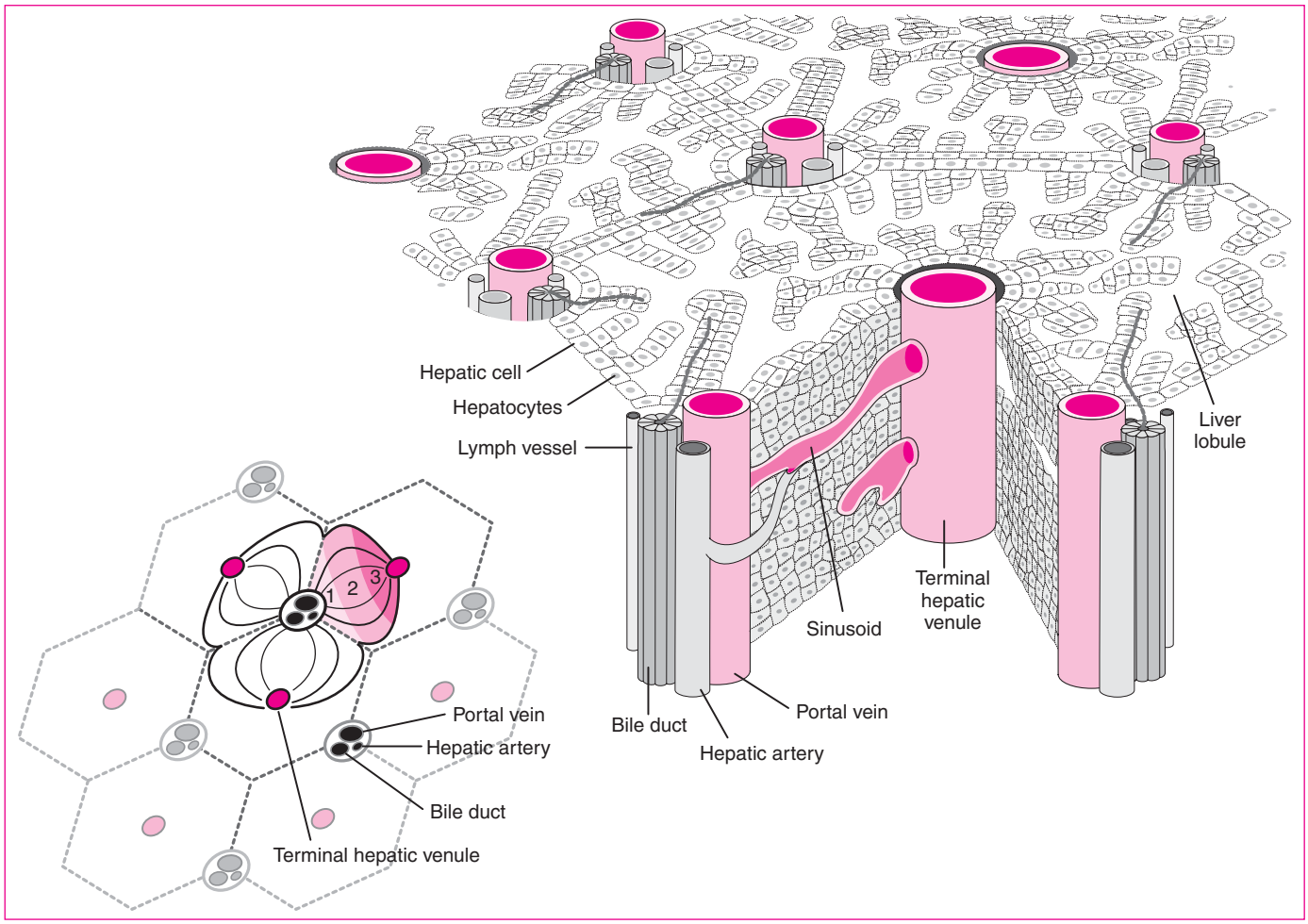


FIGURE 19–2. Relationship of sinusoids to hepatocytes and the venous system. (From Timm EJ, Stragand JJ. Portal hypertension and cirrhosis. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 695, with permission.)

modify the basic architecture of the liver, disrupting blood flow and liver function. Reduced hepatic blood flow alters normal metabolic breakdown processes and decreases protein synthesis within the liver.

The sinusoids transport both portal and arterial blood to the hepatocytes. The systemic blood delivered to the liver contains nutrients, drugs, and ingested toxins. The liver processes the nutrients (carbohydrates, proteins, lipids, vitamins, and minerals) for either immediate use or for storage, while the drugs and toxins are metabolized through a variety of processes known as "first-pass" metabolism. The liver also processes metabolic waste products for excretion. In cirrhosis, bilirubin (from the enzymatic breakdown of heme) can accumulate; this causes jaundice (yellowing of the skin), scleral icterus (yellowing of the sclera), and tea-colored urine (urinary bilirubin excretion).

Changes in steroidal hormone production, conversion, and handling are also prominent features of cirrhosis. These changes can result in decreased libido, gynecomastia (development of breast tissue in men), testicular atrophy, and features of feminization in male patients. Another deleterious effect of changes in sex hormone metabolism is the development of spider angiomata (nevi). Spider angiomata are vascular lesions found mainly on the trunk. The lesion has a central arteriole (body) surrounded by radiating "legs." When blanched, the lesions fill from the center body outward toward the legs. Spider angiomata are not specific to cirrhosis, but the number and size do correlate with disease severity and their presence relates to risk of variceal hemorrhage.[12]

Increased intrahepatic resistance to portal flow increases pressure on the entire splanchnic bed; an enlarged spleen (splenomegaly) is a common finding in cirrhotic patient and can result in thrombocytopenia due to splenic sequestration of the platelets. Portal hypertension mediates systemic and splanchnic arterial vasodilation through production of nitric oxide and other vasodilators in an attempt to counteract the increased pressure gradient. Nitric oxide causes a fall in systemic arterial pressure; unfortunately, this activates both the renin-angiotensin-aldosterone and sympathetic nervous systems and

increases antidiuretic hormone (vasopressin) production.[13] The activation of these systems is an attempt to maintain arterial blood pressure through increases in renal sodium and water retention. Increased systemic and portal pressure put increased pressure on the vascular system. The umbilical vein, which is usually eradicated in infancy, may become patent and increase blood flow to the abdominal veins. The prominent veins are called caput medusae because they resemble the head of the mythical Gorgon Medusa.

The aim of pharmacologic treatment in portal hypertension is to decrease portal pressure and reduce the effects of sympathetic activation.

Ascites

Ascites is the accumulation of fluid in the peritoneal space and is often one of the first signs of decompensated liver disease. Ascites is the most common complication of cirrhosis and portends a dire prognosis.[14]

The pathophysiologic mechanisms of portal hypertension and of cirrhosis itself are entwined with the mechanisms of ascites (Fig. 19–3). Cirrhotic changes and the subsequent decrease in synthetic function lead to a decrease in production of albumin (hypoalbuminemia). Albumin is the major intravascular protein involved in maintaining oncotic pressure in the vascular system; low serum albumin levels and increased capillary permeability allow fluid to leak from the vascular space into body tissues. This can result in peripheral edema, ascites, and fluid in the pulmonary system. The obstruction of hepatic sinusoids and hepatic lymph nodes allows fluid to seep into the peritoneal cavity, further contributing to ascitic fluid formation.

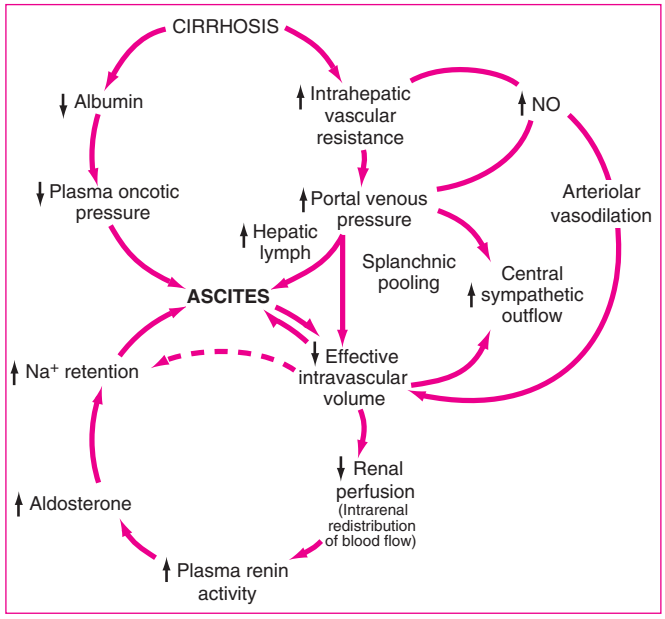


FIGURE 19–3. Factors involved in the development of ascites. NO, nitric oxide. (From Chung RT, Podolsky DK. Cirrhosis and its complications. In: Kasper DL, Braunwald E, Fauci AS, et al, (eds.) Harrison's Principles of Internal Medicine. 16th ed. New York: McGraw-Hill, 2005: 1858–1869, with permission.)

As previously discussed, increased portal pressure triggers the release of nitric oxide to directly vasodilate the splanchnic arterial bed and decrease portal pressure. Unfortunately, nitric oxide also dilates the systemic arterial system, causing a decrease in blood pressure and a decrease in renal perfusion by lowering the effective intravascular volume. The kidney reacts by activating the renin-angiotensin-aldosterone system, which increases plasma renin activity, aldosterone production, and sodium retention. This increase in intravascular volume furthers the imbalance of intravascular oncotic pressure, allowing even more fluid to escape to the extravascular spaces.

Vasodilation and decreased arterial pressure are also detected centrally. The sympathetic nervous system is activated to increase blood pressure, which in turn increases portal pressure. Unchecked, these combined effects enable the cycle of portal pressure and ascites to continue, setting up a self-perpetuating loop of ascites formation.

Most patients with large ascites also retain sodium avidly and may become hyponatremic if there is a decrease in free water excretion. Untreated, this can lead to a decrease in renal function and the hepatorenal syndrome.[4,13]

Varices

The splanchnic system drains venous blood from the GI tract to the liver. In portal hypertension there is increased resistance to drainage from the originating organ so collateral vessels (varices) develop in the esophagus, stomach, and rectum to compensate for the increased blood volume. Varices divert blood meant for hepatic circulation back to the systemic circulation; this has the unintended deleterious effect of decreasing clearance of medications and potential toxins through loss of first-pass metabolism. Varices are weak superficial vessels, and any additional increase in pressure can cause these vessels to rupture and bleed.[15]

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is an acute bacterial infection of peritoneal fluid in the absence of intra-abdominal infection or intestinal perforation. Estimates of the prevalence of SBP in patients with ascites range from 10% to 30%.[16] Enteric gram-negative aerobes are the most common bacteria isolated from ascitic fluid; usually *Escherichia coli* or *Klebsiella pneumoniae*. One proposed cause is translocation of intestinal bacteria seeding the ascitic fluid.[17] Bacterial translocation correlates with the delay in intestinal transit time and increased intestinal wall permeability observed in cirrhotic patients. Another possible mechanism is the hematogenous spread of bacteria into the peritoneal space.[18] *Streptococcus pneumoniae* is the most common gram-positive pathogen associated with SBP.[19] Once a bacterial pathogen has been identified, the antibiotic spectrum can be narrowed; SBP is rarely polymicrobial.

Hepatic Encephalopathy

Decreased cognition, confusion, and changes in behavior combined with physical signs such as asterixis (characteristic flapping of hands upon extension of arms with wrist flexion) indicate hepatic encephalopathy (HE). To objectively stage the degree of impairment, the patient should be assessed in five distinct categories:

1. Level of consciousness
2. Cognition (attention, memory, and disorientation)
3. Behavior (e.g., mood, anger, and paranoia)
4. Motor function (e.g., coordination, reflexes, and asterixis)
5. Response to psychometric tests

These changes may be acute, and therefore possibly reversible, or they may be of a more chronic, insidious nature from which patients rarely recover.

Numerous factors, many of them poorly understood, are involved in the development of HE. In severe hepatic disease, systemic circulation bypasses the liver, so many of the substances normally metabolized by the liver remain in the systemic circulation and accumulate to toxic levels. In excess, these metabolic by-products, especially nitrogenous waste, cause alterations in central nervous system functioning.[20]

Ammonia (NH_3) is just one of the toxins implicated in HE. It is a metabolic by-product of protein catabolism and is also generated by bacteria in the GI tract. In a normally functioning liver, hepatocytes take up ammonia and degrade it to form urea, which is then renally excreted. In patients with cirrhosis, the conversion of ammonia to urea is retarded and ammonia accumulates, resulting in encephalopathy. This decrease in urea formation is manifest on laboratory assessment as decreased blood urea nitrogen (BUN), but BUN levels do not correlate with degree of HE. Patients with HE commonly have elevated serum ammonia concentrations, but the levels do not correlate well with the degree of central nervous system impairment.[20]

False neurotransmitters resulting from increased levels of aromatic amino acids, high levels of γ-aminobutyric acid, and endogenous benzodiazepines have also been implicated in HE. These substances bind to both the γ-aminobutyric acid and benzodiazepine receptors and act as agonists at the active receptor sites.[20]

Patients with previously stable cirrhosis who develop acute encephalopathy often have an identifiable precipitating event that can account for the increased production and/or decreased elimination of these toxins. Infections, variceal hemorrhage, renal insufficiency, electrolyte abnormalities, and increased dietary protein have all been associated with acute development of HE.

Bleeding Diathesis and Synthetic Failure

Coagulopathies signal end-stage liver disease. The liver manufactures coagulation factors essential for blood clotting and maintenance of blood homeostasis. With advanced disease the liver is unable to synthesize these proteins, resulting in extended clotting times (e.g., prothrombin time) and bleeding irregularities.[21] An additional coagulation abnormality seen in advanced liver disease is thrombocytopenia. This is a result of decreased platelet production and splenic sequestration of platelets. Macrocytic anemia may also occur because of decreased intake, metabolism, and storage of folate and vitamin B_{12}.

Alcoholic Liver Disease

Progression of alcoholic liver disease moves through several distinct phases from development of fatty liver to the development of alcoholic hepatitis and cirrhosis. Fatty liver and alcoholic hepatitis may be reversible with cessation of alcohol intake, but cirrhosis itself is irreversible. Although the scarring of cirrhosis is permanent, maintaining abstinence from alcohol can still decrease complications and slow development to end-stage liver disease.[22] Continuing to imbibe speeds the advancement of liver dysfunction and its complications.

Metabolism of ethanol begins even prior to absorption, when alcohol dehydrogenase (ADH) within the gastric mucosa oxidizes a portion of the alcohol to **acetaldehyde**. The remaining alcohol is rapidly absorbed from the GI tract, and since it is highly lipid-soluble, it enters the body tissues quite easily. ❷ *ADH metabolizes ethanol in body tissues, primarily the liver, producing hypoxic damage.*[23] High levels of ethanol saturate the ADH enzyme system; when the ADH system is overwhelmed, the microsomal ethanol oxidizing system must take over the detoxification process. The microsomal ethanol oxidizing system is an inducible cytochrome P-450 (CYP)450 enzyme system; it participates in phase 1 metabolism and also produces acetaldehyde as its end product.[24,25] Acetaldehyde exerts direct toxic effects on the liver by damaging hepatocytes, inducing fibrosis, and by directly coupling to proteins, interfering with their intended actions. Metabolism of large amounts of ethanol shifts hepatic metabolic processes away from oxidation and toward reduction. This shift produces a change in metabolism accounting for the fatty liver, hypertriglyceridemia, and acidemia observed in alcoholic liver disease.

Less Common Causes of Cirrhosis

Genetics and metabolic risk factors mediate other less common causes of cirrhosis. These diseases vary widely in prevalence, disease progression, and treatment options.

Primary biliary cirrhosis is characterized by progressive inflammatory destruction of the bile ducts. Immune-mediated inflammation of intrahepatic bile ducts results in remodeling and scarring, causing retention of bile within the liver and subsequent hepatocellular damage and cirrhosis. The number of patients affected with primary biliary cirrhosis is difficult to estimate because many people are asymptomatic and incidental diagnosis during routine health care visits is common.



Clinical Presentation of Cirrhosis and Complications of Portal Hypertension

General

- Most signs and symptoms that bring patients to the attention of medical personnel are specific to the complication the patient is experiencing and vary with severity and suddenness of onset.

Symptoms

- Patients with cirrhosis may exhibit nonspecific symptoms such as fatigue and weakness but may be asymptomatic until acute complications develop.
- Nonspecific symptoms include anorexia, fatigue, easy bruising and bleeding from minor injuries, decreased libido, and pruritus (particularly with biliary involvement).
- Patients with ascites may complain of abdominal pain, nausea, increasing tightness and fullness in the abdomen, shortness of breath and early satiety.
- Hemorrhage associated with variceal bleeding may be associated with nausea, vomiting, and hematemesis. Patients may also present with pallor, fatigue, and weakness from blood loss.
- In patients with bleeding varices, digestion of swallowed blood represents a high protein load; this causes nausea and can precipitate symptoms of HE.
- In patients with HE, neurologic changes can be overwhelming or so subtle that they are not clinically apparent except during a targeted clinical evaluation.
- Patients with HE may complain of disruption of sleep patterns and day-to-night inversion; patients have delayed to-bed and wake times, which may progress to complete inversion of the normal diurnal cycle.
- If SBP occurs, symptoms of infection may include fever, chills, and abdominal pain.

Signs

- Nonspecific signs on physical exam include jaundice, tea-colored urine, bruising, hepatomegaly, splenomegaly, spider angiomata, caput medusae, palmar erythema, gynecomastia, and testicular atrophy.
- Ascites can be detected by increased abdominal girth accompanied by shifting dullness and a fluid wave.
- Signs of variceal bleeding depend on the degree of blood loss and abruptness of onset. Rapid and massive blood loss is more likely to result in hemodynamic instability than is slow, steady bleeding. Signs of acute bleeding may include pallor, hypotension, tachycardia, mental status changes, and hematemesis.
- Markers of hepatic encephalopathy include decreased cognition, confusion, changes in behavior, and asterixis.
- Patients with SBP may present with fever, abdominal pain, and changes in mental status.
- Decreases in clotting factors may manifest as abnormal bruising and bleeding.
- Dupuytren's contracture is a contraction of the palmar fascia that usually affects the fourth and fifth digits.[27] It is not specific to cirrhosis and can be seen in repetitive use injuries.

Laboratory Abnormalities

- Hepatocellular damage manifests as elevated serum aminotransferases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)]. The degree of transaminase elevation does not correlate with the remaining functional metabolic capacity of the liver. An AST level two-fold higher than ALT is indicative of alcoholic liver damage.
- Elevated alkaline phosphatase is nonspecific and may correlate with liver or bone disease; it tends to be elevated in biliary tract disease.
- γ-Glutamyl transferase (GGT) is specific to the bile ducts, and in conjunction with an elevated alkaline phosphatase, suggests hepatic disease. Extremely elevated GGT levels further indicate obstructive biliary disease. GGT is also elevated in those who drink three or more alcoholic drinks daily.
- Increased total, direct, and indirect bilirubin concentrations indicate defects in transport, conjugation, or excretion of bilirubin.
- Lactate dehydrogenase (LDH) is a nonspecific marker of hepatocyte damage; disproportionate elevation of LDH indicates ischemic injury.
- Thrombocytopenia may occur because of decreased platelet production and splenic platelet sequestration.
- Anemia (decreased hemoglobin and hematocrit) occurs as a result of variceal bleeding, decreased erythrocyte production, and hypersplenism.
- Elevated prothrombin time (PT) and International Normalized Ratio (INR) are coagulation derangements that indicate loss of synthetic capacity in the liver and correlate with functional loss of hepatocytes.
- Decreased serum albumin and total protein occur in chronic liver damage due to loss of synthetic capacity within the liver.
- The serum albumin-to-ascites gradient is greater than or equal to 1.1 g/dL (11 g/L) in association with portal hypertension.
- Increased blood ammonia concentration is characteristic of hepatic encephalopathy, but levels do not correlate well with the degree of impairment.
- Signs and symptoms of SBP in a patient with cirrhosis and ascites should prompt a diagnostic paracentesis (Fig. 19–4). In SBP, there is decreased total serum protein, elevated white blood cell count (with left shift), and the ascitic fluid contains at least $0.250 \times 10^3/mm^3$ ($0.250 \times 10^9/L$) neutrophils. Bacterial culture of ascitic fluid may be positive, but lack of growth does not exclude the diagnosis.

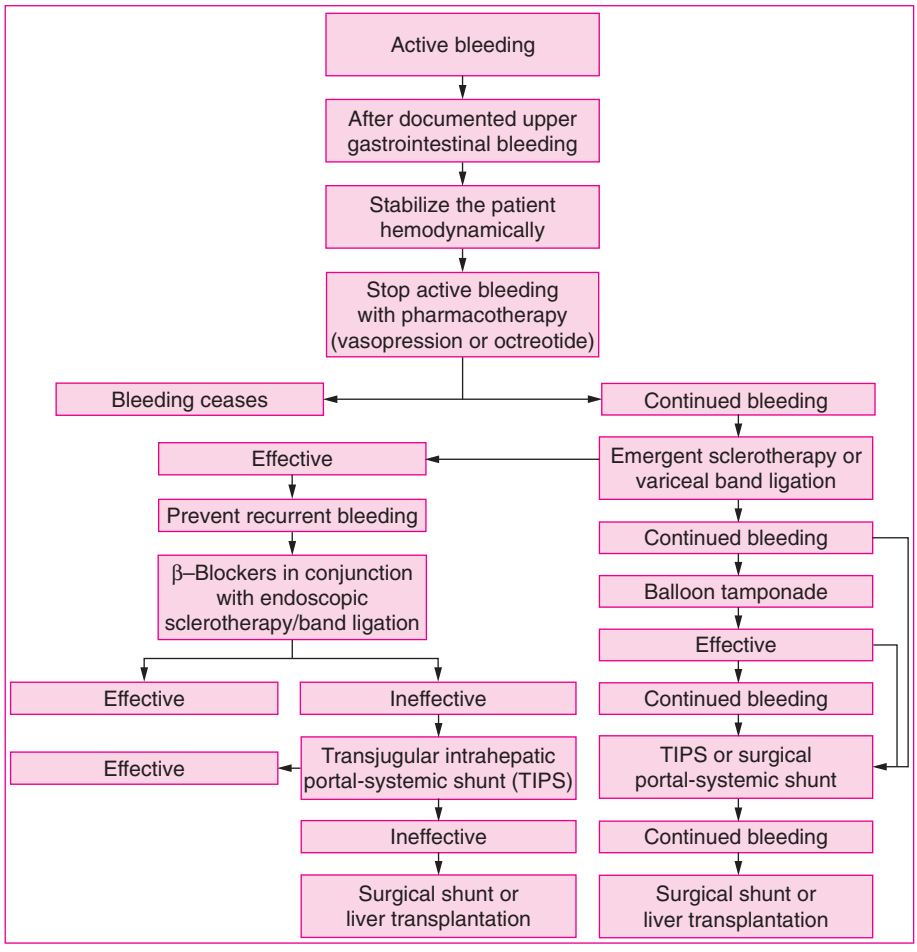


FIGURE 19–4. Treatment algorithm for active gastrointestinal bleeding resulting from portal hypertension. (From Schianotd, Bodenheimer HC. Complications of Chronic Liver Disease. In: Friedman SL, McQuaid KR, Grendell JH (eds.) Current Diagnosis & Treatment in Gastroenterology. 2nd ed. New York: McGraw-Hill, 2003, with permission)

Non-alcoholic fatty liver disease begins with asymptomatic fatty liver but may progress to cirrhosis. This is a disease of exclusion; elimination of any possible viral, genetic, or environmental causes must be made prior to making this diagnosis. Non-alcoholic fatty liver disease is related to numerous metabolic abnormalities. Risk factors include diabetes mellitus, dyslipidemia, obesity, and other conditions associated with increased hepatic fat.[26]

Hereditary hemochromatosis is an autosomal recessive disease of increased intestinal iron absorption and deposition in hepatic, cardiac, and pancreatic tissue. Hepatic iron overload results in the development of fibrosis, hepatic scarring, cirrhosis, and hepatocellular carcinoma. Hemochromatosis can also be caused by repeated blood transfusions, but this mechanism rarely leads to cirrhosis.

Wilson's disease is another autosomal recessive disease leading to cirrhosis. Protein abnormalities result in excessive copper deposition in body tissues. The faulty protein is responsible for facilitating copper excretion in the bile, so copper accumulates in hepatic tissue. High copper levels within hepatocytes are toxic, and fibrosis and cirrhosis may develop in untreated patients. Those with Wilson's disease usually present with symptoms of liver or neurologic disease while still in their teens.

A third autosomal recessive genetic disease is α_1-antitrypsin deficiency. Abnormalities in the α_1-antitrypsin protein impair secretion from the liver. α_1-Antitrypsin deficiency causes cirrhosis in children as well as adults; adults usually have concomitant pulmonary disease such as chronic obstructive pulmonary disease.

CLINICAL PRESENTATION AND DIAGNOSIS

Diagnosis of Cirrhosis

In some cases, cirrhosis is diagnosed incidentally before the patient develops symptoms or acute complications. Other patients may have decompensated cirrhosis at initial presentation; they may present with variceal bleeding, ascites, SBP, or HE. Patients may also have some of the laboratory abnormalities and/or signs and symptoms listed above that are associated with cirrhosis.[28]

Ultrasound examination is used routinely to evaluate cirrhosis; a small, nodular liver with increased echogenicity is consistent with cirrhosis. Liver biopsy is the only way to diagnose cirrhosis definitively, but it is often deferred in lieu of a

TABLE 19–1. Child-Pugh and MELD Classifications for Determining Severity of Liver Damage

Child-Pugh Classification[a] Variable	1 Point	2 Points	3 Points
Bilirubin (mg/dL)	Less than 2	2–3	Greater than 3
(μmol/L)	Less than 34	34–51	Greater than 51
Albumin (g/dL)	Greater than 3.5	2.8–3.5	Less than 2.8
(g/L)	Greater than 35	28–35	Less than 28
Prothrombin time (seconds prolonged)	1–3	4–6	Greater than 6
Ascites	None	Slight	Moderate
Encephalopathy	None	Stages 1–2	Stages 3–4

MELD Classification

The formula for the MELD score is $3.8 \times \log_e$ [bilirubin (mg/dL)] + $11.2 \times \log_e$ (INR) + $9.6 \times \log_e$ [creatinine (mg/dL)] + 6.4 × (etiology: 0 if cholestatic or alcoholic, 1 otherwise).

[a]Class A: 1–6 total points; B: 7–9 points; C: 10–15 points.
INR, International Normalized Ratio; MELD, Model for End-Stage Liver Disease.

presumptive diagnosis since it is an invasive procedure. The decision to perform a biopsy is based on the expected clinical utility of the biopsy results. If the results could change the course of treatment, it may be advisable to perform a biopsy. The Child-Pugh and Model for End-Stage Liver Disease (MELD) classification systems (Table 19–1) are used to classify disease severity and evaluate the need for transplantation.

Patients with ascites or known varices must be assumed to have portal hypertension and are treated as such, even if direct measurements of portal pressure have not been made.[29]

Diagnosis of Ascites

In obese patients or those with only small amounts of fluid accumulation, ultrasound evaluation may be necessary to detect ascites with certainty.

Analysis of ascitic fluid obtained during paracentesis provides diagnostic clues to the etiology of the ascites. Diagnostic evaluation should include cell count with differential, albumin, total protein, Gram stain, and bacterial cultures. In patients without an established diagnosis of liver disease, the serum-ascites albumin gradient (SAAG) is sensitive in determining if the ascites is caused by portal hypertension.[22] SAAG compares the serum albumin concentration to the ascitic fluid albumin concentration:

$$Alb_{serum} - Alb_{ascites} = SAAG$$

A value of greater than or equal to 1.1 g/dL (greater than or equal to 11 g/L) identifies portal hypertension as the cause of the ascites with 97% accuracy.[22,30] In portal hypertension the ascitic fluid is low in albumin; this balances the oncotic pressure gradient with the hydrostatic pressure gradient of portal hypertension. The differential diagnoses for SAAG values less than 1.1 g/dL (less than 11 g/L) include peritoneal carcinoma, peritoneal infection (tuberculosis, fungal, or cytomegalovirus), and nephrotic syndrome. Serum albumin measurements should be made at the same time ascitic fluid is obtained for an accurate comparison.[22]

TREATMENT OF CIRRHOSIS, PORTAL HYPERTENSION, AND COMPLICATIONS

Desired Outcomes

Recognizing and treating the cause of cirrhosis is paramount. ❸ *Cirrhosis is irreversible; treatments are directed at limiting disease progression and minimizing complications.* The immediate treatment goals are to stabilize acute complications such as variceal bleeding and prevent spontaneous bacterial peritonitis. Once life-threatening conditions have stabilized, the focus shifts to preventing complications and preventing further liver damage. Complication prevention involves both primary and secondary prophylaxis. To determine appropriate prophylactic therapy, a careful analysis of patient characteristics and disease history is mandatory. The sections that follow concentrate on treatment and prevention of cirrhotic complications.

Nonpharmacologic Therapy

Lifestyle modifications can limit disease complications and slow further liver damage. Avoidance of additional hepatic insult is critical for successful cirrhosis treatment. The only proven treatment for alcoholic liver disease is the immediate cessation of alcohol consumption. Patients who have cirrhosis from etiologies other than alcoholic liver disease should also abstain from alcohol consumption to prevent further liver damage.

All patients with ascites require counseling on dietary sodium restriction. Salt intake should be limited to less than 800 mg sodium (2 g sodium chloride) per day. More stringent restriction may cause faster mobilization of ascitic fluid, but adherence to such strict limits is very difficult. Patients usually respond well to sodium restriction accompanied by diuretic therapy.[14,22,31,32] The goal of therapy is to achieve urinary sodium excretion of at least 78 mEq (78 mmol) per day.[22] While a 24-hour urine collection provides this information, a spot urine sodium/ potassium ratio greater than 1.0 provides the same information and is much less cumbersome to perform.

Medication use must be monitored carefully for potential hepatotoxicity. Hepatically metabolized medications have the potential to accumulate in patients with liver disease. Little guidance is available on drug dosing in hepatic impairment because these patients are often excluded from drug trials. Daily acetaminophen use should not exceed 2 g. Dietary supplements have not been well studied in hepatic impairment and cannot be recommended.



Patient Encounter 1, Part 1

ES is a 44-year-old man who presents to the emergency department with complaints of abdominal pain.

Chief complaint
"My belly feels tight"

HPI
Increasing feelings of fullness and abdominal tightness that have become noticeable over the past 2 weeks, accompanied by nausea without vomiting and decreased food intake

PMH
Hypertension × 15 years, acute pancreatitis × 2 episodes

PSH
No surgeries

SH
Married, currently separated; denies tobacco and illicit drug use; typically drinks a 12-pack of beer daily and several shots of tequila; use has recently increased due to depression over marital separation

FH
Father died at age 45 from coronary disease, mother alive at age 62 with type 2 diabetes mellitus, hypertension, hyperlipidemia, and gastroesophageal reflux disease

Outpatient Meds
Chlorthalidone 25 mg daily

ROS
(+) Anorexia and nausea; denies vomiting, constipation, or diarrhea; patient endorses moderate shortness of breath and dyspnea on exertion

PE
VS: Blood pressure 125/75 mm Hg, pulse 84 beats per minute, temperature 37.3°C (99.1°F), respiratory rate 18/minutes, oxygen saturation 98% on room air
CV: RRR, no murmurs, rubs, or gallops
Chest: CTA bilaterally, no crackles or wheezes
Abd: Tense, distended abdomen that is tender to palpation, decreased bowel sounds, (+) hepatosplenomegaly
Exts: 2+ pedal pulses, 2+ pitting edema

- What are this patient's risk factors for liver disease?
- Identify features of his presentation that are consistent with cirrhosis.

In patients with variceal bleeding, nasogastric suction reduces the risk of aspirating stomach contents. Aspiration pneumonia is a major cause of death in patients with variceal bleeding. Nasogastric suction is also helpful in decreasing vomiting during acute episodes of variceal bleeding.[33,34] Blood within the gastrointestinal tract is very nauseating; removal of the blood can decrease vomiting.

In acute hepatic encephalopathy, temporary protein restriction to decrease the rate of ammonia production can be a useful adjuvant to pharmacologic therapy, but long-term protein restriction in cirrhotic patients is not recommended. These patients are already in a nutritionally deficient state, and prolonged protein restriction will exacerbate the problem.[20]

Vaccination against hepatitis A and B is recommended in patients with underlying cirrhosis to prevent additional liver damage from an acute viral infection.[35] Pneumococcal and influenza vaccination may also be appropriate and can reduce hospitalizations due to influenza or pneumonia.

Endoscopic band ligation and sclerotherapy are both means to stop acutely bleeding varices. Endoscopic band ligation is the application of a stricture around the varix, whereas sclerotherapy involves injecting the varix with substances designed to decrease blood flow to the area and prevent rebleeding. Endoscopic band ligation has replaced sclerotherapy as the preferred endoscopic treatment and is effective in stopping acute variceal bleeding in up to 90% of patients.[36] It is the standard of care for secondary prophylaxis of repeat bleeding in patients with a history of either esophageal or gastric variceal bleeding. Endoscopic band ligation is best used in conjunction with pharmacologic treatment.[37–39]

Balloon tamponade involves the application of direct pressure to the area of bleeding with an inflatable balloon attached to a nasogastric tube. It is an option for patients in whom drug therapy and band ligation fail to stop variceal bleeding. Balloon tamponade is used only when other methods have failed. Once the direct pressure of the balloon is removed, rebleeding often occurs, so balloon tamponade is only a temporary measure prior to more definitive treatment such as shunting.[11]

Shunts are long-term solutions to decrease elevated portal pressure. They divert blood flow either through or around the diseased liver, depending on the location and type of shunt employed. Transjugular intrahepatic portosystemic shunts (TIPS) create a communication pathway between the intrahepatic portal vein and the hepatic vein. TIPS procedures have an advantage over surgically-inserted shunts because they are placed through the vascular system rather than through an invasive surgical procedure, but they still carry a risk of bleeding and infection. TIPS placement is also associated with an increased incidence of hepatic encephalopathy.[40] This results from decreased detoxification of nitrogenous waste products because the shunt allows blood to evade metabolic processing.

Pharmacologic Therapy

Drug therapy for portal hypertension and cirrhosis can alleviate symptoms and prevent complications but it cannot reverse cirrhosis. Drug therapy is available to treat the complications of ascites, varices, spontaneous bacterial peritonitis, hepatic encephalopathy, and coagulation abnormalities.

Portal Hypertension

❹ *Non-selective β-blockers such as propranolol and nadolol are first-line treatments to reduce portal hypertension.* This effect reduces bleeding and decreases mortality in patients with known varices. Use of β-blockers to prevent variceal formation is controversial.

Only non-selective β-blockers reduce bleeding complications in patients with known varices. Blockade of β_1 receptors reduces cardiac output and splanchnic blood flow. β_2-Adrenergic blockade prevents β_2-receptor–mediated splanchnic vasodilation while allowing unopposed α-adrenergic effects; this enhances vasoconstriction of both the systemic and splanchnic vascular beds. The combination of β_1 and β_2 effects makes the non-selective β-blockers preferable to cardioselective agents in treating portal hypertension.[1,36,41]

Because β-blockers decrease blood pressure and heart rate, they should be started at low doses to increase tolerability. Propranolol is hepatically metabolized, and its half-life and pharmacologic effects are prolonged in portal hypertension. A reasonable starting dose of propranolol is 10 mg two to three times daily.

Doses should be titrated as tolerated with the goal of decreasing heart rate by 25% or to approximately 55 to 60 beats/minute.[11,36] Heart rate is not an accurate marker for portal pressure reduction, but it is the accepted surrogate marker for effectiveness because there are no other acceptable alternatives.

Nitrates have been suggested in patients who do not achieve therapeutic goals (heart rate reduction) with β-blocker therapy alone. Trials to evaluate the effects of nitrates (e.g., isosorbide mononitrate) on portal pressure, both alone and in combination with β-blockers, show enhanced reduction of portal pressure; however, there is an increase in mortality when nitrates are used alone. Adverse effects are significantly higher in patients treated with the combination of non-selective β-blockers and nitrates as opposed to β-blocker monotherapy.[42,43] Unfortunately, β-blockers either alone or in combination may be intolerable for many patients with cirrhosis.

Ascites

❺ *The goals of treating ascites are to minimize acute discomfort, re-equilibrate ascitic fluid, and prevent SBP. Treatment should modify the underlying disease pathology; without directed therapy, fluid will rapidly re-accumulate.*

In the case of tense ascites, relief of acute discomfort may be accomplished by therapeutic paracentesis. Often the removal of just 1 to 2 L of ascitic fluid provides relief of pain and fullness. When removing 5 L or more of fluid at once, volume resuscitation with 8 to 10 g of albumin given intravenously should be provided for each liter of fluid removed. If less than 5 L of fluid is removed in a hemodynamically stable patient, albumin is not warranted.[22]

Diuretics

Diuretics are often required in addition to the sodium restriction described previously. ❻ *Spironolactone and furosemide form the basis of pharmacologic therapy for ascites. Spironolactone is an aldosterone antagonist and counteracts the effects of activation of the renin-angiotensin-aldosterone system.* In hepatic disease not only is aldosterone production increased, but its half-life is prolonged because it is hepatically metabolized. Spironolactone acts to conserve the potassium that would be otherwise excreted because of elevated aldosterone levels.

Spironolactone is usually used in combination with a loop diuretic (e.g., furosemide) for more potent diuresis. A ratio of 40 mg furosemide (the most commonly used loop diuretic) to



Patient Encounter, Part 2

In the emergency department, a chest x-ray was normal. The following laboratory test results were obtained:

Sodium 128 mEq/L (mmol/L)	Platelets 178 × 10^3/mm^3 (× 10^9/L)
Potassium 3.1 mEq/L (mmol/L)	Albumin 2.7 g/dL (27 g/L)
Chloride 106 mEq/L (mmol/L)	Total bilirubin 2.3 mg/dL (39.3 μmol/L)
Bicarbonate 24 mEq/L (mmol/L)	Alk phos 177 IU/L (2.95 μKat/L)
BUN 27 mg/dL (9.64 mmol/L)	AST 443 IU/L (7.38 μKat/L)
Scr 1.1 mg/dL (97.2 μmol/L)	ALT 206 IU/L (3.43 μKat/L)
Glucose 145 mg/dL (8.05 mmol/L)	INR 1.6
Hemoglobin 12.5 g/dL (7.75 mmol/L)	GGT 185 IU/L (3.1 μKat/L)
Hematocrit 38% (0.38)	LDH 203 IU/L (3.38 μKat/L)
WBC count 7.4 × 10^3/mm^3 (× 10^9/L)	PT 29 seconds

- Which of these values are consistent with the diagnosis of cirrhosis?
- Does the current presentation imply the underlying cause of the disease?
- Are the laboratory results suggestive of complications related to cirrhosis?

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; INR, international normalized ratio; LDH, lactate dehydrogenase; PT, prothrombin time.



Patient Encounter, Part 3

ES is found to have ascites. Therapeutic paracentesis is ordered to relieve shortness of breath and abdominal pain; 4 L of ascitic fluid is removed.

- What are the goals for treating ascites in this patient?
- What lifestyle modifications should the patient make that may decrease his risk of hospitalization and death from cirrhosis?
- What pharmacologic options are available to treat ascites in this patient?

each 100 mg spironolactone usually maintains serum potassium concentrations within the normal range. Therapy is commonly initiated with oral spironolactone 100 mg and furosemide 40 mg per day.

Doses should be titrated at intervals no more frequent than every 2 to 3 days. Because spironolactone is used for its anti-aldosterone effects, much higher doses (up to 400 mg/day) are used than those used when treating hypertension. If intolerable side effects such as gynecomastia occur with spironolactone, other potassium-sparing diuretics may be used, but clinical trials have not shown equivalent efficacy.[22]

The target in treating ascites is to effect a fluid loss of approximately 0.5 L per day.[22] Because ascites equilibrates with vascular fluid at a much slower rate than does peripheral edema, aggressive diuresis is associated with intravascular volume depletion and should be avoided unless patients have concomitant peripheral edema. Patients with peripheral edema in addition to ascites may require increasing furosemide doses until euvolemia is achieved; intravenous diuretics are often necessary.[22] Diuretic therapy in cirrhosis is typically lifelong.

Varices

Unfortunately, active variceal bleeding is common; it accounts for between 10% and 30% of all cases of upper GI hemorrhage. ❼ *During acute variceal hemorrhage, crucial desired outcomes include controlling bleeding, preventing rebleeding, and avoiding acute complications such as SBP; mortality from first bleeding episode is up to 55%, and patients must by treated aggressively.* A treatment algorithm for acute variceal bleeding is depicted in Fig. 19–3.

Octreotide

Octreotide is a synthetic analogue of somatostatin; it selectively causes vasoconstriction of the splanchnic bed, decreasing portal venous pressure with few serious side effects. Vasopressin has been used, but since it causes non-selective vasoconstriction, it carries the risk of systemic consequences, which limits its usefulness. The recommended octreotide dose is a 50- to 100-mcg intravenous (IV) loading dose followed by a continuous IV infusion of 25 to 50 mcg/hour. Therapy should continue for at least 24 to 72 hours after bleeding has stopped. Some clinicians continue octreotide for a full 5 days since this is the time frame during which the risk of rebleeding is highest. Octreotide combined with endoscopic therapy results in decreased rebleeding rates and transfusion needs when compared to endoscopic treatment alone.[36]

Spontaneous Bacterial Peritonitis

Initiation of prophylactic antibiotics is recommended during acute variceal bleeding; this is typically done with an oral fluoroquinolone (e.g., ciprofloxacin 500 mg twice daily × 7 days) or an IV third-generation cephalosporin. Prophylactic antibiotic therapy reduces in-hospital infections and mortality in patients hospitalized for variceal bleeding.[44]

If the presence of SBP is suspected, empiric antibiotic therapy with a broad-spectrum anti-infective agent should be initiated until cultures and susceptibilities are available (Fig. 19–5).[45,46] In the setting of presumed infection, delaying



Patient Encounter, Part 4

ES is brought to the emergency department by ambulance 2 months after the initial presentation.

Chief complaint

"I've been vomiting black stuff and I'm really tired"

HPI

Hematemesis for the past 2 days, worsening today and accompanied by profound weakness; patient is continuing to drink alcohol at the same rate

Outpatient Meds

Spironolactone 100 mg daily

Furosemide 40 mg daily

ROS

(+) Nausea, coffee-grounds emesis, and melena; denies constipation or diarrhea; (+) bilateral lower extremity edema

PE

VS: Blood pressure 98/60 mm Hg, pulse 122 beats per minute, temperature 37.1°C (98.8°F), respiratory rate 21/minutes, oxygen saturation 91% on room air
CV: Tachycardia, no murmurs, rubs, or gallops
Chest: CTA bilaterally
Abd: Mildly distended, tender to deep palpation, decreased bowel sounds, (+) hepatosplenomegaly and fecal occult blood test
Exts: Decreased pedal pulses, 3+ pitting edema

- What are the immediate treatment goals for ES?
- Does this presentation warrant prophylaxis to prevent further disease complications?

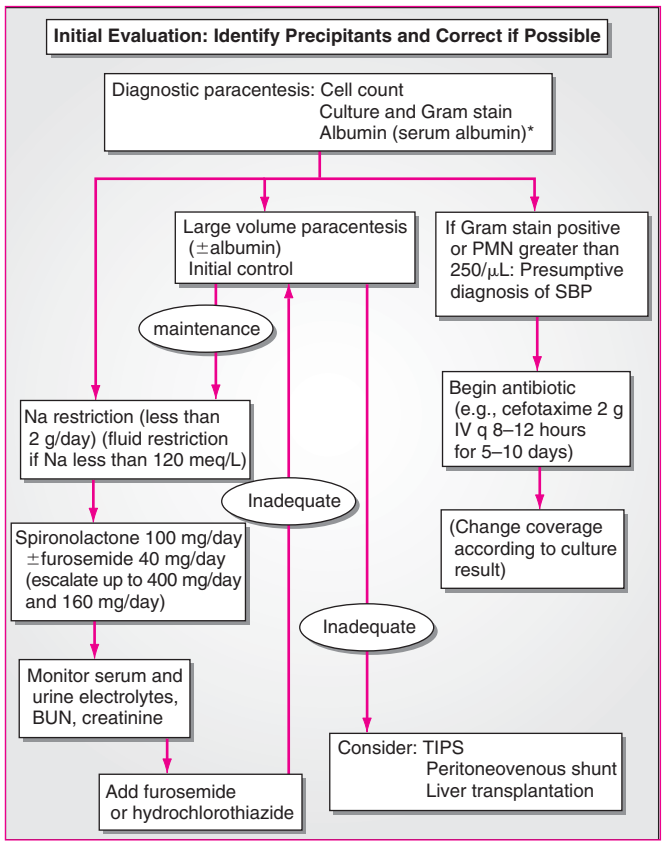


FIGURE 19–5. Approach to the patient with ascites and spontaneous bacterial peritonitis (SBP).
*If PMN greater than 250/μL but culture is negative (culture-negative neutrocytic ascites) begin empiric antibiotics and retap after 48 hours. If culture is positive but PMN less than 250/μL, treat as if PMN greater than 250/μL (presumed SBP). If polymicrobial infection exists, exclude SBP.
BUN, blood urea nitrogen; IV, intravenous; Na, sodium; PMN polymorphonuclear leukocyte; TIPS, transjugular intrahepatic portosystemic shunt. (From Chung RT, Podolsky DK. Cirrhosis and its complications. In: Kasper DL, Braunwald E, Fauci AS, et al, (eds.) *Harrison's Principles of Internal Medicine*. 16th ed. New York: McGraw-Hill, 2005: 1858–1869, with permission.)

treatment while awaiting laboratory confirmation is inappropriate and may result in death. The initial antibiotic should be an intravenous third-generation cephalosporin (e.g., cefotaxime 2 g every 4–8 hours, ceftriaxone 2 g every 24 hours), an intravenous extended-spectrum penicillin (e.g., piperacillin–tazobactam 3.375 g every 6 hours or 4.5 g every 8 hours), or an oral fluoroquinolone (e.g., levofloxacin 500 mg every day), since these agents cover the most common gram-negative and gram-positive agents. Third-generation cephalosporins are usually recommended as first-line therapy; fluoroquinolones are used if resistant (extended-spectrum β-lactamase positive) organisms are suspected. Once an infectious agent has been identified, antibiotic coverage can be narrowed to an agent that is highly active against that organism.

SBP has been associated with development of significant renal failure. Treatment with intravenous albumin can mitigate these effects when dosed at 1.5 g/kg of body weight initially, followed by 1 g/kg of body weight on day three of therapy.[47]

❽ *Patients who have previously experienced spontaneous bacterial peritonitis and have low-protein ascites* (ascitic fluid albumin less than 1 g/dL [less than 10 g/L]) *are candidates for long-term prophylactic therapy*. Recommended regimens include either a single trimethoprim-sulfamethoxazole double-strength tablet 5 days per week (Monday through Friday) or ciprofloxacin 750 mg once weekly.[19,46] Any patient who has experienced an episode of variceal bleeding should also receive prophylactic antibiotics.

Encephalopathy

Lactulose

❾ *Lactulose is the foundation of pharmacologic therapy to prevent and treat hepatic encephalopathy. It is a non-digestible synthetic disaccharide laxative that is hydrolyzed in the gut to an osmotically-active compound that draws water into the colon and stimulates defecation. Lactulose also lowers colonic pH, which favors the conversion of ammonia (NH_3) to ammonium (NH_4^+).*[48] *Ammonium is ionic and cannot cross back into systemic circulation; it is eliminated in the feces.* Lactulose is usually initiated at 15 to 30 mL two to three times per day and titrated to a therapeutic goal of two to four soft bowel movements daily.[20,49,50]



Patient Encounter, Part 5

During the hospital stay, ES had endoscopic band ligation to treat esophageal and gastric varices. Propranolol 20 mg three times a day was initiated; IV furosemide 60 mg twice daily resolved the pedal edema. Prescriptions for spironolactone 200 mg daily and furosemide 40 mg twice daily were provided at discharge. Three weeks later, ES is brought to clinic by his daughter who states that he is confused and "doesn't seem like himself." She is unsure if he has been taking his medication but says he continues to drink and has been eating poorly.

- What are the presenting signs and symptoms of hepatic encephalopathy?
- What factors could contribute to hepatic encephalopathy in this patient?
- What is the prognosis for this patient who has developed ascites, variceal bleeding, and hepatic encephalopathy within 3 months?

Flumazenil

Evidence for the false transmitter theory as the cause of encephalopathy is demonstrated by the fact that administration of flumazenil (a benzodiazepine antagonist) has resulted in functional improvement. Unfortunately, long-term benefit has not been shown, and since flumazenil can only be administered parenterally, it is not an appropriate choice for long-term therapy.

Coagulation Abnormalities

Vitamin K is an essential factor in the production of coagulation proteins within the liver. Elevated clotting times from decreased protein synthesis are indistinguishable from those produced by low vitamin K levels caused by malnutrition or poor intestinal absorption. Vitamin K (phytonadione) 10 mg subcutaneously daily for 3 days can help to establish whether the prolonged bleeding time results from loss of synthetic function in the liver or vitamin K deficiency.

OUTCOME EVALUATION

- Re-evaluate the pharmacotherapy regimen at each visit to assess effectiveness, adverse events, and need for drug titration.
- Assess the effectiveness of β-blocker therapy by measuring heart rate. Heart rate reduction of 25% from baseline or to 55 to 60 beats/minute is desirable. Ask the patient specific, directed questions regarding adverse effects of β-blockers; inquire about symptoms of orthostatic hypotension (e.g., lightheadedness, dizziness, or fainting).
- Evaluate effectiveness of diuretic therapy with regard to ascitic fluid accumulation and development of peripheral edema. Ask the patient directed questions about abdominal girth, fullness, tenderness, and pain. Weigh the patient at each visit, and ask the patient to keep a weight diary. Assess for peripheral edema at each visit.
- Measure spot urine sodium/potassium ratio to assess adherence to dietary sodium restrictions.
- Assess dietary sodium intake by patient food recall or by spot urine sodium/potassium ratio for appropriate sodium excretion.
- Obtain complete blood count and PT/INR to assess for anemia, thrombocytopenia, or coagulopathy. Ask about increases in bruising, bleeding, or development of hematemesis, hematochezia, or melena to assess for bleeding.
- Review biopsy reports and laboratory data. Transaminases and blood ammonia levels do not correlate well with disease progression, but increased coagulation times are markers of loss of synthetic function.
- Evaluate for signs and symptoms of hepatic encephalopathy. Mental status changes may be subtle; questioning family members or caregivers about confusion or personality changes may reveal mild hepatic encephalopathy even if the patient is unaware of the deficits.
- In patients taking lactulose therapy, titrate the dose to two to four soft bowel movements daily.



Patient Care and Monitoring

1. Obtain a complete history of alcohol intake and hepatotoxic drug use, including over-the-counter products and dietary supplements.
2. At each encounter, ask the patient specific questions about adherence to prescribed therapy, dietary restrictions and cessation of alcohol intake.
3. At each visit, evaluate the pharmacotherapy regimen for appropriate drug choice and dose, non-prescription drug use, adverse effects, and use of potentially hepatotoxic medications.
4. Question the patient about adverse effects, since hepatically metabolized medications may accumulate and cause adverse effects.
5. Consider antibiotic prophylaxis for SBP in patients with a history of variceal bleeding or prior SBP.
6. Conduct a review of systems and physical examination at each visit to determine if the patient has had progression of complications.
7. Ask specific questions about bleeding, bruising, and fatigue. There is a direct link between loss of synthetic function and disease progression.
8. Refer the patient to substance abuse counseling for education about alcohol cessation if appropriate.
9. Provide education regarding dietary sodium restrictions at each visit; consider a referral to a dietician if appropriate.

ABBREVIATIONS

ADH:	alcohol dehydrogenase
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
BUN:	blood urea nitrogen
CYP:	cytochrome P-450 isoenzyme
GGT:	γ-glutamyl transpeptidase
GI:	gastrointestinal
HE:	hepatic encephalopathy
INR:	International Normalized Ratio
IV:	intravenous
LDH:	lactate dehydrogenase
MELD:	Model for End-Stage Liver Disease
NG:	nasogastric
NH_3:	ammonia
NH_4^+:	ammonium
PT:	prothrombin time
SAAG:	serum-ascites albumin gradient
SBP:	spontaneous bacterial peritonitis
TIPS:	transjugular intrahepatic portosystemic shunt

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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20 PANCREATITIS

Joseph J. Kishel



LEARNING OBJECTIVES

UPON COMPLETION OF THE CHAPTER, THE READER WILL BE ABLE TO:

1. Describe the pathophysiology of acute and chronic pancreatitis.
2. Differentiate the signs and symptoms of acute from chronic pancreatitis.
3. Discuss the clinical implications of pancreatic fluid collections, pancreatic abscess, and pancreatic necrosis in acute pancreatitis.
4. Formulate care plans for managing acute pancreatitis.
5. Identify pharmacologic and nonpharmacologic means of preventing repeat episodes of chronic pancreatitis.
6. Choose appropriate pancreatic enzyme supplementation for patients with chronic pancreatitis.

KEY CONCEPTS

❶ The most common causes of acute and chronic pancreatitis in adults are ethanol abuse and biliary stones.
❷ Pancreatic necrosis occurs within the first 2 weeks of acute pancreatitis and develops in 10% to 30% of patients with acute pancreatitis.
❸ Primary therapy for acute pancreatitis is supportive, with fluid repletion, discontinuation of oral intake, and analgesia.
❹ Medications aimed at decreasing pancreatic enzyme release (e.g., somatostatin), nasogastric suction, and anticholinergic medications have all failed to show benefit in the treatment of acute pancreatitis.
❺ Treatment of chronic pancreatitis is aimed at removing the cause (ethanol abuse or biliary stones), providing analgesia, supplementing with pancreatic enzyme preparations, and implementing dietary restrictions.
❻ Long-term sequelae of chronic pancreatitis include dietary malabsorption, impaired glucose tolerance, cholangitis, and potential addiction to opioid analgesics.

The pancreas is a gland in the abdomen lying in the curvature of the stomach as it empties into the duodenum. The pancreas functions primarily as an exocrine gland, although it also has endocrine function. The exocrine cells of the pancreas are called acinar cells. They produce an alkaline fluid known as pancreatic juice that contains various digestive enzymes. These enzymes are produced and stored as inactive proenzymes within zymogen granules to prevent autolysis and digestion of the pancreas. The zymogen granules are also responsible for enzyme transport to the pancreatic duct. Amylase and lipase are released from the zymogen granules in the active form whereas the proteolytic enzymes are activated in the duodenum by enterokinase. Enterokinase triggers the conversion of trypsinogen to the active protease, trypsin. Trypsin then activates the other proenzymes to their active enzymes.

The pancreatic juice is released through the ampulla of Vater into the duodenum to aid in the digestive process as well as buffer acidic fluid released from the stomach (Fig. 20–1). The pancreas contains a trypsin inhibitor to prevent autolysis.

ACUTE PANCREATITIS

Epidemiology and Etiology

❶ In the Western hemisphere, *acute pancreatitis is caused mainly by ethanol use/abuse and gallstones.* Other common causes of acute pancreatitis include hypertriglyceridemia, endoscopic retrograde cholangiopancreatography (**ERCP**), and autodigestion due to early activation of pancreatic enzymes. Numerous medications have also been implicated as causes of acute pancreatitis (Table 20–1).

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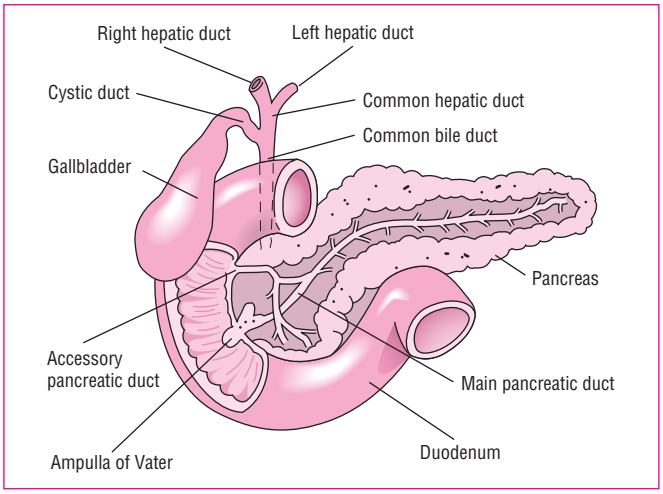


FIGURE 20–1. Anatomic structure of the pancreas and biliary tract. (From Berardi RR, Montgomery PA. Pancreatitis. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 722, with permission.)

Pathophysiology

Ethanol abuse may cause precipitation of pancreatic enzymes in the ducts of the pancreas leading to chronic inflammation and damage. Ethanol itself may be directly toxic to the pancreatic cells. Gallstones may obstruct the ampulla of Vater causing pancreatic enzymes or bile to move in a retrograde fashion into the pancreas.[1]

TABLE 20–1. Selected Medications Associated with Acute Pancreatitis

Definite Association	Probable Association
5-Aminosalicylic acid	Ampicillin
Asparaginase	Angiotensin-converting enzyme inhibitors
Azathioprine	Bumetamide
Didanosine	Calcium
Estrogens	Chlorthalidone
Furosemide	Cimetidine
Mercaptopurine	Cisplatin
Methyldopa	Clozapine
Metronidazole	Corticosteroids
Pentamidine	Cytarabine
Sulfonamides	Ethacrynic acid
Sulindac	Ifosfamide
Tetracycline	Interferon alfa-2b
Thiazides	Losartan
Valproic acid/salts	Meglumine antimoniate
	Piroxicam
	Procainamide
	Salicylates
	Sodium stibogluconate
	Zalcitabine

(From Berardi RR, Montgomery PA. Pancreatitis. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005:723, with permission.)

Autolysis of the pancreas can occur when zymogens are activated in the pancreas before being released into the duodenum. Acute pancreatitis can result from the initial injury to the zymogen-producing cells, which is followed by neutrophil invasion of the pancreas, and that ends in further activation of enzymes within the pancreas. This cascade of events can be destructive to the pancreas and harmful to the patient.

Acute pancreatitis can progress to several distinct consequences. Pancreatic fluid collections and pancreatic **abscesses** can form during the course of acute pancreatitis. Pancreatic necrosis can occur when pancreatic enzymes damage the pancreatic tissue or when pancreatic abscesses become secondarily infected. This infection is usually due to bacteria that are normally found in the gastrointestinal tract, including *Escherichia coli*, Enterobacteriaceae, *Staphylococcus aureus*, viridans group streptococci, and anaerobes.

Clinical Presentation and Diagnosis

Patients at greatest risk for mortality from acute pancreatitis are those who have multi-organ failure (e.g., hypotension, respiratory failure, or renal failure), pancreatic necrosis, obesity, volume depletion, greater than 70 years of age, and an elevated **APACHE II** score.[3,4] The Acute Physiology, Age, and Chronic Health Evaluation (APACHE) II score is a rating scale of disease severity in critically ill patients.

A patient with acute pancreatitis may develop many severe local and systemic complications. Local complications involve fluid collection, necrosis, or abscess in the pancreas. A pancreatic fluid collection (or pancreatic pseudocyst) is a collection of tissue, pancreatic enzymes, and blood that forms weeks after acute pancreatitis. Many pancreatic pseudocysts resolve spontaneously, but some require surgical drainage.[5] Rupture of a pancreatic pseudocyst with associated erosion and hemorrhage of major abdominal blood vessels can have a mortality approaching 60%; thus, continued monitoring of a pseudocyst is prudent.[6]

Pancreatic necrosis is a diffuse inflammation of the pancreas with infectious etiology. ❷ *Pancreatic necrosis occurs within the first 2 weeks of acute pancreatitis and develops in 10% to 30% of patients with acute pancreatitis.* The necrotic pancreas can become secondarily infected with enteric gram-negative bacteria (such as *E. coli*), and disseminated infection may result from pancreatic necrosis.[7,8]

Pancreatic abscess is a collection of pus that forms in the pancreas 4 to 6 weeks after acute pancreatitis. Pancreatic abscess is usually less life-threatening than pancreatic necrosis or pancreatic pseudocyst and can be managed with percutaneous drainage.[5]

Systemic complications can affect virtually any organ system but tend to target the pulmonary and cardiovascular systems and the kidneys. Multi-organ failure is a poor prognostic indicator. Acute respiratory distress syndrome (ARDS) is a life-threatening syndrome of acute lung injury with resulting hypoxia. ARDS may be due to the systemic release of pancreatic enzymes causing destruction of pulmonary surfactant, which is required for proper lung function.[9] Circulating pancreatic



Clinical Presentation of Acute Pancreatitis

Symptoms

- Abdominal pain radiating to the back is the most common presenting symptom. Pain can be due to intestinal immobility or chemical peritonitis induced by pancreatic enzymes.
- Other common symptoms include nausea, vomiting, and abdominal pain.

Signs

- Tachycardia, hypotension, fever, and abdominal distention may be present.
- There may be a positive Cullen's sign (bluish discoloration of the periumbilical skin indicating blood in the peritoneum).
- After 2 to 3 days of acute hemorrhagic pancreatitis, there may be a positive Turner's sign [local areas of discoloration (bruising) and induration of the skin near the umbilicus due to extravasation of blood].

Laboratory Tests

- The serum **amylase** can be elevated three times the upper limit of normal within the first 12 hours of the onset of acute pancreatitis. The degree of elevation does not predict the severity of disease.
- As acute pancreatitis progresses, the serum **lipase** can also become elevated.[2]
- Other possible laboratory abnormalities include elevated white blood cell count, hyperglycemia, hypocalcemia, hyperbilirubinemia, elevated serum lactate dehydrogenase (LDH), and hypertriglyceridemia.



Patient Encounter 1, Part 1

Presentation of Acute Pancreatitis

A 55-year-old man with a history of ethanol abuse is admitted to the emergency department complaining of sharp persistent pain in the right upper quadrant of the abdomen. The pain was milder 2 days ago but has progressed to the severe pain he has now. He was nauseated at home and has vomited twice in the emergency department; he is also febrile. The patient is overweight, a smoker, and has a history of dyslipidemia including hypertriglyceridemia.

- What information about the patient presentation is consistent with acute pancreatitis?
- What risk factors does the patient have for acute pancreatitis?
- What additional laboratory tests would you recommend?

enzymes can cause cardiovascular shock. Acute renal failure may result from hypovolemia and hyperkalemia.[10]

Diagnosis

Diagnosis of acute pancreatitis is based on the patient's history and presenting signs and symptoms. Evaluation of laboratory results, specifically the serum amylase and lipase, aids in diagnosis. Serum amylase is elevated early in the disease process but may return to normal within 12 hours.[10] Serum lipase will remain elevated for days after the acute event and may lend itself more to the diagnosis depending on when the patient presents for evaluation.[11]

The patient's history will identify risk factors for acute pancreatitis, such as age greater than 70 years or history of alcohol abuse. Finally, computed tomography (**CT**) scan or ultrasound of the abdomen can help to identify pancreatic fluid collections.[12]

Treatment

Desired Outcomes

The goals of treatment for acute pancreatitis include: (1) resolution of nausea, vomiting, abdominal pain, and fever; (2) ability to tolerate oral intake; (3) normalization of serum amylase, lipase, and white blood cell count; and (4) resolution of abscess, pseudocyst, or fluid collection as measured by CT scan.

Nonpharmacologic Therapy

Many medications can precipitate an attack of acute pancreatitis. If a medication is determined to be the cause of acute pancreatitis, it should be discontinued and alternative therapy considered.[13,14]

❸ *Therapy of acute pancreatitis is primarily supportive unless a specific etiology is identified (Fig. 20–2). Supportive therapy involves fluid repletion, discontinuation of oral intake, and analgesia.* Patients with acute pancreatitis are administered intravenous fluids to maintain hydration and blood pressure. Fluids may be given in the form of crystalloids (e.g., 0.9% sodium chloride for infusion) or colloids (e.g., dextran or albumin for infusion).[15] Sodium chloride 0.9% for infusion (normal saline) at a rate of 50 to 100 mL/hour is reasonable for patients with mild to moderate fluid depletion. However, as much as 200 mL/hour may be required for patients with severe fluid losses.[16] Electrolytes such as potassium and magnesium may be added to the infusions if necessary. Hyperglycemia can be managed with insulin-containing intravenous infusions.

It is common practice to discontinue oral feedings during an attack of acute pancreatitis. In theory, discontinuation of oral intake will decrease the secretory functions of the pancreas and minimize further complications from the disease. Some patients can be fed with minimal oral intake. Tube feeding delivered via a nasojejunal tube will feed the patient beyond the ampulla of Vater, minimizing stimulation of the pancreas.[15,16] If oral intake is discontinued for a protracted period, total parenteral nutrition must be used to maintain adequate nutrition.[17,18]

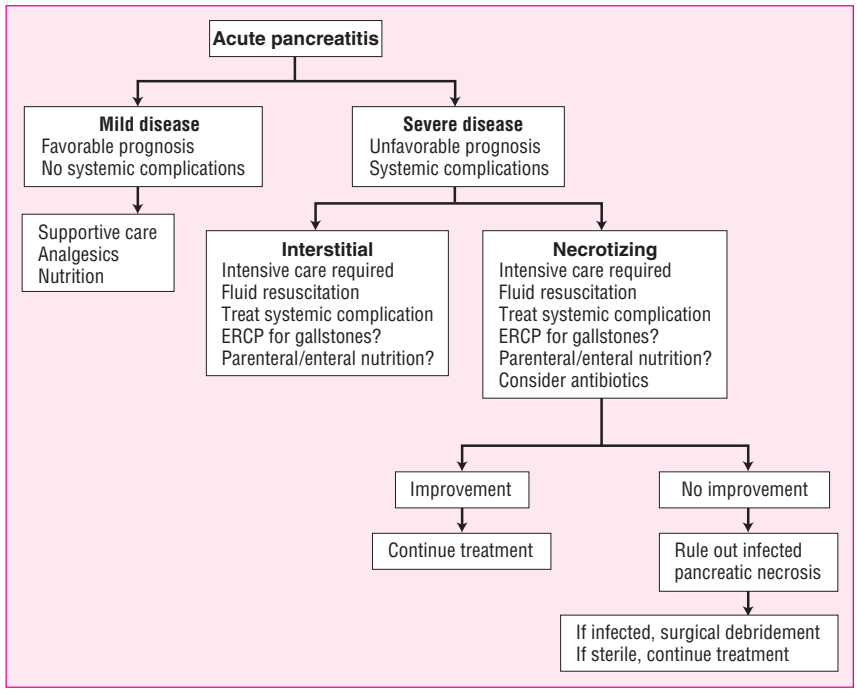


FIGURE 20–2. Algorithm for evaluation and treatment of acute pancreatitis. ERCP, endoscopic retrograde cholangiopancreatography. (From Berardi RR, Montgomery PA. Pancreatitis. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 726, with permission.)

If pancreatic necrosis has been identified, surgical debridement is necessary because mortality approaches 100% without drainage or surgical intervention. Percutaneous drainage is an option for managing pancreatic necrosis but is best used only in unstable patients as a bridge to surgery. Repeated surgery may be required in patients with a protracted or progressing disease state.[5,19]

Pharmacologic Therapy

Analgesics

Meperidine has historically been the most popular analgesic in acute pancreatitis since it is purported to cause less spasm and resulting pain in the **sphincter of Oddi** than other opioids. However, the clinical importance of this phenomenon is unclear.[15,20] As a result, patients with acute pancreatitis should be given the most effective analgesic. Morphine and fentanyl are reasonable alternatives to meperidine and may be more desirable due to other adverse effects associated with meperidine. Refer to Chapter 30 on pain management for guidance in selecting an analgesic dose.

Antibiotics

Empiric antibiotics are not necessary if the patient has mild disease or a non-infectious etiology of acute pancreatitis. Antibiotics have not been shown to prevent the formation of pancreatic abscess or necrosis when given early in the course of acute pancreatitis.

Antibiotics are appropriate for pancreatic necrosis, which can be infected initially or be susceptible to a secondary infection.[21] Selected intravenous antibiotic regimens are shown in Table 20–2. If necrosis is confirmed, antibiotics are insufficient as sole therapy; surgical debridement is necessary for cure.

Broad-spectrum antibiotics with activity against enteric gram-negative bacilli are appropriate. Imipenem/cilastatin reduces **sepsis** resulting from necrotizing pancreatitis and provides antibacterial coverage for the organisms likely to be causing pancreatic necrosis.[22]

It is often difficult to narrow the spectrum of activity of the antibiotic choice since the infections are usually polymicrobial. As such, patients may receive long courses of broad-spectrum antibiotics such as imipenem/cilastatin and

TABLE 20–2. Intravenous Antimicrobial Regimens for Pancreatic Necrosis

Drug	Usual Dose[a]	Notes
Imipenem/cilastatin	500 mg every 6 hours	~5% incidence of seizure; nausea is also a concern
Piperacillin/tazobactam	3.375 g every 6 hours	Avoid if allergic to penicillin
Cefepime + metronidazole	2 g every 12 hours + 500 mg every 6 hours	Will not cover enterococci
Aztreonam + vancomycin + metronidazole	1 g every 8 hours + 15 mg/kg every 12 hours + 500 mg every 6 hours	Option for penicillin-allergic patients

[a]Doses must be adjusted for the degree of renal impairment.



Patient Encounter 1, Part 2: Medical History, Physical Exam, and Diagnostic Tests in Acute Pancreatitis

PHM
Dyslipidemia, diagnosed "years ago"; obesity

FH
Father's whereabouts unknown; mother deceased at age 78 from heart failure; two half brothers, alive and well

SH
Consumes 6 to 9 alcoholic beverages per evening; smokes 1 pack cigarettes per day

Meds
No prescription medications; does not see a physician regularly

Maalox 15 mL PO 4 times daily as needed for heartburn, stomach upset

Loperamide 2 mg PO as needed diarrhea

Guaifenesin 200 mg PO 4 times daily as needed for cough
Ranitidine 75 mg PO once daily (when patient remembers to take it)

ROS
Positive for sharp right upper quadrant abdominal pain radiating to the back, nausea, vomiting, recent unintentional weight loss (although patient is still obese) and chronic cough; negative for chest pain or shortness of breath

PE
Wt: 120 kg, Ht: 5'10", blood pressure 100/66 mm Hg, pulse 120 beats per minute, respiratory rate 18/minutes, temperature 38.5°C
CV: Regular rate and rhythm, no murmurs
Abd: Distended, (+) rebound tenderness, (+) bowel sounds, marked hepatosplenomegaly

Labs
Amylase 200 units/L (3.3 µKat/L), lipase 1000 units/L
Abdominal CT: Pending

- Given this additional information, what is your assessment of the patient's condition?
- Why is the amylase low and the lipase high?
- What pharmacologic and nonpharmacologic goals are available for this patient?

may develop superinfections due to more resistant bacteria or bacteria not susceptible to imipenem/cilastatin. Antifungal agents such as fluconazole may be considered if peritonitis or gastrointestinal perforation develops due to the presence of fungi such *Candida albicans* in the gastrointestinal tract.[23]

Ineffective Therapies

❹ *Several pharmacologic therapies have been proven to be ineffective in reducing morbidity or mortality from the disease. Ineffective therapies include: reducing pancreatic secretion by administering somatostatin or atropine, reducing gastric acidity and decreasing pancreatic secretion with histamine$_2$-receptor antagonists, inhibition of pancreatic enzymes using* ***protease*** *inhibitors such as aprotinin, and immunomodulation.*[11,24–26] *Nasogastric suction has only been effective in patients with ileus or persistent vomiting.*[27]



Patient Encounter 1, Part 3: Treatment and Monitoring for Acute Pancreatitis

The patient has been transferred from the CT scanner to the surgical intensive care unit for mechanical ventilation, blood pressure support, and surgical evaluation. A diagnosis of acute pancreatitis with pancreatic necrosis is made.

- Formulate a care plan for this patient.
- What are some possible causes of respiratory failure and hypotension in this patient? Are these findings poor prognostic indicators?
- What is the recommended treatment for pancreatic necrosis?
- What empiric antibiotic regimen would be a reasonable choice in this patient? Provide a drug, dose, route, and frequency.
- Suppose a surgeon requested piperacillin/tazobactam 3.375 g IV every 6 hours for this patient. Would this be a reasonable choice? Why or why not?

Outcome Evaluation

Given the severity of acute pancreatitis, patients are monitored closely in the intensive care setting. Patients with mild disease can be managed more conservatively with observation and supportive care. Critically ill patients may require surgery and aggressive life support measures.[16,28]

CHRONIC PANCREATITIS

Epidemiology and Etiology

The incidence of chronic pancreatitis is approximately 1 in 10,000 people. ❶ *The most common cause of chronic pancreatitis in adults in Western countries is ethanol abuse.* The most common cause in children is cystic fibrosis, due to preexisting pancreatic insufficiency inherent in the disease. Gallstones can occur at the same time as chronic pancreatitis but are not often implicated as the cause. Unlike acute pancreatitis, chronic pancreatitis has an unknown etiology in a significant number of cases (30%).[29,30]

Pathophysiology

Chronic pancreatitis is an inflammatory process that occurs over a long period of time. The inflammation damages the enzyme-producing cells in the pancreas and can also disrupt or destroy the endocrine function of the pancreas by causing diffuse

scarring and fibrosis.[29] Ethanol abuse may cause precipitation of pancreatic enzymes in the ducts of the pancreas leading to chronic inflammation and damage. Ethanol may also be directly toxic to pancreatic cells.[31] Counterintuitively, the amount of ethanol consumed does not correlate with the incidence or progression of chronic pancreatitis. A patient who "binge drinks" by consuming large amounts of ethanol over short periods of time is as likely to develop chronic pancreatitis as someone who chronically consumes socially acceptable amounts of alcohol. Patients who die from the first diagnosed episode of chronic pancreatitis may have had undiagnosed chronic pancreatitis for some time.[32]

As patients lose exocrine function of the pancreas, they have decreased ability to absorb lipids and protein ingested with normal dietary intake. Weight loss from nutritional malabsorption is a common symptom of chronic pancreatitis not often seen in acute pancreatitis. Fatty- or protein-containing stools are also common; carbohydrate absorption is usually unaffected. Even though patients with chronic pancreatitis have decreased ability to absorb lipid from the gastrointestinal tract, there does not appear to be an increased incidence of fat-soluble vitamin deficiency in these patients.[34]

Clinical Presentation and Diagnosis



Clinical Presentation of Chronic Pancreatitis

General
- The presentation of chronic pancreatitis can be similar to that of acute pancreatitis.

Symptoms
- Pain is the most common chief complaint. Pain can be dull or sharp, and it may be localized to the area around the stomach or can radiate to the back. The pain is not relieved by antacids and can be provoked by ethanol ingestion or a fatty meal.[33]
- Weight loss can result from chronic fat and protein malabsorption.

Signs
- Patients often present with chronic fat-containing diarrhea due to dietary lipid malabsorption.
- Gastrointestinal bleeding can result from erosion of intestinal blood vessels by pancreatic enzymes or as a result of thrombosis.
- Chronic obstruction of the common bile duct by the inflamed pancreas can cause icterus, cholangitis, and biliary cirrhosis.[36]

Laboratory Tests
- Glucose intolerance may occur because of chronic destruction of the endocrine function of the pancreas.[35]
- Serum amylase and lipase levels are not usually elevated in chronic pancreatitis.
- The serum bilirubin or alkaline phosphatase may be elevated due to inflammation near the common bile duct.

Diagnosis

Differentiating an episode of acute pancreatitis from chronic pancreatitis may be difficult because the clinical presentations can be similar. The diagnosis of chronic pancreatitis is made by looking for the effects of chronic pancreatic inflammation and scarring on the pancreas and the patient as a whole. Computed tomography or ERCP will allow visualization of chronic calcified lesions in the pancreas when present.[37]

Treatment

Desired Outcomes

The goals of pharmacotherapy for chronic pancreatitis are: (1) prevention and resolution of chronic abdominal pain; and (2) correction of dietary malabsorption with exogenous pancreatic enzymes.

Nonpharmacologic Therapy

Lifestyle modifications are an important part of the therapy for chronic pancreatitis. ❺ *Avoidance of ethanol and fatty meals can decrease the pain of chronic pancreatitis.*

Many surgical procedures have been employed to reduce the inflammation or remove the strictures that cause pain in chronic pancreatitis. However, most procedures have not been proven effective in clinical trials and carry a high risk of morbidity and mortality.[39]

Pharmacologic Therapy

Analgesics

Pain management is an important component of therapy and is similar to that of acute pancreatitis. Non-opioid analgesics are preferred, but the severe and persistent nature of the pain often requires opioid therapy. Patients can require chronic doses of opioid analgesics, with a resulting risk of addiction. Pain can also be managed by removing the stimulus of exacerbation if identified.[31,38]

Pancreatic Enzymes

The goal of pancreatic enzyme supplementation is to deliver exogenous enzyme to the duodenum without causing further gastrointestinal side effects from the medication, risking noncompliance due to the large number of dosage units required, or causing undue medication expense.[40]

Supplementation with pancreatic enzymes may reduce the pain and fatty diarrhea associated with chronic pancreatitis (Table 20–3). Best results are achieved in patients who have mild non-alcoholic pancreatic disease. Common pancreatic enzyme supplements contain lipase, amylase, and protease in varying proportions. Thus, the dose can be tailored to the patient's requirement for exogenous enzyme supplementation and response to therapy.

Non–enteric-coated pancreatic enzyme supplements require high doses to compensate for loss of enzyme due to

TABLE 20–3. Frequently Used Pancreatic Enzyme Preparations

Product	Dosage Form	Enzyme Content (Units)[a]		
		Lipase	Amylase	Protease
Creon-10	ECMS	10,000	33,200	37,500
Creon-20	ECMS	20,000	66,400	75,000
Ku-Zyme HP	C	8000	30,000	30,000
Lipram-CR10	ECMS	10,000	33,200	37,500
Lipram-PN16	ECMS	16,000	48,000	48,000
Lipram-CR20	ECMS	20,000	66,400	75,000
Lipram-PN20	ECMS	20,000	56,000	44,000
Lipram-UL12	ECMS	12,000	39,000	39,000
Lipram-PN10	ECMS	10,000	30,000	30,000
Lipram-UL18	ECMS	18,000	58,500	58,500
Lipram-UL20	ECMS	20,000	65,000	65,000
Pancrease	ECMS	4500	20,000	25,000
Pancrease MT-4	ECMT	4000	12,000	12,000
Pancrease MT-10	ECMT	10,000	30,000	30,000
Pancrease MT-16	ECMT	16,000	48,000	48,000
Pancrease MT-20	ECMT	20,000	56,000	44,000
Ultrase MT 12	ECMT	12,000	39,000	39,000
Ultrase MT 18	ECMT	18,000	58,500	58,500
Ultrase MT 20	ECMT	20,000	65,000	65,000
Viokase[b]	P	16,800	70,000	70,000
Viokase 8	UCT	8000	30,000	30,000
Viokase 16	UCT	16,000	60,000	60,000

[a]All listed products contain pancrelipase. Pancrelipase contains not less than 24 USP units of lipase activity, not less than 100 USP units of amylase activity, and not less than 100 USP units of protease activity per milligram.
[b]Units of 0.7 g of powder.
C, powder encased in a cellulose capsule; ECMS, enteric-coated microspheres encased in a cellulose or gelatin capsule; ECMT, enteric-coated microtablets encased in a cellulose capsule; UCT, uncoated tablet; P, powder.
(From Berardi RR, Montgomery PA. Pancreatitis. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 733, with permission.)

destruction by the low pH of the stomach. This effect can be minimized by administering a histamine$_2$-receptor antagonist or proton pump inhibitor. Non–enteric-coated pancreatic enzyme supplements may have an advantage in minimizing pain early in the disease state through regulation of proteases in the duodenum.

Non–enteric-coated pancreatic enzyme supplements can be used for initial therapy. The relative dose of amylase, lipase, and protease may be increased until control of pain and fatty diarrhea is achieved or the patient experiences intolerable side effects. If pain and diarrhea control are achieved, the patient can be transitioned to an enteric-coated supplement to maximize compliance. A reasonable example starting regimen is Viokase-8, six tablets with each meal and at bedtime, given with famotidine 20 mg at bedtime.

Most pancreatic enzyme supplements are enteric coated to release enzymes in the alkaline environment of the intestine; this minimizes enzyme destruction in the stomach. Enteric-coated pancreatic enzyme supplements require fewer daily dosage units, but delivery of the drug to the site of action and effectiveness may be delayed by gastric emptying time.[41]



Patient Encounter 2

Chronic Pancreatitis

The same patient described in the first encounter is now 57 years old. He presents to the clinic with right upper quadrant pain radiating to his back. He is also jaundiced and nauseated.

PMH

Dyslipidemia, with preponderance of hypertriglyceridemia
Hypertension
Weight loss, initially intentional through diet and exercise, but now unintentionally excessive
Type 2 diabetes, requiring insulin
Gastroesophageal reflux disease

SH

Consumes 1 to 2 alcoholic beverages per evening; quit smoking 2 years ago

Meds

Atorvastatin 40 mg PO once daily
Hydrochlorothiazide 25 mg PO once daily
Amlodipine 5 mg PO once daily
Lantus insulin 30 units per day
Multivitamin 1 tablet daily
Pantoprazole 40 mg PO once daily
Maalox 15 mL PO 4 times daily as needed for heartburn/stomach upset
Acetaminophen 325 mg PO every 6 hours as needed for pain/headache

ROS

Positive for sharp right upper quadrant abdominal pain radiating to the back, nausea, and recent unintentional weight loss; negative for chest pain or shortness of breath, fatty diarrhea present for months.

PE

Wt: 70 kg Ht 5′10″, blood pressure 130/86 mm Hg, pulse 80 beats per minute, respiratory rate 16/minute, temperature 37.0°C (98.6°F)
CV: Regular rate and rhythm, no murmurs noted
Abd: Distended, (+) rebound tenderness, (+) bowel sounds, marked hepatosplenomegaly

Labs

Amylase 100 units/L (1.67 μKat/L), lipase 100 units/L
CT scan: Diffuse pancreatic scarring and calcifications

- Formulate a care plan for this patient.
- Why are the serum amylase and lipase normal?
- What lifestyle modifications can this patient make to minimize impact from his disease state?
- Is this patient taking any medication(s) that could exacerbate pancreatitis? If so, what alternatives can you offer?
- What medications may help alleviate the fatty diarrhea the patient is experiencing?
- How would you monitor the effectiveness of your recommendations?

Pancreatic enzyme supplements should be taken immediately prior to meals to aid in the digestion and absorption of food. Alternately, patients can supplement their diet with medium chain triglycerides (MCTs) or ingest foods rich in MCTs since they do not require pancreatic enzymes for absorption. An appropriate regimen incorporates the successful doses of each enzyme (amylase, lipase, and protease) from the starting non–enteric-coated regimen. As with the previous example, a patient stabilized on Viokase-8, six tablets with each meal, can be transitioned to Pancrease MT-16 three tablets with meals. The famotidine can then be discontinued.

Outcome Evaluation

- Monitor for adequate pain control and the need for escalation or de-escalation of analgesia.
- If pain relief is achieved by avoiding ethanol or fatty meals, encourage continuation of these practices.
- When dietary malabsorption exists, monitor patients for weight gain or loss, activity level, and ability to perform activities of daily living.
- Ask patients to monitor the frequency and consistency of stool output as an indicator of malabsorption.
- Educate patients that compliance with and proper use of dietary pancreatic enzyme supplementation is key to improved outcomes.[31,33,38]



Patient Care and Monitoring

1. Determine whether ethanol is a contributing causative factor. If so, reinforce counseling on the need for abstinence and provide appropriate resources to maintain abstinence (e.g., professional counseling, alcoholics anonymous).
2. Obtain a thorough history of prescription, non-prescription, and dietary supplement use to identify products that may exacerbate chronic pancreatitis.
3. Refer the patient for nutritional counseling if there is decreased caloric intake and weight loss. Compare actual body weight to ideal body weight.
4. Make a plan for analgesia, in conjunction with a pain management service if possible, to control and prevent pain. Recommend an analgesic with ease of dosing and minimal side effects, realizing that patients with chronic pancreatitis may require large doses of opioids.
5. Optimize pancreatic enzyme supplementation, starting first with a non–enteric-coated enzyme supplement and an H_2RA. When pain and diarrhea are stabilized, consider switching to an enteric-coated enzyme supplement for ease of dosing.
6. Develop a plan for reassessing pancreatic enzyme supplementation and analgesia on an outpatient basis.
7. Assess improvement in quality of life measures such as physical, psychological, and social functioning and well-being.

ABBREVIATIONS

APACHE:	Acute Physiology, Age, and Chronic Health Evaluation
ARDS:	acute respiratory distress syndrome
CT:	computed tomography
ERCP:	endoscopic retrograde cholangiopancreatography
LDH:	lactate dehydrogenase
MCT:	medium chain triglycerides
RUQ:	right upper quadrant

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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21 Viral Hepatitis

Juliana Chan



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Differentiate the five types of viral hepatitides by their epidemiology, etiology, pathophysiology, clinical presentation and natural history.
2. Identify modes of transmission and risk factors among the major types of viral hepatitis.
3. Evaluate hepatic serologies to diagnose the type of hepatitis infection a patient acquired.
4. Create treatment goals for a patient with viral hepatitis.
5. Recommend an appropriate pharmacotherapeutic agent for prevention of viral hepatitis.
6. Develop a pharmaceutical care plan for the treatment of viral hepatitis.
7. Formulate a monitoring plan to assess the untoward effects of agents used to treat viral hepatitis.

Key Concepts

❶ Prevention and treatment of viral hepatitis may prevent progression to chronic hepatitis, cirrhosis, and end-stage liver disease.
❷ There is no specific pharmacologic treatment for acute viral hepatitis A, B, C, D, or E; only supportive care is available.
❸ Good personal hygiene and proper disposal of sanitary waste are required to prevent the fecal-oral transmission of the hepatitis A virus.
❹ Individuals may minimize their risk of acquiring both hepatitis B and C infection by avoiding contaminated blood products and not indulging in high-risk behavior such as intravenous drug use.
❺ Persons at high risk of acquiring the hepatitis B virus should be vaccinated with the hepatitis B vaccine at months 0, 1, and 6.
❻ A vaccine that combines both inactivated hepatitis A and recombinant hepatitis B (Twinrix) is approved for immunizing individuals greater than 18 years of age with indications for both hepatitis A and B vaccines.
❼ The drug of choice for chronic hepatitis B depends on the patient's past medical history, aminotransferase level, HBV DNA level, and most importantly, HBeAg status.
❽ Hepatitis D infection is possible only if the patient also has the hepatitis B virus present; therefore, hepatitis B vaccination can indirectly prevent hepatitis D infection.

There are five types of viral hepatitis: hepatitis A (HAV), B (HBV), C (HCV), D (HDV), and E (HEV). These types may present as either acute or chronic illnesses, which are primarily differentiated based on disease duration. Acute hepatitis may be associated with all five types of hepatitis and rarely exceeds 6 months in duration.

Chronic hepatitis (disease lasting longer than 6 months) is usually associated with hepatitis B, C, and D. ❶ *Chronic viral hepatitis may lead to the development of* ***cirrhosis****, which may induce* ***end-stage liver disease*** *(ESLD).* Complications of ESLD include **ascites**, edema, jaundice, **hepatic encephalopathy**, infections, and bleeding **esophageal varices**. Therefore, prevention and treatment of viral hepatitis may prevent ESLD.

Viral hepatitis can occur at any age and is the most common cause of liver disease in the world. The true prevalence and incidence may be underreported because most patients are asymptomatic. The epidemiology, etiology, and pathogenesis vary depending on the type of hepatitis and will be considered separately below.

HEPATITIS A

Epidemiology and Etiology

Hepatitis A affects 1.4 million people yearly worldwide.[1] The prevalence is highest in underdeveloped countries including Africa, parts of South America, the Middle East, and Southeast

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Asia. In contrast, developed parts of the world including Australia, parts of western and northern Europe, Japan, and the United States have a lower prevalence. This is primarily due to vaccination programs, but outbreaks still can happen as evidenced by an outbreak in Pennsylvania in 2003.[2,3]

Thirty-one percent of the American population has been infected with the HAV.[1] Overall, Mexican Americans are at greatest risk for HAV infection, and African Americans are more likely to be infected than Caucasians.

The hepatitis A virus is primarily detected in contaminated feces and infects people via the fecal-oral route. Outbreaks occur primarily in areas of poor sanitation.[1,4] Individuals at greatest risk of acquiring HAV are listed in Table 21–1. Approximately 50% of the reported cases have no identifiable risk factors.[1]

To date, there are no documented cases of chronic hepatitis A.[1] Death associated with HAV is rare and is mostly associated with fulminant hepatitis, with which approximately 100 people die annually.[1]

Pathophysiology

Hepatitis A is a non-enveloped single-stranded ribonucleic acid (RNA) virus classified as the Hepatovirus genus under the Picornaviridae family.[1] The only host for the HAV is humans, with hepatic cells as the primary site for viral replication. As part of the viral degradation process, the HAV is released into the biliary system causing elevated concentrations of the virus in the feces.[5]

TABLE 21–1. Risk Factors for Acquiring Viral Hepatitis

Hepatitis A
International travelers to endemic areas (e.g., Africa, Asia, and parts of South America)
Sexual contact with infected persons (e.g., men having sex with other men)
Shellfish infected with HAV (e.g., raw oysters)
Day care centers or household contacts with people infected with HAV
Health care workers
Intravenous drug users using unsterilized needles
Workers involved with non-human primates
Food service handlers
Patients with clotting factor disorders
Individuals residing in health care institutions
Hepatitis B and Hepatitis D
Men having sex with other men
Individuals with multiple heterosexual partners
Intravenous drug users using unsterilized needles
Recipients of blood products
Household contacts with acute hepatitis B with open cuts
Health care providers in contact with contaminated needles
Patients undergoing dialysis
Hepatitis C
Recipients of blood products
Health care providers in contact with infected needles
Individuals having multiple sexual partners
Perinatal transmission (less than 5%)
Unprofessional body piercing and tattooing
Hepatitis E
International travelers to endemic areas (e.g., parts of Asia, Africa, and Mexico)
Ingesting foods and drinks contaminated with bodily waste

HEPATITIS B

Epidemiology and Etiology

Hepatitis B is a blood-borne infection affecting more than 2 billion people in the world. Approximately 350 million people have chronic infection, which may lead to cirrhosis and complications of ESLD. Deaths related to hepatitis B range from 500,000 to 750,000 yearly.[6] Despite having an effective vaccine against HBV, more than 300,000 newly-diagnosed infections emerge each year. The prevalence of chronic hepatitis B is geographically dependent; the rate is about 1% in North America and Western Europe compared to 10% to 15% in developing areas such as Southeast Asia.[7]

The highest concentration of the HBV is found in blood and serous fluids. Therefore, the primary mode of hepatitis B transmission is either by blood or body fluids through perinatal, sexual, or percutaneous exposure.[8] Infants born of mothers who are infected with HBV that is actively replicating have a 90% risk of developing chronic hepatitis B. If an infant residing in an endemic area is not infected at birth, the risk of acquiring chronic hepatitis B is still 30% to 60% within the first 5 years of life from horizontal transmission.[9,10] Individuals at greatest risk of acquiring HBV are listed in Table 21–1. Approximately 33% of the reported hepatitis B cases have no identifiable risk factors.[8]

Pathophysiology

Hepatitis B (also known as the Dane particle) belongs to the Hepadnaviridae family that was first discovered by associating individuals who developed hepatitis from blood transfusions.[11] The HBV is unique in that it is a partially double-stranded deoxyribonucleic acid (DNA) virus with a phospholipid layer containing hepatitis B surface antigen (HBsAg) that surrounds the nucleocapsid. The nucleocapsid contains the core protein that produces hepatitis B core antigen (HBcAg), which is undetectable in the serum. The exact mechanism of hepatocellular injury from hepatitis B is still being investigated but it is thought that a cytotoxic immune reaction occurs when HBcAg is expressed on the surface of the hepatic cells. Fortunately, antibodies against hepatitis B core antigen (anti-HBc) are measurable in the blood, where anti-HBc to immunoglobulin M (IgM) indicates active infection and anti-HBc to IgG relates to either chronic infection or possible immunity against HBV.

Viral replication occurs when hepatitis B envelope antigen (HBeAg) is present and circulating in the blood. HBV DNA is utilized to measure viral infectivity and assess and quantify viral replication. Once the hepatitis B infection resolves, antibodies against hepatitis B envelope (anti-HBe) and

antibodies against hepatitis B surface antigen (anti-HBs) develop, and HBV DNA levels become undetectable. However, if these antibodies do not develop, then the likelihood of developing chronic hepatitis B increases. This is primarily dependent on the host's immune system at the time the infection was attained. If an individual is immunocompetent, the disease resolves spontaneously in most cases with no further sequelae. In an immunocompromised person, the infection is less likely to be eradicated.[11]

Natural History of Hepatitis B

Approximately 90% of adults infected with HBV develop anti-HBs resulting in lifelong immunity. About 2% develop acute infections leading to fulminant hepatitis, which has a 60% to 90% mortality rate.[7] Fifteen percent of individuals who do not develop anti-HBs develop chronic hepatitis B. Of this population, the chance of developing chronic disease is less than 20% if the infection was acquired during adulthood. The risk of developing chronic hepatitis B increases to greater than 40% if the infection occurred perinatally.[7] It may take 20 to 40 years from the time cirrhosis is confirmed before signs and symptoms associated with ESLD develop.

HEPATITIS C

Epidemiology and Etiology

More than 170 million people are infected with hepatitis C worldwide, and more than 4 million have the disease in the United States.[12,13] The prevalence is higher among non-Hispanic blacks (3.2%) than non-Hispanic whites (1.5%), and men are more likely to be infected than women.[14] Additionally, genotypes are geographically specific. For example, genotype 1 is commonly found in patients in the United States whereas genotype 4 is common in the Middle East.[12] Approximately 75% of those infected with HCV in the United States have genotype 1, and about 14% and 5% have genotypes 2 and 3, respectively. Genotype does not dictate disease severity or clinical outcomes but is used to determine the duration of therapy and the likelihood of therapeutic response.

Prior to routine screening of blood products in the early 1990s, the primary route of transmission of the HCV was blood transfusions, when the risk was 0.02% per unit transfused. Since then, the risk has decreased significantly (0.001% per unit transfused).[13] Today, intravenous drug users utilizing contaminated paraphernalia are responsible for most HCV transmission. Other populations at risk for acquiring HCV are listed in Table 21–1. Approximately 10% of the individuals infected with HCV have no identifiable risk factors.

Pathophysiology

Hepatitis C, first known as non-A, non-B hepatitis, is a bloodborne infection that is a single-stranded RNA virus belonging to the Flaviviridae family and the Hepacivirus genus.[12] The true mechanism of hepatic injury is still in question, but it is theorized that structural and nonstructural (NS) peptides may be responsible for RNA viral replication, specifically the NS5 peptide. Currently, there are six genotypes (numbered 1 to 6) and more than 90 subtypes (genotype 1a, 1b, 2a, 3b, etc.) that are unique to hepatitis C.

Antibodies against HCV (anti-HCV) in the blood indicate infection with the HCV. If the infection persists for more than 6 months and viral replication is confirmed by HCV RNA levels, then the person has chronic hepatitis C. Chronic disease may be due to an ineffective host immune system against the HCV. Cytotoxic T lymphocytes are ineffective in eradicating the HCV, thus allowing persistent damage to hepatic cells. Therefore, immunocompromised individuals are less likely to eliminate HCV.[12]

Natural History of Hepatitis C

Only 10% to 15% of patients have acute hepatitis C that resolves without any further sequelae.[10] In more than 85% of cases, hepatitis C develops into a chronic disease. Approximately 70% of chronic HCV cases progress to mild, moderate, or severe hepatitis. While the natural history of the progression to cirrhosis is not clear, it is estimated that 10% to 20% of cases may take up to 20 to 40 years from the time of exposure to advance from fibrosis to cirrhosis.[10] Fifteen to twenty percent of patients infected with HCV develop complications associated with cirrhosis. Once cirrhosis is confirmed, the rate of developing hepatocellular carcinoma increases to 1% to 4% per year.[10] The estimated death rate from HCV infection is 1.8 deaths per 100,000 persons per year.[12,15]

HEPATITIS D

Epidemiology and Etiology

Hepatitis D affects approximately 15 million people worldwide. The highest prevalence is in southern Italy, parts of Russia, and Romania; prevalence is moderate in northern Italy, Spain, Turkey, and Egypt.[16] Southeast Asia and China have the lowest prevalence of HDV despite having the highest prevalence of HBV infections.

There are three major HDV genotypes that are geographically specific. Genotype 1a primarily affects those residing in the United States, and genotype 1b affects the Asian population. Both 1a and 1b are equally represented in the Mediterranean Basin. Individuals residing in Japan and Taiwan are mostly diagnosed with genotype 2. Patients in South America (specifically Colombia, Venezuela, and Peru) are mostly infected with genotype 3.[16]

The most likely modes of transmitting the HDV are similar to those of HBV, including intravenous drug users using unsterilized needles and recipients of contaminated blood products. Sexual and perinatal transmission are rare for HDV.[16] Individuals at greatest risk of acquiring HDV are similar to those seen in HBV (Table 21–1).

Pathophysiology

Hepatitis D (originally referred to as delta hepatitis) belongs to the genus Deltavirus of the Deltaviridae family.[16] The HDV virion is a defective single-stranded circular RNA virus that requires the presence of HBV for HDV viral replication. This is because the hepatitis D virus antigen (HDVAg) is coated by the hepatitis B surface antigen (HBsAg).

The exact mechanism of hepatic damage induced by HDV is still being investigated, but it is known that replication of HDV cannot occur without HBV being present causing either co-infection (both hepatitis B and D infection occurring simultaneously) or superinfection (acquiring HDV after having long-standing disease with HBV).[17]

HEPATITIS E

Epidemiology and Etiology

Hepatitis E is associated with more than 50% of the acute hepatitis cases in endemic areas (Afghanistan, Bangladesh, Burma, China, India, Indonesia, Kazakhstan, Kyrgyzstan, Malaysia, Mongolia, Nepal, Pakistan, Tajikistan, Turkmenistan, Uzbekistan, Mexico, the Middle East, Northern Africa, and sub-Saharan Africa). The virus is primarily transmitted by the fecal-oral route. Transmission of HEV is more prominent in underdeveloped countries where sanitation is poor.

The mortality rate in pregnant women with acute infections may reach 25%. Rarely does HEV cause endemics in industrialized countries, where the prevalence rate is 1% to 5%.[18,19]

Pathophysiology

Hepatitis E is a non-enveloped single-stranded messenger RNA virus of unclassified genus.[18] The HEV is similar to HAV in that the virus is harvested in contaminated feces, thus infecting people via the fecal-oral route. High HEV levels in the bile often prompt viral shedding in the feces. The severity of hepatic damage is dependent on the HEV strain: Mex 14, Sar 55, or the US 2 strain.[19] No cases of chronic hepatitis E have yet been documented.

CLINICAL PRESENTATION AND DIAGNOSIS

Diagnosis of Viral Hepatitis

Diagnosing viral hepatitis may be difficult because most infected individuals are asymptomatic. Because symptoms cannot identify the specific type of hepatitis, laboratory serologies must be obtained (Table 21–2). In addition, liver function tests may be obtained to assess the extent of cholestatic and hepatocellular injury. However, the definitive test to determine the amount of damage and inflammation of hepatic cells is a **liver biopsy**.



Clinical Presentation of Viral Hepatitis

Symptoms

- Most patients infected with any type of viral hepatitis have no symptoms.
- Those who have symptoms may experience any of the following: flulike symptoms, fevers, fatigue/malaise, anorexia, nausea, vomiting, diarrhea, dark urine, pale-appearing stools, pruritus, and abdominal pain.

Signs

- Jaundice may be evident in the whites of the eyes (scleral icterus) or skin.
- An enlarged liver (hepatomegaly) and spleen (splenomegaly) may be present.
- In fulminant hepatitis with hepatic encephalopathy, patients may have asterixis and coma.
- In rare instances, extrahepatic symptoms may develop: arthritis, postcervical lymphadenopathy, palmar erythema, cryoglobulinemia, and vasculitis.

Hepatitis A

The diagnosis of hepatitis A is made by detecting immunoglobulin antibody to the capsid proteins of the HAV. The presence of IgM anti-HAV in the serum indicates an acute infection. IgM appears approximately 3 weeks after exposure and becomes undetectable within 6 months. In contrast, IgG anti-HAV appears in the serum at approximately the same time IgM anti-HAV develops but indicates protection and lifelong immunity against hepatitis A.[1]

Hepatitis B

Hepatitis B is diagnosed when HBsAg is detectable in the serum. The nucleocapsid of the HBsAg contains the core protein that produces HBcAg, which is undetectable in the serum. The presence of antibodies against anti-HBc to IgM indicates active infection, and anti-HBc to IgG relates to either chronic infection or possible immunity against HBV.

Viral replication occurs when HBeAg is present. Measurement of HBV DNA is used to determine viral infectivity and assess and quantify viral replication. Once the hepatitis B infection resolves, anti-HBe and anti-HBs develop, and HBV DNA levels becomes undetectable.

Hepatitis C

Hepatitis C is diagnosed by testing for anti-HCV in the serum. The disease is confirmed by the presence of HCV RNA. HCV RNA levels quantify viral replication and are used to determine if antiviral treatment for HCV is effective.

Hepatitis D

Hepatitis D infection requires the presence of HBV for HDV viral replication. Measuring HDV RNA levels in the serum by polymerase chain reaction (PCR) confirms the presence of

TABLE 21–2. Interpretation of Viral Hepatitis Serology Panels

Type	Laboratory Test	Result	Interpretation of Panel
Hepatitis A	IgM anti-HAV IgG anti-HAV	Negative Negative	Susceptible to infection
	IgM anti-HAV	Positive	Acutely infected
	IgG anti-HAV	Positive	Immune due to either natural infection or HAV vaccine
Hepatitis B[a]	HBsAg anti-HBc anti-HBs	Negative Negative Negative	Susceptible to infection
	HBsAg anti-HBc anti-HBs	Negative Positive Positive	Immune due to natural infection
	HBsAg anti-HBc anti-HBs	Negative Negative Positive	Immune due to hepatitis B vaccination
	HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Positive Positive Negative	Acutely infected
	HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Positive Negative Negative	Chronically infected
	HBsAg anti-HBc anti-HBs	Negative Positive Negative	Four interpretations possible[b]
Hepatitis C	anti-HCV	Negative	Susceptible to infection
	anti-HCV	Positive	Acutely or chronically infected
Hepatitis D[c]	IgM anti-HDV HDVAg HBsAg HBeAg anti-HBc	Positive Positive Positive Positive Positive	Acute HBV-HDV coinfection
Hepatitis E	IgM anti-HEV IgG anti-HEV	Negative Negative	Susceptible to infection
	IgM anti-HEV	Positive	Acutely infected
	IgG anti-HEV	Positive	Immune due to natural infection

[a]Centers for Disease Control and Prevention. Hepatology. Available at: http://www.cdc.gov/ncidod/diseases/hepatitis/b/Bserology.htm. Accessed February 19, 2006.
[b](1) May be recovering from acute HBV infection; (2) May be distantly immune and test is not sensitive enough to detect very low level of anti-HBs in serum; (3) May be susceptible with a false-positive anti-HBc; (4) May be undetectable level of HBsAg present in the serum and the person is actually a carrier.
[c]Hepatitis D should be suspected in those who have HBsAg positivity. Hepatitis D may present as either coinfection where both HDV and HBV serologies appear simultaneously whereas for superinfection, HBV has been present for some time, and later HDV develops.
anti-HAV, hepatitis A antibody; anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; anti-HCV, hepatitis C antibody; anti-HDV, hepatitis D antibody; anti-HEV, hepatitis E antibody; HAV, hepatitis A virus; HBV, hepatitis B virus; HDV, hepatitis D virus; HDVAg, hepatitis D antigen; IgG, immunoglobulin G; IgM, immunoglobulin M.

HDV and is the most accurate diagnostic test. The presence of IgM antibodies to HDV Ag (IgM anti-HD) indicates active disease, and IgG anti-HD also becomes detectable if the infection does not resolve spontaneously. Unlike the antibodies developed against HAV, HDV antibodies do not confer immunity.

Hepatitis E

The diagnosis of hepatitis E is based on the presence of anti-HEV antibodies. A test for hepatitis E RNA levels is not yet available for commercial use but is used in clinical trials.



Patient Encounter, Part 1

A 41-year-old Caucasian man is required by his employer to obtain a physical exam. He has no medical complaints but does report some stress from an impending divorce and from needing to take care of his five young children.

PMH
Non-contributory

PSH
Appendectomy in 1987 at the age of 27 that required blood transfusions

FH
Mother and father alive and well

SH
Smoked cigarettes 1 pack per day × 15 years but quit 5 years ago; used illicit drugs once in the past; drinks daily for the past 30 years; has 1 tattoo on the left arm done unprofessionally; works as a mail carrier

Meds
None

ROS
Complains only of irritability and mild depression; no nausea, vomiting, diarrhea, abdominal pain, or anorexia; never had an episode of jaundice, pale stools, or tea-colored urine

PE
VS: blood pressure 128/80 mm Hg, pulse 80 beats per minute, respiratory rate 20/minutes, temperature 37.0°C (98.6°F), Wt 81 kg (178 lbs), Ht 5′9″ (175 cm)
Abd: Soft, non-tender, normal liver span; no hepatosplenomegaly, no ascites.

Labs
All within normal limits except for aspartate aminotransferase 69 IU/L (1.15 µKat/L) and alanine aminotransferase 92 IU/L (1.53 µKat/L); anti-HCV (+), genotype 2; HCV RNA 91,230 IU/mL
Liver biopsy: Mild inflammation and minimal fibrosis (grade 1, stage 1 disease) that is consistent with chronic hepatitis C

- What information is suggestive of viral hepatitis?
- What risk factors does he have for viral hepatitis?
- What additional information do you need before creating a treatment plan for this patient?

PREVENTION AND TREATMENT OF VIRAL HEPATITIS

Desired Outcomes

General outcomes for treating hepatitis are to: (1) prevent the spread of the disease; (2) prevent and treat symptoms; (3) suppress viral replication; (4) normalize hepatic aminotransferases; (5) improve histology on liver biopsy; and (6) decrease morbidity and mortality by preventing cirrhosis, hepatocellular carcinoma, and ESLD.

For hepatitis B, additional treatment goals include: (1) seroconversion or loss of HBsAg; (2) seroconversion or loss of HBeAg; and (3) achieving undetectable HBV DNA levels. Additional goals for chronic hepatitis C include: (1) achieving undetectable HCV RNA; and (2) obtaining a sustained virologic response.

General Approach

Managing viral hepatitis involves both prevention and treatment. Prevention of hepatitis A and B (and indirectly for hepatitis D) can be achieved with immune globulin or vaccines. ❷ *There is no specific pharmacologic treatment for acute viral hepatitis A, B, C, D, or E; only supportive care is available.* Individuals with mild to moderate symptoms rarely require hospitalization. Occasionally, hospitalization is required in individuals experiencing significant nausea, vomiting, diarrhea, and encephalopathy. Liver transplantation may be required in rare instances if fulminant hepatitis develops.

Patients with viral hepatitis B, C, and D may develop chronic disease leading to ESLD. Treatment is only available for chronic liver disease associated with HBV, HCV, and HDV.[20,21]

Hepatitis A Prevention

❸ *Good personal hygiene and proper disposal of sanitary waste are required to prevent the fecal-oral transmission of the HAV.*[1,4] This includes frequent handwashing with soap and water after using the bathroom and prior to eating meals. Drinking bottled water and avoiding fruits, vegetables, and raw shellfish harvested from sewage-contaminated water in areas where HAV is most endemic will also minimize the risk of becoming infected with hepatitis A.

Individuals at high risk of acquiring hepatitis A (see Table 21–1) should receive either serum immune globulin or the hepatitis A vaccine, depending on their personal circumstances, as described below.[1,5]

Immune Globulin

Immune globulin (IG) is a solution containing antibodies from sterilized pooled human plasma that provides passive immunization against various infectious diseases, including hepatitis A.[5] Immune globulin is available for either intravenous (IVIG)

or intramuscular (IGIM) administration, but only IGIM is used for prevention of hepatitis A. IGIM does not confer lifelong immunity, but it is effective in providing pre-exposure and postexposure prophylaxis against HAV.[5]

Adverse effects of IGIM are rare. There have been reports of anaphylaxis in individuals who have immunoglobulin A deficiency after receiving repeated IG administration. Therefore, these patients should not receive IGIM. IGIM is not contraindicated in pregnant or lactating women or infants requiring hepatitis A immunization. The thimerosal-free preparation should be used in infants.[1]

IGIM should be injected into a deltoid or gluteal muscle. It does not affect the immune response of inactivated vaccines, oral polio virus, or yellow fever vaccine. The administration of live vaccines [e.g., measles, mumps, rubella (MMR) vaccine] concomitantly with IGIM may decrease the immune response significantly; thus, MMR and varicella vaccine should be delayed for at least 3 and 5 months, respectively, after IGIM has been administered. Additionally, IGIM should not be given within 2 weeks of the MMR administration or within 3 weeks of the varicella vaccine to maximize the efficacy of the immunization.[1]

Pre-exposure Prophylaxis

Pre-exposure prophylaxis with IGIM is indicated for individuals at high risk of acquiring the HAV who cannot receive the hepatitis A vaccine (e.g., because of allergy to the components alum or 2-phenoxyethanol). Additionally, travelers who plan to depart for endemic areas within 2 weeks and have not yet received the hepatitis A vaccine should receive IGIM because active vaccine immunity takes several weeks to develop.

The dose of the IGIM determines the duration of coverage. A dose of 0.02 mL/kg confers immunity against hepatitis A for less than 3 months and doses of 0.06 mL/kg provide immunity up to 5 months. If protection against HAV is required beyond 5 months, then readministration of IGIM may be indicated.[1,5]

Postexposure Prophylaxis

Individuals in contact with people infected with acute HAV, including household and sexual partners, staff and children from day care facilities, and food handlers of restaurant establishments may be candidates for postexposure prophylaxis. The risk of infection may be decreased by 90% if IGIM is given within 2 weeks of being exposed to the hepatitis A virus. IGIM may still be beneficial if it is given more than 2 weeks after exposure to a known case of HAV, as it may decrease the severity of hepatic damage.[1,5]

Hepatitis A Vaccine

Persons at risk of acquiring the HAV should receive the hepatitis A vaccine when appropriate.

There is no benefit in administering the vaccine after a person has been exposed to the HAV. Two inactivated hepatitis A vaccines, Havrix and VAQTA, are available in the United States and are effective in providing active immunization. The major difference between the two vaccines is that HAVRIX contains 2-phenoxyethanol as a preservative whereas VAQTA is preservative-free.[1] Either vaccine is effective in providing active pre-exposure prophylaxis when given in two injections 6 months apart (referred to as months 0 and 6). The two vaccines are considered interchangeable, and doses are dependent on age (Table 21–3).

Efficacy is defined by measuring antibody response. For HAVRIX, levels greater than 20 mIU/mL measured with the modified enzyme immunoassay, and for VAQTA, levels greater than 10 mIU/mL measured with the modified radioimmunoassay are considered protective. After the first dose of vaccine has been administered, 94% to 100% of adults and 97% to 100% of children and adolescents develop protective antibody concentrations against the HAV. All recipients over the 2 years of age receiving the second dose at month 6 have 100% antibody coverage, therefore, postvaccination measurement of antibody response is not required.[1]

The hepatitis A vaccine may provide effective immunity for 8 years in adults and children. Additionally, kinetic models have theorized that immunity with the vaccine may be longer than 20 years, but this has not been confirmed in clinical trials.[1]

The most common adverse effects in adults include injection site reactions (e.g., tenderness, pain, and warmth), headaches within 5 days after vaccination, and fatigue. Local reactions may be minimized by using an appropriate needle length based on the person's age and size and by administering the injection intramuscularly in the deltoid muscle. Children may also have feeding disturbances. Hepatitis A vaccine given

TABLE 21–3. Recommended Intramuscular Doses of Hepatitis A Vaccines

Product	Recipient Age (Years)	Dose	Volume (mL)	No. of Doses	Schedule (Months)
VAQTA	1–18	25 units	0.5	2	0, 6–18
	Greater than or equal to 19	50 units	1	2	0, 6
Havrix	1–18	720 EL units	0.5	2	0, 6–12
	Greater than or equal to 19	1440 EL units	1	2	0, 6–12

EL units, enzyme-linked immunosorbent assay units.
From Chan J. Viral hepatitis. Pharmacotherapy Self-Assessment Program. 5th ed. Kansas City: MO, American College of Clinical Pharmacy, 2005:1, 4, with permission.

during pregnancy has not been evaluated in clinical trials. Since both brands of vaccine are made from inactivated HAV, the risk of developing fetal complications should be minimal.

Hepatitis B Prevention

❹ *Individuals may minimize their risk of acquiring the hepatitis B infection by avoiding contaminated blood products or indulging in high-risk behavior such as intravenous drug use.* In addition, those who are at high risk of acquiring the HBV (Table 21–1) should be vaccinated with the hepatitis B vaccine.[8] In some cases, postexposure prophylaxis with hepatitis B immune globulin (HBIG) may be recommended to prevent the development of acute infection and complications associated with HBV.

Hepatitis B Immune Globulin

Hepatitis B immune globulin (HBIG) is a sterile solution containing antibodies prepared from pooled human plasma that has a high concentration of anti-HBs (antibodies to hepatitis B surface antigen). HBIG provides passive immunization for postexposure prophylaxis against the HBV. Similar to IGIM, HBIG should only be administered intramuscularly.

The most common side effects of HBIG include erythema at the injection site, headaches, myalgia, fatigue, urticaria, nausea, and vomiting. Serious adverse effects are rare and may include liver function test abnormalities, arthralgias, and anaphylactic reactions. HBIG should be used with caution in individuals who have experienced hypersensitivity reactions to immune globulin or those who have immunoglobulin A deficiency. Similar to IGIM, concomitant administration of HBIG and live vaccines should be avoided because the efficacy of the immunization may decrease significantly.[8]

Hepatitis B Vaccine

The two hepatitis B vaccines available in the United States are Recombivax HB and Engerix-B. These vaccines are produced with recombinant DNA technology by inserting the gene for HBsAg into the plasmid that is synthesized by *Saccharomyces cerevisiae* cells. ❺ *Both vaccines are effective in providing protection against acquiring the HBV when the immunization is given at months 0, 1, and 6.* The two non-dialysis formulations of the hepatitis B vaccines are considered interchangeable, but the same brand should be used for the entire three-dose series. Additionally, the doses depend on the person's age (Table 21–4). The difference between the two vaccines is that Engerix-B contains trace amounts of thimerosal that is not used as a preservative but is produced during the manufacturing process; Recombivax HB is completely free of thimerosal.

For optimal response, the hepatitis B vaccine should be administered intramuscularly only (into the anterolateral thigh region in neonates and infants; the deltoid region in adults) and not intravenously or intradermally. The vaccine should not be given in the gluteal region, as it may result in lower rates of immunity. In rare cases, the vaccine may be given subcutaneously in individuals at risk for hemorrhage (e.g., hemophiliacs); however, this route of administration should be used with caution, as subcutaneous nodules have developed when other similar vaccines have been used.[8]

The efficacy of the hepatitis B vaccine is established when antibody concentrations are greater than 10 mIU/mL. After completing the vaccination series given at months 0, 1, and 6, 96% of recipients obtain adequate antibody levels; for this reason, postvaccination testing is not usually recommended. However, protective antibody levels may be decreased in immunocompromised patients (e.g., human immunodeficiency virus (HIV)-positive, hemodialysis, or immunosuppressive therapy); postvaccine testing may be warranted 1 to 6 months after completing the vaccination series in these patients.[8] The duration of immunity and whether a booster dose of the hepatitis B vaccine is required are still being investigated.

The most frequent adverse effects are local reactions at the injection site (pain, tenderness, erythema, swelling, and pruritus), fevers (greater than 37.5°C or 99.5°F), headaches, dizziness, and irritability. Anaphylaxis and hypersensitivity reactions have been reported rarely and occur within a few hours after vaccine administration. In rare instances, a serum sickness–like apparent hypersensitivity syndrome (arthralgia, urticaria, ecchymoses, erythema multiforme, and erythema nodosum) has been

TABLE 21–4. Recommended Intramuscular Dosing Regimens for Hepatitis B Vaccines

Product	Patient Categories	Dose (mcg)	Volume (mL)	No. of Doses	Schedule (months)
Recombivax HB	0–19 years of age	5	0.5	3	0, 1, 6
	11–15 years of age[a]	10	1	2	1, 4–6
	Greater than or equal to 20 years of age	10	1	3	0, 1, 6
	Hemodialysis	40	1	3	0, 1, 6
Engerix-B	0–19 years of age	10	0.5	3	0, 1, 6
	Greater than or equal to 20 years of age	20	1	3	0, 1, 6
	Hemodialysis	40[b]	2	4	0, 1, 2, 6

[a]Adolescents 11 through 15 years of age may receive either the 5 mcg, 3-dose pediatric formulation or a 10 mcg, 2-dose regimen using the adult formulation.
[b]Two × 20 mcg in one or two injections.
From Chan J. Viral hepatitis. Pharmacotherapy Self-Assessment Program. 5th ed. Kansas City: MO, American College of Clinical Pharmacy, 2005:1, 8, with permission.

reported days to weeks postvaccination. Hepatitis B vaccine given during pregnancy has not been evaluated in clinical trials. However, if the mother is at risk of acquiring the hepatitis B virus, then vaccination should be considered.

Hepatitis A and B Combination Vaccine

❻ *A vaccine that combines both inactivated hepatitis A and recombinant hepatitis B (Twinrix) is approved for immunizing individuals greater than 18 years of age with indications for both hepatitis A and B vaccines.*[22] A 1 mL dose of Twinrix contains the antigenic components of not less than 720 ELISA units of Havrix and 20 mcg of recombinant HBsAg protein of Engerix-B and should be administered at months 0, 1, and 6. 2-Phenoxyethanol is used as a preservative, and trace amounts of thimerosal are present due to the manufacturing process. Antibody seroconversion for hepatitis A and B was greater than 98% in adult volunteers tested 1 month after a three-dose vaccine series. The side-effect profile of Twinrix is similar to giving each vaccine separately.[23]

Postexposure Prophylaxis

HBIG and hepatitis B vaccine are indicated after exposure to the HBV to prevent chronic hepatitis B disease. The dose and immunization regimen depend on how the individual acquired the virus.[8] Adults acutely exposed to blood containing HBsAg from an accidental needlestick, sexual contacts, or intravenous drug use should be immunized based on the source of exposure and the vaccination status of the exposed person (Table 21–5). A single dose of HBIG of 0.06 mL/kg is 75% effective in preventing chronic hepatitis B infections if administered within 14 days of exposure.

Postexposure prophylaxis for perinatal exposure depends upon the mother's HBsAg status.[24] Mothers who are HBsAg-positive should have their newborns immunized with both the hepatitis B vaccine and HBIG 0.5 mL. This regimen is 85% effective in preventing the hepatitis B carrier status if administered within 24 hours of birth.[8] If the mother is HBsAg negative, the newborn should be given only the hepatitis B vaccine (Table 21–6).

Chronic Hepatitis B Treatment

Persons with confirmed chronic hepatitis B should be evaluated for treatment, which may include interferon, pegylated interferon, lamivudine, adefovir dipivoxil, or entecavir. ❼ *The drug of choice for chronic hepatitis B depends on the patient's past medical history, aminotransferase level, HBV DNA level, and most importantly, HBeAg status.*

Patients who are hepatitis B carriers (defined as having a positive HBsAg, normal alanine aminotransferase (ALT) levels, and negative HBeAg) should not be treated because hepatitis B antiviral agents rarely result in HBeAg seroconversion, and long-term treatment leads to drug resistance. Patients with elevated ALT and HBV DNA levels (regardless of the presence or absence of HBeAg) require treatment to delay progression to cirrhosis and prevent the development of ESLD. The treatment response for a patient who is positive for HBeAg is different from that of a patient who is negative for HBeAg because obtaining seroconversion is less likely to occur.

Interferon and Peyglated Interferon

Interferon alfa is an antiviral agent that is effective in suppressing hepatitis B viral replication. Interferon alfa-2b and pegylated interferon alfa-2a are the only interferon therapies approved for the treatment of chronic hepatitis B.

Interferon therapy has an advantage over other antiretroviral treatment in that it is effective in suppressing, and in some cases ceasing, viral replication without inducing resistance. Approximately one-third of HBsAg-positive patients become seronegative after 4 to 6 months of treatment.[25] The HBeAg seroconversion rate is 18% greater than those who are not treated.[25]

TABLE 21–5. Recommendations for Prophylaxis after Exposure to Hepatitis B Virus

	Treatment to Administer if Serology Test of Source Person Is:		
Exposed Person's Vaccination Status	**HBsAg Positive**	**HBsAg Negative**	**Unknown or Unavailable for Testing**
Unvaccinated	HBIG × 1 and initiate HB vaccine series	Initiate HB vaccine series	Initiate HB vaccine series
Previously vaccinated:			
Known responder	No treatment	No treatment	No treatment
Known non-responder	HBIG × 1 and initiate HB revaccination or HBIG × 2	No treatment	If known high-risk source, treat as if source were HBsAg-positive
Antibody response unknown	Test exposed person for anti-HBs: (1) if adequate, no treatment; (2) if inadequate, HBIG × 1 and vaccine booster	No treatment	Test exposed person for anti-HBs: (1) if adequate, no treatment; (2) if inadequate, vaccine booster and recheck titer in 1–2 months

HB, hepatitis B; anti-HBs, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBIG, hepatitis B immune globulin.
From Chan J. Viral hepatitis. Pharmacotherapy Self-Assessment Program. 5th ed. Kansas City: MO, American College of Clinical Pharmacy, 2005:1, 9, with permission.

TABLE 21–6. Recommendations for Hepatitis B Prophylaxis to Prevent Perinatal Transmission

	Mother's HBsAg Status:		
Treatment	**Positive**	**Negative**	**Unknown**
HBIG[a]	Given within 12 hours of birth	None	If positive, give within 7 days; if negative, give none
AND			
Hepatitis B vaccine[b]			
Dose 1	Within 12 hours of birth	Based on infant's weight[c]	Within 12 hours of birth
Dose 2	At month 1–2	At month 1–2	At month 1–2
Dose 3	At month 6	At month 6–18	At month 6

[a]0.5 mL intramuscularly.
[b]See Table 21–4 for appropriate hepatitis B vaccine dose.
[c]Full-term infants who are medically stable and weigh greater than or equal to 2000 grams born to HBsAg-negative mothers should receive the hepatitis B vaccine before hospital discharge. Preterm infants weighing less than 2000 grams born to HBsAg-negative mothers should receive the first dose of hepatitis B vaccine 1 month after birth or at hospital discharge.
From Centers for Disease Control and Prevention. A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States. Recommendations of the Advisory Committee on Immunization Practices (ACIP) Part 1: Immunization of Infants, Children, and Adolescents. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5416a1.htm?s_cid=rr5416a1_e. Accessed February 16, 2006.

Additionally, the durability (likelihood of developing and sustaining HBeAg seroconversion) is greater than 80% after treatment has been discontinued. If interferon treatment duration is extended to 12 to 24 weeks, HBsAg loss is observed in about 10% of patients.

Pegylated interferon is interferon that is attached to a polyethylene glycol molecule that increases the half-life of the drug, thus allowing once-weekly dosing versus thrice-weekly administration required for the unmodified formulation. Pegylated interferon is well tolerated and is superior in efficacy to unmodified interferon for the treatment of chronic hepatitis B.[26]

Patients with chronic hepatitis B who are HBeAg-negative may achieve undetectable HBV DNA levels and normalize ALT levels during treatment with any of the antiviral therapies; however, once treatment has ceased, these endpoints return to pretreatment values.[27] Patients treated with unmodified interferon have an end-of-treatment response (defined as undetectable HBV DNA and normal ALT levels) ranging from 60% to 70%; however, the rate of sustaining virologic response once therapy has been discontinued is approximately 20%.[20] Patients with HBeAg-negative chronic hepatitis B should be treated with more than 12 months of therapy.[28] When the duration of interferon therapy is prolonged beyond 12 months, undetectable HBV DNA may be sustained, as well as increasing the chance of losing HBsAg.

Factors associated with a higher likelihood of response to interferon therapy are baseline HBV DNA levels less than 200 pg/mL and ALT concentrations greater than 5 times the upper limit of normal.[29]

The subcutaneous dose of interferon alfa-2b (Intron A) in patients who are HBsAg-positive is either 5 million units daily (better tolerated) or 10 million units three times weekly. The dose for HBsAg-negative patients is 5 to 6 million units three times weekly. The approved dose for pegylated interferon alfa-2a (Pegasys) for chronic hepatitis B is 180 mcg subcutaneously once weekly. Interferon doses may need to be adjusted in patients with renal impairment.

Even though the advantages of interferon therapy include a finite duration of treatment, lack of resistance, and possible HBsAg loss or seroconversion (development of anti-HBs), there are several significant disadvantages. These include the need for subcutaneous injections, and more importantly, the pronounced adverse-effect profile that may require treatment discontinuation. The most common complaints include injection site reactions and flulike symptoms of fevers, chills, joint pain, and muscle aches. Systemic adverse effects include anorexia, nausea, diarrhea, fatigue, headache, insomnia, irritability, depression, alopecia, and dermatitis. Hematologic abnormalities are common including neutropenia, anemia, and thrombocytopenia, which require either a dose reduction or treatment discontinuation.[28,29] Uncommon side effects include cardiac arrhythmias, diabetes, thyroid disorders, amenorrhea, and vision disturbances.

Lamivudine

Lamivudine (Epivir-HBV) is an oral synthetic cytosine nucleoside analogue having antiviral effects against HIV and hepatitis B virus. In patients with chronic hepatitis B, lamivudine is effective in suppressing hepatitis B viral replication, normalizing

ALT levels, and improving liver histology.[30,31] Patients with HBeAg-positive chronic hepatitis B may have a similar or a superior response in achieving these endpoints when compared to interferon. A significant loss of serum HBV DNA level was observed in 44% of subjects receiving lamivudine compared to 16% receiving placebo. Normalization of ALT levels and improvement in histology occurred in approximately 50% of patients with HBeAg-positive hepatitis B. HBeAg loss, 18% at the end of 52 weeks of treatment, is quite similar between interferon and lamivudine. However, prolonged lamivudine therapy may be needed to sustain seroconversion, as durability of response is only 50% to 80%.[32] Extending the duration of treatment is not without consequences, as lamivudine resistance has been reported at 14% after 1 year of treatment and increases to 70% at 5 years.[29]

Compared to those treated with placebo, 60% to 70% of patients with HBeAg-negative hepatitis B treated with lamivudine for 52 weeks have undetectable HBV DNA levels and normalization of ALT levels. However, the rate of relapse is 80% to 90% once the treatment has been discontinued.[20] Lamivudine therapy beyond 12 months may be considered to sustain response, but biochemical and virologic breakthrough commonly occurs due to the development of drug resistance.[29]

The dose of lamivudine is 100 mg orally once daily for treatment of chronic hepatitis B. The dose must be adjusted in patients with renal dysfunction [creatinine clearance (CrCl) less than 50 mL/minute].

Adverse effects are minimal and include fatigue, diarrhea, nausea, vomiting, and headaches. In rare cases, pancreatitis, hepatomegaly, and potentially fatal lactic acidosis have been reported. ALT levels should be monitored carefully, especially when lamivudine has been discontinued, as an elevation may indicate a flare in disease activity that may lead to liver failure.

The advantages of lamivudine over interferon are oral administration and low drug cost with minimal adverse effects. The major disadvantage is the prolonged treatment duration required to achieve and sustain HBeAg and HBsAg seroconversion. Even so, this approach increases the drug resistance rate significantly with each additional year of treatment.

Adefovir Dipivoxil

Adefovir dipivoxil (Hepsera) is a prodrug of adefovir, an adenosine nucleotide analog that inhibits DNA polymerase. It is effective against HIV and HBV, specifically lamivudine-resistant HBV. Treatment with adefovir dipivoxil 10 mg daily is comparable to lamivudine in normalizing aminotransferase levels and improving histologic activity.[33,34] Undetectable HBV DNA levels were observed in 21% of patients treated for 48 weeks and in 56% of patients when the treatment duration was extended to 144 weeks.[33] Unlike lamivudine, extending the duration of adefovir dipivoxil therapy resulted in a relatively low resistance rate, approximately 11% after 3 years. The percentage of seroconversion and loss of HBeAg are comparable to patients who received lamivudine.[20]

Patients infected with HBeAg-negative chronic hepatitis B have a significant response while on adefovir dipivoxil, but the response is not sustained after treatment discontinuation. Serum ALT levels normalized in 72% of patients treated for 48 weeks compared to 29% who received placebo. Additionally, 51% had undetectable HBV DNA levels with adefovir dipivoxil, whereas none achieved this in the placebo arm.[20,27,32]

Resistance rates to adefovir dipivoxil are lower than with lamivudine, potentially allowing for prolonged treatment duration. At present, the longest trial with adefovir dipivoxil is 5 years with a resistance rate of 29%,[35] compared to 5 years of lamivudine therapy with a resistance rate of 70%.

The dose of adefovir dipivoxil is 10 mg once daily. The most common side effects include asthenia, abdominal pain, diarrhea, dyspepsia, headaches, nausea, and flatulence. Lactic acidosis, pancreatitis, and hepatomegaly have been reported rarely. Unlike lamivudine, adefovir dipivoxil is associated with dose-related nephrotoxicity, which was most commonly seen in HIV patients receiving doses larger than 60 mg. Therefore, the dose of adefovir dipivoxil must be adjusted in patients with renal insufficiency (CrCl less than 50 mL/minute).

Entecavir

Entecavir (Baraclude) is a guanosine nucleoside analogue that inhibits HBV DNA polymerase, thereby inhibiting DNA replication. Unlike the other two oral antiretroviral agents, entecavir has no activity against HIV and is only effective against HBeAg-positive, HBeAg-negative, and lamivudine-resistant chronic hepatitis B. In treatment-naïve patients with either HBeAg-positive or HBeAg-negative HBV, doses of 0.5 mg once daily for 52 weeks are comparable to lamivudine 100 mg daily in histologic improvement, viral load reduction, and normalization of ALT levels.

Patients who develop resistance to lamivudine have significant improvement in histology while receiving entecavir, but higher doses (1 mg daily) are required. Additionally, 19% of lamivudine-resistant patients had undetectable HBV DNA levels compared to 1% of those who continued treatment with lamivudine.[36] At present, no resistance has been associated with entecavir in patients treated for 1 year, but the data beyond 1 year of therapy are unknown. Entecavir resistance has only been seen in patients who already had lamivudine resistance.[37]

The side-effect profile for entecavir is similar to lamivudine and adefovir dipivoxil and comparable to placebo. Patients treated with entecavir should be monitored for signs and symptoms associated with lactic acidosis and severe hepatomegaly with steatosis, because some cases have been fatal. Dosage adjustments are required in patients with renal dysfunction.

Hepatitis C Prevention

The risk factors for hepatitis C and hepatitis B are quite similar; thus, the risk of acquiring the HCV is minimized by avoiding contaminated blood products and high-risk behaviors

such as sharing needles among intravenous drug users. No vaccines are available for preventing hepatitis C. However, individuals at high risk (Table 21–1) should be tested for the hepatitis C virus because the disease presents asymptomatically.

Chronic Hepatitis C Treatment

Individuals with confirmed chronic hepatitis C should be evaluated for treatment with pegylated interferon with or without ribavirin.

Interferon or Peyglated Interferon plus Ribavirin

Interferon alfa-2a (Roferon A), interferon alfa-2b (Intron-A), and interferon alfacon-1 (Infergen) are approved for chronic hepatitis C. However, they are not prescribed alone because only 12% to 16% of patients achieve a sustained virologic response (SVR). Adding ribavirin, a synthetic guanosine analogue that inhibits viral polymerase, increases the SVR rate to 35% to 45%.

Pegylated interferon alfa-2a (Pegasys) and pegylated interferon alfa-2b (PEG-Intron) are also effective FDA-approved treatments for hepatitis C.[38,39] These pegylated interferons are similar to those used to treat hepatitis B, where the interferon is attached to a polyethylene glycol molecule that extends the interferon's half-life allowing for once-weekly administration. Pegylated interferon therapy alone for 48 weeks achieves a 25% to 40% SVR, which is similar to the unmodified interferon plus ribavirin regimen. Therefore, the combination of pegylated interferon and ribavirin would be expected to have SVR rates of 45% to 55% when used for treatment of hepatitis C.[38,39]

Patient variables associated with a higher virologic response include low baseline HCV RNA levels, female gender, acquiring the infection at a later age, lower body weight, and a minimal fibrosis score on liver biopsy.[40] However, the most important pretreatment factor is the patient's genotype. Individuals with genotype 2 or 3 achieve an SVR of 75% to 85% compared to 40% to 50% for patients with genotype 1.[38,39]

Genotype also determines the duration of therapy. Those with non–genotype 1 are treated for 24 weeks and genotype 1 patients are treated for 48 weeks. Additionally, for genotype 1 patients the dose of ribavirin is weight based (less than 75 kg or 165 lbs = 1,000 mg daily; greater than or equal to 75 kg or 165 lbs = 1200 mg daily), whereas non–genotype 1 patients receive 800 mg daily regardless of weight.[41]

Adherence to therapy is another important factor in increasing and maintaining SVR. Patients who were adherent with interferon and ribavirin therapy (taking more than 80% of doses for more than 80% of the treatment duration) had an SVR of 52% whereas those who were not compliant had an SVR of 44%.[42]

At present, pegylated interferon plus ribavirin is the regimen of choice for the treatment of hepatitis C.[41] Interferon, pegylated interferon, and ribavirin have significant adverse effects, as discussed below.

Management of the Adverse Effects of Interferon, Pegylated Interferon, and Ribavirin

The type and incidence of adverse effects associated with unmodified interferon and pegylated interferon are comparable. Approximately 10% to 30% of patients receiving interferon and/or ribavirin require a dosage reduction or treatment discontinuation to minimize side effects. Patients should be screened for uncommon adverse effects and laboratory abnormalities prior to starting interferon and ribavirin because treatment may exacerbate or worsen some medical conditions.

Most patients treated with either interferon or pegylated interferon experience flulike symptoms (fevers, chills, rigors, and myalgias). These symptoms may be mild to moderate in severity and usually occur with the first injection and diminish as the treatment continues. The flulike symptoms may be minimized by premedication with acetaminophen or a nonsteroidal anti-inflammatory drug.

Psychiatric adverse effects occur frequently and may include irritability, depression, and rarely, suicidal ideation. Individuals with a history of uncontrolled psychiatric disorders must weigh the risk versus benefit of treatment, as interferon may exacerbate or worsen the psychiatric condition. Patients who develop mild to moderate symptoms may require antidepressants or anxiolytics. Those with severe symptoms including suicidal ideation should have the treatment discontinued immediately.[43]

There are several hematologic abnormalities associated with either interferon or pegylated interferon plus ribavirin therapy. Up to 35% of patients treated for hepatitis require either a dosage reduction or drug discontinuation due to either thrombocytopenia, neutropenia, or anemia.[43] With either formulation of interferon, a decrease in platelet count of about 25% to 30% usually occurs within 6 to 8 weeks after initiation of treatment. Decreasing the dose or discontinuing interferon therapy is rarely required because of significant thrombocytopenia [(defined as a platelet count less than 50,000 cells/mm^3 less than 50×10^9/L)]. However, caution is required in patients with cirrhosis because they may already have low platelet counts prior to starting treatment. At present there are no adjunctive therapies for interferon-induced thrombocytopenia. Interferon should either be reduced or discontinued if the platelet counts significantly decline or symptoms of bruising and bleeding are present.

Neutropenia associated with interferon or pegylated interferon therapy is defined as an absolute neutrophil count (ANC) of less than 1000 cells/mm^3; in rare cases, an ANC less than 500 cells/mm^3 may be observed. The neutropenia is more common and in some cases more severe with pegylated interferon than with unmodified interferon. Neutropenia usually occurs within the first 2 weeks after initiating either formulation of interferon, with the WBC count stabilizing by week four or six. The neutropenia is reversible upon discontinuing therapy. Granulocyte colony-stimulating factor has been used as an adjunctive therapy for interferon-induced neutropenia in hepatitis patients.[44]

Ribavirin causes a dose-related hemolytic anemia. Once treatment has been initiated, the hemoglobin concentration may

decrease by 2.9 to 3.7 g/dL (29 to 37 g/L or 1.8 to 2.3 mmol/L) within 4 weeks. In addition, interferon may slightly suppress bone marrow erythroprogenitor cells. Therefore, a "mixed" anemia (hemolytic anemia and bone marrow suppression occurring simultaneously) develops when both interferon and ribavirin are used. This is a reversible process with the hemoglobin level returning to baseline within 7 to 8 weeks after either drug has been discontinued.

About 10% to 25% of patients treated with interferon and ribavirin require dosage reductions when hemoglobin levels decrease or they develop intolerable symptoms such as shortness of breath or severe fatigue. If warranted, erythropoietin may be used as adjunctive therapy for ribavirin-induced hemolytic anemia.[45]

All women of childbearing age and men who are able to father a child should use two forms of contraception during ribavirin therapy and 6 months after treatment because ribavirin has been documented to cause teratogenic and embryocidal effects.

Hepatitis D Prevention and Treatment

❽ *Hepatitis D infection is possible only if the patient also has the hepatitis B virus present; therefore, hepatitis B vaccination can indirectly prevent hepatitis D infection.*

While there are no FDA-approved treatments for hepatitis D, interferon has been shown to be effective.[46–48] Various doses have been evaluated, with the most effective treatment being 9 million units three times weekly.[47] Seventy-one percent of patients who were treated with this regimen for 48 weeks had normalized ALT levels.[47] Adverse effects and monitoring parameters for interferon therapy are similar to treatment for hepatitis C. In some situations, patients infected with hepatitis D who develop hepatic decompensation and ESLD may need to undergo liver transplantation.

Hepatitis E Prevention and Treatment

Hepatitis E is similar to hepatitis A in that the mode of transmission is via the fecal-oral route. Therefore, the most effective ways to prevent acquiring the virus are good personal hygiene and proper disposal of sanitary waste. Frequent handwashing and avoiding contaminated foods and vegetables decrease the risk of infection.



Patient Encounter, Part 2

Creating a Care Plan

Based on the information presented, create a care plan for this patient's hepatitis. Your plan should include: (1) a statement of the drug-related needs and/or problems; (2) the goals of therapy; (3) a patient-specific detailed therapeutic plan; and (4) a follow-up plan to determine whether the goals have been achieved and to identify potential adverse effects of therapy.

At present, only acute cases of hepatitis E have been documented. There are no vaccines available to prevent hepatitis E; however, a recombinant hepatitis E vaccine is undergoing Phase II/III study to determine its efficacy in preventing hepatitis E infections.[49] Supportive care is the only treatment available for acute hepatitis E infection.[19]

OUTCOME EVALUATION

- Monitoring for efficacy in patients treated for chronic hepatitis B or C includes evaluating aminotransferase levels and viral loads.

Hepatitis B

- In patients with either HBeAg-positive or HBeAg-negative hepatitis B, monitor hepatitis B serologies and HBV DNA levels every 3 months to determine treatment response regardless of the therapy given.[28,32]
- At month 3, if the viral count is still positive or fails to decrease at least 1 log, the patient is deemed a treatment failure. Reevaluate the patient for a different hepatitis B antiviral agent.
- Patients are considered responders if at least a 1-log drop in viral count and normalization of ALT levels occur. Continue treatment.
- Patients are considered to have relapsed if the viral load increases during treatment. The beginnings of drug resistance may also be evidenced by increasing ALT and HBV DNA levels during treatment.

Hepatitis C

- The National Institutes of Health Consensus Development Conferences in 1997 and 2002 defined several therapeutic endpoints in the management of hepatitis C:[40]
  - Virologic response is defined as having an undetectable viral load or HCV RNA level.
  - Biochemical response is defined as normalization of aminotransferase levels, specifically ALT concentrations.
  - Histologic response is defined as improving inflammation and fibrosis as noted by pretreatment and posttreatment biopsy scores.
- Measure these outcomes at the end of treatment to determine the end-of-treatment response and at 24 weeks after treatment has been discontinued to determine SVR.
- In patients with genotype 1 HCV, check the HCV RNA level at week 12 of therapy to determine the effectiveness of treatment.[41]
- Discontinue treatment if the HCV RNA has not decreased by at least 2 logs or become undetectable.
- Continue treatment for at least another 36 weeks (48 weeks total) if the HCV RNA level becomes negative or decreases by at least 2 logs.
- At the end of the 48-week treatment, obtain an HCV RNA level to determine end-of-treatment response and repeat at 6 months post-therapy to determine SVR.

- In patients infected with non–genotype 1 HCV disease, check the HCV RNA level at the end of treatment (24 weeks). If HCV RNA is undetectable, continue treatment for another 24 weeks. Repeat the HCV RNA 24 weeks after completion of therapy to determine SVR.[41]
- Monitor patients carefully during treatment with interferon or pegylated interferon with or without ribavirin.
  - Monitor the WBC count, ANC, platelets, and hemoglobin levels either weekly or biweekly during the first month of therapy and monthly thereafter if stable.
  - Monitor serum creatinine because patients with renal insufficiency (CrCl less than 50 mL/minute) may have reduced ribavirin elimination resulting in increased drug accumulation and toxicity (e.g., hemolytic anemia).



Patient Care and Monitoring

1. Evaluate the patient for risk factors for acquiring viral hepatitis (Table 21–1).
2. Educate patients to avoid hepatotoxic agents (e.g., some dietary supplements).
3. Educate patients to avoid consuming any alcohol if viral hepatitis has been diagnosed.
4. Determine if the patient has been vaccinated against hepatitis A and B. If not, then vaccinate accordingly (Tables 21–3 and 21–4).
5. Obtain a thorough past medical history focusing on psychiatric disorders, cardiac disorders, endocrine disease, and renal insufficiency.
6. Review the liver biopsy report (if available) to determine the severity of liver damage and need for chronic hepatitis B or C treatment.
7. Assess for adverse effects in patients with hepatitis C treated with interferon or pegylated interferon with or without ribavirin.
8. Encourage medication compliance with viral hepatitis treatments to increase sustaining virologic response.
9. Encourage patients to drink at least 8 glasses of water to prevent dehydration while on hepatitis C medications.
10. Educate all women of childbearing age and men who are able to father a child to use two forms of contraception during and 6 months after ribavirin therapy.
11. Provide patient education:
    - How to prevent viral hepatitis transmission
    - Who should be vaccinated against hepatitis A and B
    - The importance of taking all medications at scheduled times
    - Adverse effects of interferon, pegylated interferon, and ribavirin therapy
    - How to self-administer interferon and pegylated interferon injections
    - The importance of appropriate disposal of used needles

ABBREVIATIONS

ALT:	alanine aminotransferase
ANC:	absolute neutrophil count
anti-HAV:	hepatitis A virus antibody
anti-HBc:	hepatitis B core antibody
anti-HBe:	hepatitis B envelope antibody
anti-HBs:	hepatitis B surface antibody
anti-HCV:	hepatitis C antibody
anti-HDV:	hepatitis D antibody
anti-HEV:	hepatitis E antibody
AST:	aspartate aminotransferase
CrCl:	creatinine clearance
DNA:	deoxyribonucleic acid
ESLD:	end-stage liver disease
HAV:	hepatitis A virus
HBcAg:	hepatitis B core antigen
HBeAg:	hepatitis B envelope antigen
HBIG:	hepatitis B immunoglobulin
HBsAg:	hepatitis B surface antigen
HBV:	hepatitis B virus
HBV DNA:	hepatitis B deoxyribonucleic acid
HCV:	hepatitis C virus
HCV RNA:	hepatitis C virus ribonucleic acid
HDV:	hepatitis D virus
HDVAg:	hepatitis D antigen
HDV RNA:	hepatitis D virus ribonucleic acid
HEV:	hepatitis E virus
HIV:	human immunodeficiency virus
IgG:	immunoglobulin G
IgG anti-HD:	IgG antibodies to hepatitis D virus antigen
IgM:	immunoglobulin M
IgM anti-HD:	IgM antibodies to hepatitis D virus antigen
IG:	immune globulin
IGIM:	immune globulin for intramuscular administration
IGIV:	immune globulin for intravenous administration
MMR:	measles, mumps, rubella vaccine
PCR:	polymerase chain reaction
RNA:	ribonucleic acid
SVR:	sustained virologic response

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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22 Acute Renal Failure

Mary K. Stamatakis



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Assess a patient's kidney function based on clinical presentation, laboratory results, and urinary indices.
2. Identify pharmacotherapeutic outcomes and endpoints of therapy in a patient with acute renal failure.
3. Apply knowledge of the pathophysiology of acute renal failure to the development of a treatment plan.
4. Design a diuretic regimen that considers the pharmacokinetic and pharmacodynamic characteristics of the drug.
5. Select pharmacotherapy to treat complications associated with acute renal failure.
6. Develop strategies to minimize the occurrence of acute renal failure.
7. Monitor and evaluate the safety and efficacy of the therapeutic plan.

Key Concepts

❶ Equations to estimate creatinine clearance that incorporate a single creatinine concentration (e.g., Cockcroft-Gault) may underestimate or overestimate kidney function depending on whether acute renal failure is worsening or resolving.
❷ There is no evidence that supports drug therapy in hastening the recovery period, decreasing length of hospitalization, or improving survival in acute renal failure.
❸ Loop diuretics are the diuretics of choice for the management of volume overload in acute renal failure.
❹ Renal dose dopamine is not recommended in the prevention or treatment of acute renal failure.
❺ Identifying patients at high risk for development of acute renal failure and implementing preventive methods to decrease its occurrence or severity is critical.

Acute renal failure (ARF) is a potentially life-threatening clinical syndrome that occurs primarily in hospitalized patients and frequently complicates the course of the critically ill. It is characterized by a rapid decrease in glomerular filtration rate (GFR) and the resultant accumulation of nitrogenous waste products (e.g., creatinine and urea nitrogen), with or without a decrease in urine output. A recent consensus statement defines ARF as a 50% increase in baseline serum creatinine concentration, a 25% decrease in GFR, or a urine output of less than 0.5 mL/kg per hour for at least 6 hours.[1] It should be noted that no single serum creatinine value is a threshold for ARF.

EPIDEMIOLOGY

Between 5% and 25% of all hospitalized patients develop ARF.[2] A greater prevalence of ARF is found in critically ill patients.[3] Despite improvements in the medical care of individuals with ARF, mortality generally exceeds 50%.[4]

PATHOPHYSIOLOGY

There are typically three categories of ARF: prerenal, intrinsic, and postrenal ARF. The pathophysiologic mechanisms differ for each of the categories.

Prerenal Acute Renal Failure

Prerenal ARF is characterized by reduced blood delivery to the kidney. A common cause is intravascular volume depletion due to conditions such as hemorrhage, dehydration, or

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gastrointestinal fluid losses. Prompt correction of volume depletion can restore renal function to normal because no structural damage to the kidney has occurred. Conditions of reduced cardiac output (e.g., congestive heart failure or myocardial infarction) and hypotension can also reduce renal blood flow, resulting in decreased glomerular perfusion and prerenal ARF. With a mild to moderate decrease in renal blood flow, intraglomerular pressure is maintained by dilation of afferent arterioles (arteries supplying blood to the glomerulus), constriction of efferent arterioles (arteries removing blood from the glomerulus), and redistribution of renal blood flow to the oxygen-sensitive renal medulla.[5] Functional ARF occurs when these adaptive mechanisms are compromised and is often caused by drugs. Nonsteroidal anti-inflammatory drugs (NSAIDs) impair prostaglandin-mediated dilation of afferent arterioles. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) inhibit angiotensin II–mediated efferent arteriole vasoconstriction. Cyclosporine and tacrolimus, especially in high doses, are potent renal vasoconstrictors. All of these agents can reduce intraglomerular pressure, with a resultant decrease in GFR. Prompt discontinuation of the offending drug can often return renal function to normal. Other causes of prerenal ARF are renovascular obstruction (e.g., renal artery stenosis), hyperviscosity syndromes (e.g., multiple myeloma), or systemic vasoconstriction (e.g., hepatorenal syndrome). Prerenal ARF occurs in approximately 10% to 25% of patients diagnosed with ARF.[6]

Intrinsic Acute Renal Failure

Intrinsic renal failure, also referred to as intrarenal ARF, is caused by diseases that can affect the integrity of the tubules, glomerulus, interstitium, or blood vessels. Damage is within the kidney; changes in kidney structure can be seen on microscopy.[7] Acute tubular necrosis (ATN) represents a pathophysiologic condition that results from toxic (aminoglycosides, contrast agents, or amphotericin B) or ischemic insult to the kidney. ATN results in necrosis of the proximal tubule epithelium and basement membrane, decreased glomerular capillary permeability, and backleak of glomerular filtrate into the venous circulation.[8] Maintenance of ATN is mediated by intrarenal vasoconstriction.[8] The most common cause of intrinsic renal failure is ATN and it accounts for approximately 50% of all cases of ARF.[6] Glomerular, interstitial, and blood vessel diseases may also lead to intrinsic ARF, but occur with a much lower incidence. Examples include glomerulonephritis, systemic lupus erythematosus, interstitial nephritis, and vasculitis. In addition, prerenal ARF can progress to intrinsic ARF if the underlying condition is not promptly corrected.[7]

Postrenal Acute Renal Failure

Postrenal ARF is due to obstruction of urinary outflow. Causes include benign prostatic hypertrophy, pelvic tumors, and precipitation of renal calculi.[7] Rapid resolution of postrenal ARF without structural damage to the kidney can occur if the underlying obstruction is corrected. Postrenal ARF accounts for less than 10% of cases of ARF.[6]

ASSESSMENT OF RENAL FUNCTION

The most common measure of overall kidney function is GFR. It is defined as the volume of plasma filtered across the glomerulus per unit time and correlates well with the filtration, secretion, reabsorption, endocrine, and metabolic functions of the kidney. In addition to aiding in the diagnosis and assessment of the severity of ARF, an accurate estimate of GFR can assist in proper dosing of drugs that undergo renal elimination. In an individual with normal kidney function, GFR ranges from approximately 90 to 120 mL/minute. Because GFR is difficult to measure directly, it is routinely estimated by determining the renal clearance of a substance that is filtered at the glomerulus and which does not undergo significant tubular reabsorption or secretion. Creatinine is an endogenous substance that is a normal by-product of muscle metabolism. Ninety percent of creatinine is eliminated by glomerular filtration; tubular secretion is responsible for the remaining 10%.

Direct measurement of creatinine clearance (CrCl) requires collection of urine over an extended time interval (usually 24 hours) with measurement of urine volume, urine creatinine concentration, and serum creatinine concentration (Table 22–1). Because kidney function can fluctuate significantly during ARF, this method may underestimate or overestimate kidney function depending on whether ARF is worsening or resolving.

Numerous equations have been developed for a quick bedside estimate of creatinine clearance or GFR. They incorporate patient-specific variables such as serum creatinine concentration, body weight, age, gender, albumin, and blood urea nitrogen (BUN) concentration. Two of the most widely used equations are the Cockcroft-Gault equation and the Modification of Diet in Renal Disease (MDRD) equation (Table 22–1).[9,10] They are generally considered acceptable in individuals whose renal function is relatively constant. ❶ *Because only a single serum creatinine concentration is factored into these equations, the calculated creatinine clearance or GFR may underestimate or overestimate kidney function depending on whether acute renal failure is worsening or resolving.*

TABLE 22–1. Equations for Estimation of Creatinine Clearance (CrCl)

Urine Collection Method

$$\text{CrCl (mL/minute)} = \frac{(\text{Ucr})(\text{V})}{(\text{Scr})(\text{T})}$$

Ucr = urine creatinine concentration, mg/dL
V = volume of urine, mL
Scr = serum creatinine concentration, mg/dL
T = time of urine collection, minute
(Note: time equals 1440 minutes for a 24-hour collection)

Cockcroft-Gault Equation for Adults[9]

$$\text{CrCl (mL/minute)} = \frac{(140 - \text{age}) \times \text{BW}}{(\text{Scr}) \times 72} \quad (\times 0.85 \text{ if women})$$

Age, in years
BW = actual body weight (kg)[a]
Scr = serum creatinine concentration, mg/dL

MDRD[10]

4-Variable Method

$$\text{GFR} = 186 \times [\text{Scr}]^{-1.154} \times [\text{age}]^{-0.203} \times [0.742 \text{ if female}] \times [1.212 \text{ if African-American}]$$

6-Variable Method

$$\text{GFR} = 170 \times [\text{Scr}]^{-0.999} \times [\text{age}]^{-0.176} \times [0.762 \text{ if female}] \times [1.180 \text{ if African-American}] \times [\text{BUN}]^{-0.170} \times [\text{albumin}]^{+0.318}$$

Jelliffe Equation for Changing Renal Function[11]

Males

$E^{SS} = \text{IBW}\ [29.3 - 0.203\ (\text{age})]$
$E^{SS}_{corr} = E^{SS}[1.035 - 0.0337\ (\text{Scr}_2)]$
$E = E^{SS}_{corr} - [4 \times \text{IBW} \times (\text{Scr}_2 - \text{Scr}_1)/\Delta t$
$\text{CrCl (mL/minute/1.73 m}^2) = E/14.4\ (\text{Scr})$

Females

$E^{SS} = \text{IBW}\ [25.1 - 0.175\ (\text{age})]$
$E^{SS}_{corr} = E^{SS}\ [1.035 - 0.0337\ (\text{Scr})]$
$E = E^{SS}_{corr} - [4\ \text{IBW}\ (\text{Scr}_2 - \text{Scr}_1]/\Delta t$
$\text{CrCl (mL/minute/1.73 m}^2) = E/14.4(\text{Scr})$

E^{SS} = steady-state creatinine excretion
Δt = time in days between measurement of Scr_1 and Scr_2
IBW = ideal body weight, kg
age = years
E^{SS}_{corr} = corrected steady-state creatinine excretion
Scr_1 = first serum creatinine concentration
Scr_2 = second serum creatinine concentration
E = creatinine excretion

MDRD, per the Modification of Diet in Renal Disease study.
[a]Often substituted with ideal body weight, or adjusted body weight when body weight is significantly greater than ideal body weight.

Several equations have been developed to assess unstable kidney function. The Jelliffe equation (Table 22–1) estimates creatinine clearance by considering the change in serum creatinine over a specified time period.[11] While it is more mathematically difficult to calculate, it better estimates creatinine clearance in patients with rapidly changing kidney function compared to an equation that only includes a single creatinine concentration.

Estimating creatinine clearance is only one part of evaluating a patient's overall kidney function. Other factors, such as symptomatology, laboratory test results, urinary indices, and results of diagnostic procedures will aid in the diagnosis and assessment of the severity of disease. By monitoring serum creatinine concentrations on a routine basis, it can be estimated whether kidney function is improving or worsening. Kidney function can also be evaluated based on urine output. Oliguria and anuria are defined as urine outputs of less than 400 mL and 50 mL over 24 hours, respectively. Patients with reduced urine output often have an increased mortality and may represent a more severe form of ARF. Non-oliguric ARF is defined as a urine output of greater than 400 mL per day. It may still represent severe ARF but may be associated with better patient outcomes.[12]



Patient Encounter, Part 1

A 73-year-old man with a history of diabetes mellitus, chronic kidney disease, gout, osteoarthritis, and hypertension is hospitalized with possible urosepsis. He recently completed a 10-day course of antibiotics and was ready for discharge when his morning labs showed an increase in BUN and serum creatinine concentration. Upon examination, he was found to have 2+ pitting edema, weight gain, nausea, elevated blood pressure, and rales on chest auscultation.

- What sign and symptoms does the patient have that may indicate ARF?
- What risk factors does he have for the development of ARF?
- What additional information do you need to fully assess this patient?



Clinical Presentation and Diagnosis

While some clinical and laboratory findings assist in the general diagnosis of ARF, others are used to differentiate between prerenal, intrinsic, and postrenal ARF. For example, patients with prerenal ARF typically demonstrate enhanced sodium reabsorption, which is reflected by a low urine sodium concentration and a low fractional excretion of sodium. Urine is typically more concentrated with prerenal ARF and there is a higher urine osmolality and urine:plasma creatinine ratio compared to intrinsic and postrenal ARF.

Signs and Symptoms of Uremia

- Peripheral edema
- Weight gain
- Nausea/vomiting/diarrhea/anorexia
- Mental status changes
- Fatigue
- Shortness of breath
- Pruritus
- Volume depletion (prerenal ARF)
- Weight loss (prerenal ARF)
- Anuria alternating with polyuria (postrenal ARF)
- Colicky abdominal pain radiating from flank to groin (postrenal ARF)

Physical Examination Findings

- Hypertension
- Jugular venous distention
- Pulmonary edema
- Rales
- Asterixis
- Pericardial or pleural friction rub
- Hypotension/orthostatic hypotension (prerenal ARF)
- Rash (acute interstitial nephritis)
- Bladder distention (postrenal bladder outlet obstruction)
- Prostatic enlargement (postrenal ARF)

Laboratory Tests

- Elevated serum creatinine concentration (normal range approximately 0.6 to 1.2 mg/dL [53 to 106 µmol/L])
- Elevated BUN concentration (normal range approximately 8 to 25 mg/dL [2.9 to 8.9 mmol/L])
- Decreased creatinine clearance (normal 90 to 120 mL/minute)
- BUN:creatinine ratio (elevated in prerenal ARF)
  Greater than 20:1 (prerenal ARF)
  Less than 20:1 (intrinsic or postrenal ARF)
- Hyperkalemia
- Metabolic acidosis

Urinalysis

- Sediment
  Scant or bland (prerenal or postrenal ARF)
  Brown, muddy granular casts (highly indicative of ATN)
  Proteinuria (glomerulonephritis or allergic interstitial nephritis)
  Eosinophiluria (acute interstitial nephritis)
  Hematuria/red blood cell casts (glomerular disease or bleeding in urinary tract)
  White blood cells or casts (acute interstitial nephritis or severe pyelonephritis)

Urinary Indices

	Prerenal ARF	Intrinsic and Postrenal ARF
Urine osmolality (concentration of solutes in the urine)	Greater than 500 mOsm	Less than 350 mOsm
Urine sodium concentration (mEq/L)	Less than 20	Greater than 40
Fractional excretion of sodium (FENa)	Less than 1%	Greater than 1%
Specific gravity	Greater than 1.020	Less than 1.015
Urine:plasma creatinine ratio	Greater than 40:1	Less than 20:1

Loop diuretics such as furosemide enhance sodium excretion and increase FENa, confounding the interpretation of the test.

Common Diagnostic Procedures

- Urinary catheterization (insertion of a catheter into a patient's bladder; an increase in urine output may occur with postrenal obstruction)
- Renal ultrasound (uses sound waves to assess size, position, and abnormalities of the kidney; dilatation of the urinary tract can be seen with postrenal ARF)
- Renal angiography (administration of intravenous contrast dye to assess the vasculature of the kidney)
- Retrograde pyelography (injection of contrast dye into the ureters to assess the kidney and collection system)
- Kidney biopsy (collection of a tissue sample of the kidney for the purpose of microscopic evaluation; may aid in the diagnosis of glomerular and interstitial diseases)

TREATMENT

Desired Outcomes and Goals

A primary goal of therapy is ameliorating any identifiable underlying causes of ARF such as hypovolemia, nephrotoxic drug administration, or ureter obstruction. Prerenal and postrenal ARF can be reversed if the underlying problem is promptly identified and corrected, while treatment of intrinsic renal failure is more supportive in nature. ❷ *There is no evidence that drug therapy hastens patient recovery in ARF, decreases length of hospitalization, or improves survival.*[13] Therefore, options are limited to supportive therapy, such as fluid, electrolyte, and nutritional support, renal replacement



Patient Encounter, Part 2: The Medical History, Physical Examination, and Laboratory Tests

PMH
- Type 1 diabetes mellitus since the age of 32
- Chronic kidney disease (BUN and serum creatinine were 30 mg/dL [10.7 mmol/L] and 2.5 mg/dL [221 µmol/L], respectively, on admission)
- Hypertension
- Gout
- Osteoarthritis

FH
Father with a history of type 2 diabetes mellitus, hypertension, and stage 5 chronic kidney disease; he died from a myocardial infarction at age 68; mother with a history of hypertension; she died from injuries sustained in a motor vehicle accident at the age of 52

SH
Retired coal miner; no smoking, occasional alcohol use

Hospital Meds
Gentamicin 120 mg intravenous piggyback every 12 hours (dose discontinued after 3 days)
Gentamicin 120 mg intravenous piggyback every 24 hours (days 4 through 10, discontinued this morning)
Ampicillin 2 g intravenous piggyback every 8 hours (10-day course, discontinued this morning)
Sliding scale insulin
Allopurinol 100 mg orally daily
Ranitidine 150 mg orally every 12 hours
Atenolol 50 mg orally daily
Enalapril 2.5 mg orally daily

Home Meds
NPH insulin 20 units in the morning and 10 units in the evening
Regular insulin 10 units in the morning and 10 units in the evening
Allopurinol 100 mg orally daily
Naproxen 275 mg orally every 12 hours
Atenolol 50 mg orally daily

ROS
(–) fever or chills, (+) N, (–) V/D

PE
VS: blood pressure 154/95 mm Hg, pulse 80 beats per minute, respiratory rate 26/minute, temperature 37.7°C, current wt 79 kg (admission wt 75 kg), ht 5'10" (178 cm)
Chest: Basilar crackles, inspiratory wheezes
CV: S_1, S_2 normal, no S_3
MS/Exts: 2+ pedal edema

Urinalysis
Color, yellow; character, hazy; glucose (–); ketones (–); specific gravity 1.020; pH 5.0; (+) protein; coarse granular casts, 5 to 10/low-powered field; white blood cell (WBC) count, 5 to 10/high-powered field; red blood cell (RBC) count, 2 to 5/high-powered field; no bacteria; nitrite (–); blood small; osmolality 325 mOsm; urinary sodium 77 mEq/L (77 mmol/L); creatinine 63 mg/dL (5569 µmol/L)

Day 3 Labs

Gentamicin concentrations
3.4 mcg/mL (7.12 µmol/L) = trough concentration drawn immediately prior to the next dose
6.4 mcg/mL (13.38 µmol/L) = peak concentration drawn 1 hour after the end of the infusion
Urine (+) *Enterococcus* spp.

- Given this additional information, what is your assessment of the patient's condition?
- Identify your treatment goals for the patient.

therapy (RRT), and treatment of non-renal complications such as sepsis and gastrointestinal bleeding while regeneration of the renal epithelium occurs. In addition, prevention of adverse drug reactions by discontinuing nephrotoxic drugs or adjustment of drug dosages based on the patient's renal function is desired.

Pharmacologic Therapy

Loop Diuretics

There is significant controversy over the role of loop diuretics in the treatment of ARF. Theoretical benefits in hastening recovery of renal function include decreased metabolic oxygen requirements of the kidney, increased resistance to ischemia, increased urine flow rates that reduce intraluminal obstruction and filtrate backleak, and renal vasodilation.[6] Theoretically, these effects could lead to increased urine output, decreased need for dialysis, improved renal recovery, and ultimately, increased survival. However, there are conflicting reports in the literature over the efficacy of loop diuretics. Most studies demonstrate an improvement in urine output, but with no effect on survival or need for dialysis. There are some reports that loop diuretics may worsen renal function.[14] This may be due in part to excessive preload reduction that results in renal vasoconstriction. Thus, loop diuretics are limited to instances of volume overload and edema and are not intended to hasten renal recovery or improve survival.

Loop diuretics (furosemide, bumetanide, torsemide, and ethacrynic acid) are all equally effective when given in equivalent doses. Therefore, selection is based on the side-effect profile, cost, and pharmacokinetics of the agents. The incidence of ototoxicity is significantly higher with ethacrynic acid compared to the other loop diuretics; therefore, its use is limited to patients who are allergic to the sulfa component in the other loop diuretics.[15] While ototoxicity is a well-established side effect of furosemide, its incidence is greater when administered by the intravenous route at a rate exceeding 4 mg per minute.[16] Torsemide has not been reported to cause ototoxicity.

There are several pharmacokinetic differences between loop diuretics. Fifty to sixty percent of a dose of furosemide is excreted unchanged by the kidney with the remainder undergoing glucuronide conjugation in the kidney.[17] In contrast, liver metabolism accounts for 50% and 80% of the elimination of bumetanide and torsemide, respectively.[17] Thus, patients with ARF may have a prolonged half-life of furosemide. The bioavailability of both torsemide and bumetanide is higher than for furosemide. The intravenous (IV):oral ratio for bumetanide and torsemide is 1:1, bioavailability of oral furosemide is approximately 50%, with a reported range of 10% to 100%.[18]

Furosemide and bumetanide are both available in generic formulations and are generally less expensive than torsemide.

The pharmacodynamic characteristics of loop diuretics are similar when equivalent doses are administered. Because loop diuretics exert their effect from the luminal side of the nephron, urinary excretion correlates with diuretic response. Substances that interfere with the organic acid pathway, such as endogenous organic acids which accumulate in renal disease, competitively inhibit secretion of loop diuretics. Therefore, large doses of loop diuretics may be required to ensure that adequate drug reaches the nephron lumen. In addition, loop diuretics have a ceiling effect where maximal natriuresis occurs. Thus, very large doses of furosemide (e.g., 1 g) are generally not considered necessary and may unnecessarily increase the risk of ototoxicity.[16]

Several adaptive mechanisms by the kidney limit effectiveness of loop diuretic therapy. Postdiuretic sodium retention occurs as the concentration of diuretic in the loop of Henle decreases. This effect can be minimized by decreasing the dosage interval (i.e., dosing more frequently) or by administering a continuous infusion. Continuous infusion loop diuretics may be easier to titrate than bolus dosing, requires less nursing administration time, and may lead to fewer adverse reactions.

Prolonged administration of loop diuretics can lead to a second type of diuretic resistance. Enhanced delivery of sodium to the distal tubule can result in hypertrophy of distal convoluted cells.[17] Subsequently, increased sodium chloride absorption occurs in the distal tubule which diminishes the effect of the loop diuretic on sodium excretion. Addition of a distal convoluted tubule diuretic, such as metolazone or hydrochlorothiazide, to a loop diuretic can result in a synergistic increase in urine output. There are no data to support the efficacy of one distal convoluted tubule diuretic over another. The common practice of administering the distal convoluted tubule diuretic 30 to 60 minutes prior to the loop diuretic has not been studied, although this practice may first inhibit sodium reabsorption at the distal convoluted tubule before it is inundated with sodium from the loop of Henle.

A usual starting dose of IV furosemide for the treatment of ARF is 40 mg (Fig. 22–1). Reasonable starting doses for bumetanide and torsemide are 1 mg and 20 mg, respectively.[17] Efficacy of diuretic administration can be determined by comparison of a patient's hourly fluid balance. Other methods to minimize volume overload, such as fluid restriction and concentration of IV medications, should be initiated as needed. If urine output does not increase to about 1 mL/kg per hour, the dosage can be increased to a maximum of 160 to 200 mg of furosemide or its equivalent (Fig. 22–1).[18] Other methods to improve diuresis can be initiated sequentially, such as: (1) shortening the dosage interval; (2) adding hydrochlorothiazide or metolazone; and (3) switching to a continuous infusion loop diuretic. A loading dose should be administered prior to both initiating a continuous infusion and increasing the infusion rate.[17] When high doses of loop diuretics are administered, especially in combination with distal convoluted tubule diuretics, the hemodynamic and fluid status of the patient should be monitored every shift, and the electrolyte status of the patient should be monitored at least daily to prevent profound diuresis and electrolyte abnormalities, such as hypokalemia. Patients will not benefit from switching from one loop diuretic to another because of the similarity in mechanisms of action.

Thiazide diuretics, when used as single agents, are generally not effective for fluid removal when creatinine clearance is less than 30 mL/minute. Mannitol is also not recommended for the treatment of volume overload associated with ARF. Mannitol is removed by the body by glomerular filtration. In patients with renal dysfunction, mannitol excretion is decreased, resulting in expanded blood volume and hyperosmolality.[18] Potassium-sparing diuretics, which inhibit sodium reabsorption in the distal nephron and collecting duct, are not sufficiently effective in removing fluid. In addition, they increase the risk of hyperkalemia in patients already at risk. ❸ *Thus, loop diuretics are the diuretics of choice for the management of volume overload in ARF.*

Dopamine

Low-dose dopamine, in doses ranging from 0.5 to 3 mcg/kg per minute, predominantly stimulates dopamine-1 receptors, leading to renal vascular vasodilation and increased renal blood flow. While this effect has been substantiated in healthy, euvolemic individuals with normal kidney function, a lack of efficacy data exists in patients with ARF. Although there are more than 50 published reports evaluating the efficacy of low-dose dopamine in the treatment of ARF, numerous flaws in their study design limit their applicability to clinical practice. Most of the studies were retrospective, and lacked randomization, blinding, and inclusion of a control group. Lack of concise endpoints, insufficient power to detect a significant difference, and concurrent treatment with drugs that can affect study endpoints makes interpretation of the results difficult.

The most comprehensive study evaluating the efficacy of low-dose dopamine to date is the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group study.[19] Low-dose dopamine was compared to placebo in critically ill

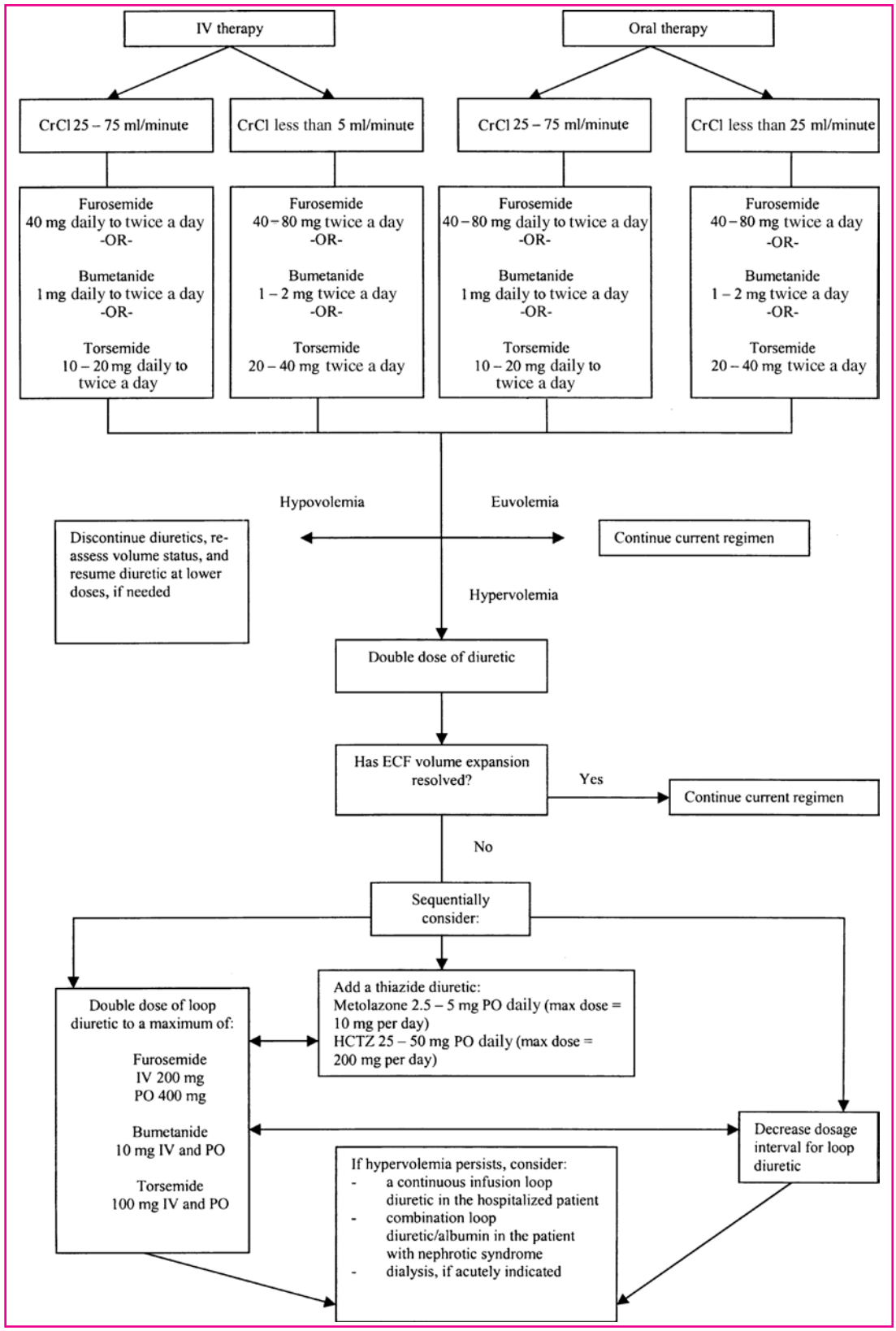


FIGURE 22–1. Algorithm for treatment of extracellular fluid expansion. CrCl, creatinine clearance; ECF, extracellular fluid; HCTZ, hydrochlorothiazide; IV, intravenous; PO, oral.

patients with at least one indicator of early renal failure and two indicators of the systemic inflammatory response. Results indicate that administration of low-dose dopamine compared to placebo did not alter peak serum creatinine concentration or secondary outcome endpoints such as need for renal replacement therapy (RRT), duration of stay in the intensive care unit (ICU), or survival to hospital discharge. Use of loop diuretics was similar between groups and may have been responsible for the increase in urine output demonstrated in the study. More than half of the patients in the study were non-oliguric. Therefore, the results cannot be directly extrapolated to the oliguric or anuric patient.

A recent meta-analysis was performed on all published human trials that used low-dose dopamine in the prevention or treatment of ARF.[20] A total of 61 studies were identified that randomized more than 3300 patients to low-dose dopamine or placebo. Results reveal no significant difference between the treatment and control groups for mortality, requirement for RRT, or adverse effects.

Low-dose dopamine is not without adverse reactions and most studies have failed to evaluate its potential toxicities. Adverse reactions that may be associated with low-dose dopamine include: tachycardia, arrhythmias, myocardial ischemia, depressed respiratory drive, and gut ischemia. Low-dose dopamine has also been postulated to impair resistance to infection through a reduction in prolactin concentrations.[21] Furthermore, significant overlap in receptor activation occurs. Therefore, doses considered to activate only dopamine receptors may increase cardiac output and blood pressure through dopamine's effect on β- or α-adrenergic receptors.

Based on the results of the ANZICS trial, the lack of conclusive evidence in many earlier studies, and several meta-analyses, routine use of low-dose dopamine solely for increasing renal blood flow is not recommended. ❹ *While recent surveys continue to show that low-dose dopamine is used in many ICUs, benefits of low-dose dopamine in the prevention or treatment of ARF remain unproven.*

Fenoldopam

Fenoldopam is a selective dopamine-1 receptor agonist that is approved for short-term management of severe hypertension. Because it does not stimulate dopamine-2, α-adrenergic, and β-adrenergic receptors, fenoldopam causes vasodilation in the renal vasculature with potentially fewer non-renal effects than dopamine. In normotensive individuals with normal kidney function, intravenous fenoldopam increases renal blood flow without lowering systemic blood pressure.[22] While preliminary studies in animal models of ARF are encouraging, few studies are available assessing its effectiveness in the treatment of ARF. A prospective randomized study comparing fenoldopam to placebo in early ATN did not find a difference in need for dialysis or mortality.[23] However, in two separate subset analyses, patients with ATN after cardiothoracic surgery and patients without diabetes mellitus demonstrated a decreased incidence of death or dialysis in the fenoldopam-treated group. Large, prospective trials are needed before fenoldopam can be recommended. Other agents that are under evaluation for the treatment of ARF include atrial natriuretic peptide, urodilatin, and nesiritide.

Nonpharmacologic Treatment

Renal Replacement Therapy

RRT may be necessary in patients with established ARF to treat volume overload that is unresponsive to diuretics, to minimize the accumulation of nitrogenous waste products, and to correct electrolyte and acid-base abnormalities while renal function recovers. Five to thirty percent of patients with ARF treated with dialysis will not have recovery of their renal function and will need to remain on long-term dialysis.[24] This may be due in part to underlying illnesses, as ARF is often seen in the setting of multiorgan failure. There are two types of dialysis modalities commonly used in ARF: intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT). CRRT is a pump-driven form of dialysis which provides slow fluid and solute removal on a continuous, 24-hour basis. IHD is a higher-efficiency form of dialysis which is provided for several hours a day at a variable frequency (usually daily or 3 to 5 times per week) at a higher blood flow rate. The primary advantage of CRRT is hemodynamic stability and better volume control, particularly in patients who are unable to tolerate rapid fluid removal. The primary disadvantages associated with CRRT are continuous nursing requirements, continuous anticoagulation, frequent clotting of the dialyzer, patient immobility, and increased cost. There is no conclusive evidence that one type of dialysis is preferred to another in terms of mortality and recovery of renal function.[25] Thus, selection of CRRT over IHD is often governed by the critical illness of the patient and by the comfort level of the institution with one particular type of dialysis.

With either type of dialysis, studies suggest that recovery of renal function is decreased in ARF patients who undergo dialysis compared with those not requiring dialysis. Decreased recovery of renal function may be due to hemodialysis-induced hypotension causing additional ischemic injury to the kidney. Also, exposure of a patient's blood to bioincompatible dialysis membranes (cuprophane or cellulose acetate) results in complement and leukocyte activation which can lead to neutrophil infiltration into the kidney and release of vasoconstrictive substances that can prolong renal dysfunction.[26] Synthetic membranes composed of substances such as polysulfone, polyacrylonitrile, and polymethylmethacrylate are considered to be more biocompatible and would be less likely to activate complement. Synthetic membranes are generally more expensive than cellulose-based membranes. Several recent meta-analyses found no difference in mortality between biocompatible and bioincompatible membranes. Whether biocompatible membranes lead to better patient outcomes continues to be debated.



Patient Encounter, Part 3

Creating a Care Plan
Based on the information presented, create a care plan for this patient's ARF. Your plan should include: (1) a statement of the drug-related need and/or problems, (2) the goals of therapy, (3) a detailed patient-specific therapeutic plan, and (4) a plan for follow-up to determine whether the goals have been achieved and adverse effects avoided.

Supportive Therapy

Supportive therapy in ARF includes adequate nutrition, correction of electrolyte and acid-base abnormalities (particularly hyperkalemia and metabolic acidosis), fluid management, and correction of any hematologic abnormalities. Because ARF is often associated with multiorgan failure, treatment includes the medical management of infections, cardiovascular and gastrointestinal conditions, and respiratory failure. Finally, all drugs should be reviewed, and dosage adjustments made based on an estimate of the patient's glomerular filtration rate.

PREVENTION OF ACUTE RENAL FAILURE

Avoidance

The best preventive measure for ARF, especially in individuals at high risk, is to avoid medications that are known to precipitate ARF. Nephrotoxicity is a significant side effect of aminoglycosides, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, amphotericin B, nonsteroidal anti-inflammatory drugs, cyclosporine, tacrolimus, and radiographic contrast agents.[6] Unfortunately, an effective, non-nephrotoxic alternative may not always be appropriate for a given patient and the risks and benefits of selecting a drug with nephrotoxic potential must be considered. For example, serious gram-negative infections may require double antibiotic coverage, and based on culture and sensitivity reports, aminoglycoside therapy may be necessary. In cases such as this, other measures to reduce the risk of ARF should be instituted. ❺ *Thus, identifying patients at high risk for development of ARF and implementing preventive methods to decrease its occurrence or severity is critical.*

Drug-Induced Acute Renal Failure

Aminoglycosides

Treatment with aminoglycosides (gentamicin, tobramycin, and amikacin) can cause non-oliguric intrinsic ARF. Injury is due to the binding of aminoglycosides to proximal tubular cells, and subsequent cellular uptake and cell death.[27] In clinical practice, all of the aminoglycosides are considered equally nephrotoxic, and the same precautions should be used for all the agents. High cumulative drug exposure increases the incidence of aminoglycoside-induced ARF. A prolonged course of aminoglycoside therapy (typically longer than 7 to 10 days) is a risk factor for the development of ARF, especially in those with preexisting chronic kidney disease and in the elderly.[28] Alternative antibiotics should be selected when culture and sensitivity reports are available. Methods to minimize drug exposure include maintaining trough concentrations less than 2 mcg/mL for gentamicin and tobramycin (less than 10 mcg/mL for amikacin), minimizing length of therapy, avoiding repeated courses of aminoglycosides, and utilizing extended-interval dosing methods.[29] There is conflicting evidence as to whether the combination of vancomycin and an aminoglycoside has a higher incidence of ARF than aminoglycoside therapy alone. ARF due to aminoglycosides can be mild if the drug is discontinued, although severe ARF requiring dialysis can occur.

The goal of extended-interval dosing is to provide greater efficacy against the microorganism with a lower incidence of toxicity. Because aminoglycosides demonstrate concentration-dependent killing and a post-antibiotic effect, extended-interval dosing of antibiotics can be efficacious in the treatment of most conditions. Extended-interval aminoglycoside dosing may reduce the incidence of nephrotoxicity by providing high concentrations of drug which saturate proximal tubule uptake sites. Once saturated, the remaining aminoglycoside molecules pass through the proximal tubule and are excreted in the urine with less tubular accumulation. A primary concern with extended-interval dosing is the risk of ototoxicity that can occur with high aminoglycoside concentrations. However, a consistent finding in studies is that extended-interval aminoglycoside dosing is as effective as traditional dosing and is not more toxic, and in some studies is less toxic than traditional dosing. Extended-interval dosing is not recommended in patients with preexisting renal dysfunction, conditions where high concentrations are not needed (e.g., urinary tract infections), hyperdynamic patients that may demonstrate increased drug clearance (e.g., burn patients), and others where you would suspect altered pharmacokinetics or increased risk of ototoxicity.

Amphotericin B

Amphotericin B–induced ARF occurs in as many as 40% to 65% of patients treated with the conventional desoxycholate formulation.[30] Nephrotoxicity is due to renal arterial vasoconstriction and distal renal tubule cell damage. Risk factors include high doses, treatment for at least 7 days, preexisting kidney dysfunction, and concomitant use of other nephrotoxic drugs.[31] Three lipid-based formulations of amphotericin B have been developed in an attempt to decrease the incidence of ARF: amphotericin B lipid complex, amphotericin colloidal dispersion, and liposomal amphotericin B. The range of

nephrotoxicity reported is 15% to 25% for these formulations. The mechanism for decreased nephrotoxicity has not been completely elucidated, but it is thought to be due to preferential release of amphotericin B from macrophages at the site of infection, with less of an affinity for the kidney.[30] Whether there are significant differences in nephrotoxicity between the three lipid-based formulations remains unclear, as there have been no head-to-head comparisons of the three agents in humans. In one prospective, randomized study, the incidence of nephrotoxicity was lower with liposomal amphotericin B (14%) compared to amphotericin B lipid complex (42%) in febrile, neutropenic patients.[32] Therefore, large, prospective studies comparing the incidence of nephrotoxicity between these agents are needed. Lipid-based formulations are recommended in individuals with risk factors for development of ARF. In addition, use of alternative antifungal agents should be considered in the presence of worsening renal function. Administration of intravenous normal saline may also attenuate nephrotoxicity associated with amphotericin B.

Radiocontrast Agents

Intravascular radiographic contrast agents are administered during radiologic studies and carry with them the well-documented risk of ARF. Patients at risk for developing ARF include patients with chronic kidney disease, diabetic nephropathy, dehydration, and higher dose of contrast dye.[33] Contrast agents are water-soluble, triiodinated, benzoic acid salts that cause an osmotic diuresis due to their osmolality, which exceeds that of plasma. The mechanism of nephrotoxicity is not fully understood; however, direct tubular toxicity, renal ischemia, and tubular obstruction have been implicated.[34] Diatrizoate and iothalamate are ionic contrast agents. Iohexol, iopamidol, ioversol, and iopromide represent non-ionic agents. The incidence of nephrotoxicity with ionic and non-ionic agents is similar in patients at low risk for developing ARF; however, in high-risk patients, nephrotoxicity is significantly greater when ionic contrast agents are used. In diabetic patients with chronic kidney disease and a serum creatinine concentration of greater than 1.5 mg/dL, nephrotoxicity occurred in 33.3% and 47.7% of patients receiving non-ionic and ionic contrast agents, respectively.[35] The cost of non-ionic agents is approximately 10-fold higher, which may limit their routine use in all patients undergoing radiographic studies.

Therapeutic measures that have been used to decrease the incidence of contrast-induced nephropathy include extracellular volume expansion, minimization of the amount of contrast administered, and treatment with oral acetylcysteine. Theophylline, fenoldopam, loop diuretics, mannitol, dopamine, and calcium antagonists have no effect or may worsen ARF.

The most common therapeutic maneuver to decrease the incidence of contrast-induced nephropathy is extracellular volume expansion.[36] Several recent studies have compared the efficacy of isotonic sodium chloride (0.9%) to half normal saline (0.45%) or to oral hydration.[37,38] Isotonic fluid appears to provide the best benefit for prevention of nephropathy. A common regimen is intravenous isotonic sodium chloride (1 mL per kilogram of body weight per hour) administered for 12 hours before and 12 hours after the procedure. Fluid should be administered cautiously to patients with congestive heart failure (CHF), left ventricular dysfunction, and significant renal dysfunction. Early evidence suggests that hydration plus sodium bicarbonate to alkalize renal tubule fluid may reduce free radical formation. More studies are needed before bicarbonate can be recommended.

Minimizing the quantity of contrast media administered may be beneficial in preventing nephropathy. Some studies, but not all, have directly associated dose of contrast media and nephrotoxicity. Avoidance of contrast dye with alternative diagnostic procedures should be considered in high-risk patients, but may not always be feasible. In addition, avoidance of multiple contrast studies in a short time period will allow renal function to return to normal between procedures.

Because production of reactive oxygen species have been implicated in the pathophysiology of contrast-induced ARF, prophylactic administration of the antioxidant acetylcysteine has been investigated. A dose of 600 mg twice daily the day before and the day of the procedure decreased the incidence of renal failure in one small study, although patient outcomes such as mortality and length of hospitalization were not evaluated.[39] Since then, approximately eight additional studies evaluating the efficacy of oral acetylcysteine have been conducted, with mixed results. In addition, a series of meta-analyses have also analyzed the results of the studies. The studies were varied in terms of study population, sample size, definition of contrast nephropathy, type of contrast agent used, hydration, and formulation of acetylcysteine administered, thus making collective interpretation of the results difficult. Although data are not conclusive, they suggest a beneficial effect of oral acetylcysteine in combination with adequate hydration.

Fenoldopam does not decrease the incidence of contrast nephropathy.[40] Due to its hypotensive effect, it may worsen kidney function.

Cyclosporine and Tacrolimus

Cyclosporine and tacrolimus are calcineurin inhibitors that are administered as part of immunosuppressive regimens in kidney, liver, heart, lung, and bone marrow transplant recipients. In addition, they are used in autoimmune disorders such as psoriasis and multiple sclerosis. The pathophysiologic mechanism for ARF is renal vascular vasoconstriction.[41] It often occurs within the first 6 to 12 months of treatment, and can be reversible with dose reduction or drug discontinuation. Risk factors include high dose, elevated trough blood concentrations, increased age, and concomitant therapy with other nephrotoxic drugs.[41] Cyclosporine and tacrolimus are extensively metabolized by

the liver through the cytochrome P-450 (CYP)3A4 pathway and drugs that inhibit their metabolism (e.g., erythromycin, clarithromycin, fluconazole, ketoconazole, verapamil, diltiazem, and nicardipine) can precipitate ARF. Because ARF is dose dependent, careful monitoring of cyclosporine or tacrolimus trough concentrations can minimize its occurrence; however, ARF can develop with normal or low blood concentrations. In addition, there is some evidence that calcium channel blockers have a renoprotective effect through dilation of the afferent arterioles and are often used preferentially as antihypertensive agents in kidney transplant recipients.

It is often difficult to differentiate ARF from acute rejection in the kidney transplant recipient, as both conditions may present with similar symptoms and physical examination findings. However, fever and graft tenderness are more likely to occur with rejection while neurotoxicity is more likely to occur with cyclosporine or tacrolimus toxicity. Kidney biopsy is often needed to confirm the diagnosis of rejection.[42]

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

In instances of decreased renal blood flow, production of angiotensin II increases, resulting in efferent arteriole vasoconstriction and maintenance of glomerular capillary pressure and GFR (Fig. 22–2). In patients initiated on ACE inhibitors or ARBs, angiotensin II synthesis decreases thereby dilating efferent arterioles and decreasing glomerular capillary pressure and GFR. Risk factors for developing ARF are preexisting renal dysfunction, severe atherosclerotic renal artery stenosis, volume depletion, and severe CHF.[43] ARF often develops within days, with a rapid rise in BUN and serum creatinine concentration. Discontinuation of the drug usually results in return of renal function to baseline, although a small decrease in kidney function may be acceptable in patients with severe CHF who would benefit from the hemodynamic effect of ACE inhibitors or ARBs.



Patient Encounter, Self-Study Questions

1. What would have been an appropriate gentamicin dosage regimen that would have avoided elevated plasma concentrations?
2. Based on the patient's renal function, would other drug therapy recommendations be warranted at this time?

Non-steroidal Anti-Inflammatory Drugs

Non-steroidal anti-inflammatory agents can likewise cause prerenal ARF through inhibition of prostaglandin-mediated renal vasodilation. Risk factors are similar to those of ACE inhibitors and ARBs. Additional risk factors include hepatic disease with ascites, systemic lupus erythematosus, and advanced age. The onset is often within days of initiating therapy and patients typically present with oliguria. It is usually reversible with drug discontinuation. Agents that preferentially inhibit cyclooxygenase-2 pose a similar risk as traditional, non-selective NSAIDs.[44]

Other Drugs

Other drugs that are commonly implicated in causing ARF include acyclovir, adefovir, carboplatin, cidofovir, cisplatin, foscarnet, ganciclovir, indinavir, methotrexate, pentamidine, ritonavir, sulfinpyrazone, and tenofovir.[45]

OUTCOME EVALUATION

Goals of therapy are to maintain a state of euvolemia with good urine output (at least 1 ml/kg per hour), to return serum creatinine and BUN to baseline, and to correct electrolyte and acid-base abnormalities. Vital signs, weight, fluid intake, urine output, BUN, creatinine, and electrolytes should be assessed daily in the unstable patient.

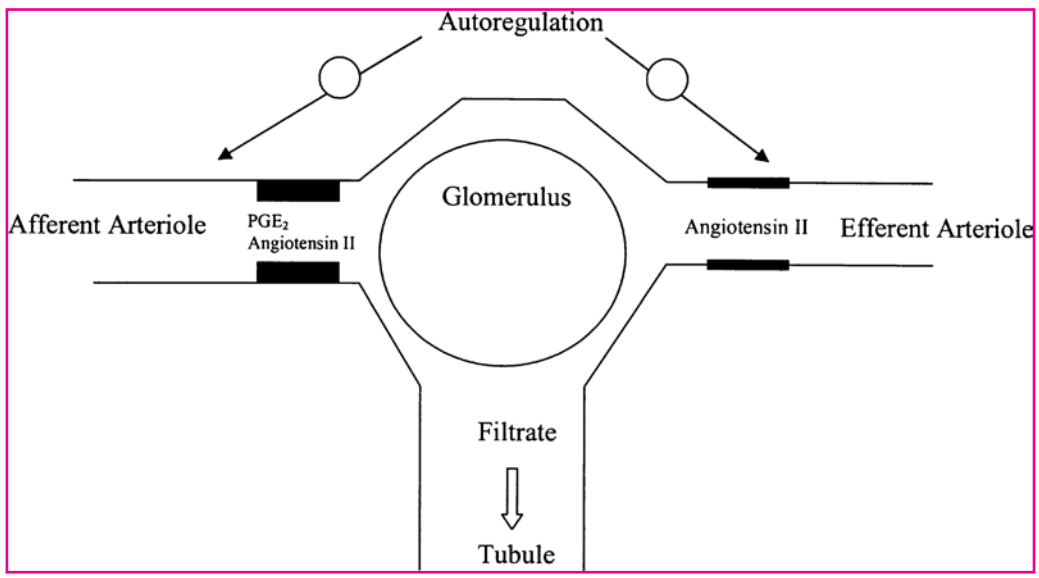


FIGURE 22–2. Normal glomerular autoregulation serves to maintain intraglomerular capillary hydrostatic pressure, glomerular filtration rate (GFR), and ultimately, urine output. This is accomplished by modulation of afferent and efferent arterioles. Afferent and efferent arteriolar vasoconstriction are primarily mediated by angiotensin II, whereas afferent vasodilation is primarily mediated by prostaglandins. PGE_2, prostaglandin E_2.



Patient Care and Monitoring

1. Assess kidney function by evaluating a patient's signs and symptoms, laboratory test results, and urinary indices. Calculate a patient's creatinine clearance to evaluate the severity of kidney disease.
2. Obtain a thorough and accurate drug history, including the use of non-prescription drugs such as NSAIDs.
3. Evaluate a patient's current drug regimen to:

- Determine if drug therapy may be contributing to ARF. Consider not only drugs that can directly cause ARF (e.g., aminoglycosides, amphotericin B, NSAIDs, cyclosporine, tacrolimus, ACE inhibitors, and ARBs), but also drugs that can predispose a patient to nephrotoxicity or prerenal ARF (i.e., diuretics and antihypertensive agents).
- Determine if any drugs need to be discontinued, or alternate drugs selected, to prevent worsening of renal function.
- Adjust drug dosages based on the patient's creatinine clearance or evidence of adverse drug reactions or interactions.

4. Develop a plan to provide symptomatic care of complications associated with ARF, such as diuretic therapy to treat volume overload. Monitor the patient's weight, urine output, electrolytes (such as potassium), and blood pressure to assess efficacy of the diuretic regimen.

CONCLUSION

ARF is a potentially life-threatening condition that can lead to significant morbidity and mortality. Supportive therapy, prompt correction of hypo- or hypervolemia, treatment of underlying conditions, and avoidance of nephrotoxic drugs is essential.

ABBREVIATIONS

ACE:	angiotensin-converting enzyme
ANZICS:	Australian and New Zealand Intensive Care Society
ARB:	angiotensin receptor blocker
ARF:	acute renal failure
ATN:	acute tubular necrosis
BUN:	blood urea nitrogen
BW:	body weight
CHF:	congestive heart failure
CrCl:	creatinine clearance
CRRT:	continuous renal replacement therapy
CYP:	cytochrome P-450
FE_{Na}:	fractional excretion of sodium
GFR:	glomerular filtration rate
IBW:	ideal body weight
ICU:	intensive care unit
IHD:	intermittent hemodialysis
IV:	intravenous
JVD:	jugular venous distention
MDRD:	Modification of Diet in Renal Disease (study)
NSAID:	non-steroidal anti-inflammatory drug
RBC:	red blood cell
RRT:	renal replacement therapy
Scr:	serum creatinine concentration
Ucr:	urine creatinine
WBC:	white blood cell

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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23 Chronic and End-Stage Renal Disease

Kristine S. Schonder



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. List the risk factors for progression of chronic kidney disease (CKD).
2. Explain the mechanisms associated with progression of CKD.
3. Identify the desired outcomes for treatment of CKD.
4. Develop a therapeutic approach to slow progression of CKD, including lifestyle modifications and pharmacologic therapies.
5. Identify specific consequences associated with CKD.
6. Design an appropriate therapeutic approach to specific consequences associated with CKD.
7. Recommend an appropriate monitoring plan to assess the effectiveness of pharmacotherapy for CKD and specific consequences.
8. Educate patients with CKD about the disease state, the specific consequences, lifestyle modifications, and pharmacologic therapies used for treatment of CKD.

Key Concepts

❶ Chronic kidney disease is a progressive disease that eventually leads to renal failure [end-stage renal disease (ESRD)].
❷ Early detection and treatment of CKD are fundamental factors in minimizing morbidity and mortality associated with CKD.
❸ Declining renal function disrupts the homeostasis of the systems regulated by the kidney, leading to fluid and electrolyte imbalances, anemia, and metabolic bone disease.
❹ Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers decrease protein excretion and are the drugs of choice for hypertension in patients with CKD.
❺ The most common complication of CKD is anemia, which is caused by a decline in erythropoietin production by the kidneys and can lead to cardiovascular disease.
❻ The goal of anemia management is to increase hemoglobin levels to greater than 11 g/dL (6.82 mmol/L), which generally requires a combination of erythropoiesis-stimulating agents and iron supplements.
❼ Renal osteodystrophy stems from disruptions in calcium, phosphorus, and vitamin D homeostasis through the interaction with the parathyroid hormone.
❽ The management of secondary hyperparathyroidism involves correction of serum calcium and phosphorus levels, and decreasing parathyroid hormone secretion.
❾ Patient education and planning for dialysis should begin at stage 4 CKD, before end-stage renal disease is reached, to allow for time to establish appropriate access for dialysis.
❿ Dialysis involves the removal of metabolic waste products by diffusion and ultrafiltration from the bloodstream across a semipermeable membrane into an external dialysate solution.

The kidney is made up of approximately 2 million **nephrons** that are responsible for filtering, reabsorbing and excreting solutes and water. As the number of functioning nephrons declines, the primary functions of the kidney that are affected include:

- production and secretion of **erythropoietin**
- activation of vitamin D
- regulation of fluid and electrolyte balance
- regulation of acid-base balance

Chronic kidney disease (CKD), also known as chronic renal insufficiency, progressive kidney disease, or nephropathy, is defined as the presence of kidney damage or decreased

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Patient Encounter, Part 1

A 62-year-old obese female with a history of diabetes and hypertension presents to clinic for routine follow-up. Her fasting blood sugars have been elevated recently, averaging 180 to 250 mg/dL (10 to 13.8 mmol/L).

PMH
- Diabetes mellitus for 8 years, not currently controlled
- Hypertension for 5 years, not currently controlled
- Hyperlipidemia, currently managed by diet therapy

FH
Mother is alive at age 87 with coronary artery disease; father is deceased from diabetes; she has no siblings.

SH
She does not work; she smokes 1 pack of cigarettes per day, but denies alcohol or illicit drug use; she is sedentary

Meds
Furosemide 20 mg orally daily
Nifedipine XL 30 mg orally daily
Glyburide 10 mg orally daily

ROS
Unremarkable

PE
VS: Blood pressure 145/92 mm Hg, pulse 82 beats per minute, temperature 36.9°C (98.4°F), Ht 5′4″ (162.5 cm), Wt 190 lb (86.4 kg)
CV: Regular rate and rhythm, normal S_1, S_2; no murmurs, rubs or gallops; lungs clear
Abd: Obese; no organomegaly, bruits or tenderness, (+) bowel sounds; heme (–) stool
Exts: Trace pedal edema bilaterally; decreased sensation in feet to light touch; no lesions

Labs (fasting)
Sodium 145 mEq/L (145 mmol/L); potassium 3.2 mEq/L (3.2 mmol/L); chloride 112 mEq/L (112 mmol/L); carbon dioxide 26 mEq/L (26 mmol/L); blood urea nitrogen 20 mg/dL (7.14 mmol/L urea); serum creatinine 1.4 mg/dL (123.76 µmol/L); glucose 240 mg/dL (13.32 mmol/L); total cholesterol 196 mg/dL (5.07 mmol/L); low-density lipoprotein cholesterol 112 mg/dL (2.90 mmol/L); high-density lipoprotein cholesterol 28 mg/dL (0.72 mmol/L); triglycerides 280 mg/dL (3.16 mmol/L); hemoglobin$_{A1c}$ (Hb_{A1c}) 10% (0.1); urine microalbumin 270 mg/dL (2.7 g/L)

- What risk factors does the patient have for the development of CKD?
- What signs and symptoms are consistent with CKD?
- How would you classify her CKD?
- Identify your treatment goals for the patient.
- What lifestyle modifications would you recommend for the patient with CKD?
- What pharmacologic alternatives are available for the patient for treatment of CKD?
- What other interventions are appropriate to minimize the progression of CKD?

glomerular filtration rate (GFR) for 3 months or more.[1] Generally, CKD is a progressive decline in kidney function (a decline in the number of functioning nephrons) that occurs over a period of several months to years. A decline in kidney function that occurs more rapidly, over a period of days to weeks, is known as acute renal failure (ARF), which is discussed in Chapter 22. The decline in kidney function in CKD is often irreversible. Therefore, measures to treat CKD are aimed at slowing the progression to end-stage renal disease (ESRD).

EPIDEMIOLOGY AND ETIOLOGY OF CKD

The National Kidney Foundation (NKF) developed a classification system for CKD (Table 23–1).[1] The staging system defines the stages of CKD based on GFR level, but also accounts for evidence of kidney damage in the absence of changes in GFR, as in stage 1 CKD. The GFR is calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) study equation:

$$GFR = 186 \times (SCr)^{-1.154} \times (age)^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if African-American})$$

Because of the slow onset of CKD and the lack of symptoms in earlier stages, the prevalence of CKD is difficult to determine until patients reach ESRD. It is estimated that approximately 19 million people (11% of the United States population) have some degree of CKD.[2] Approximately 8 million people have a GFR less than 60 mL/minute/1.73 m^2,[2] at which point CKD is generally diagnosed as a clinical condition. The prevalence of CKD is correlated with specific demographic factors: increased age, African-American race, and hypertension.

TABLE 23–1. NKF-DOQI Classification for Chronic Kidney Disease

State	Glomerular Filtration Rate (mL/minute/1.73 m^2)
1	Greater than or equal to 90[a]
2	60–89
3	30–59
4	15–29
5	Less than 15 (includes patients on dialysis)

[a]CKD can be present with a normal or near normal GFR if other markers of kidney disease are present, such as proteinuria, hematuria, biopsy results showing kidney damage, or anatomic abnormalities (e.g., cysts). NKF-DOQI, National Kidney Foundation-Dialysis Outcome Quality Initiative.

❶ *CKD is a progressive disease that eventually leads to ESRD*. The prevalence of ESRD has increased more than five-fold since 1980 to more than 450,000 people in 2003 with more than 100,000 new cases of ESRD diagnosed in 2003.[2] Although the incidence of ESRD is declining in certain populations, the incidence of ESRD is increasing in African-Americans to as much as 44% in patients with diabetes 30 to 39 years of age.

Because of the progressive nature of CKD, determination of risk factors for CKD is difficult. Risk factors identified for CKD are classified into three categories (Table 23–2):

- **Susceptibility factors**, which are associated with an increased risk of developing CKD, but are not directly proven to cause CKD. These factors are generally not modifiable by pharmacologic therapy or lifestyle modifications.
- **Initiation factors**, which directly cause CKD. These factors are modifiable by pharmacologic therapy.
- **Progression factors**, which result in a faster decline in kidney function and cause worsening of CKD. These factors may also be modified by pharmacologic therapy or lifestyle modifications to slow the progression of CKD.

Susceptibility Factors

Susceptibility factors can be readily used to develop screening programs for CKD. For example, older patients, those with low kidney mass or birth weight, and those with a family history of kidney disease should be routinely screened for CKD.

TABLE 23–2. Risk Factors Associated with Chronic Kidney Disease

Susceptibility
• Advanced age
• Reduced kidney mass
• Low birth weight
• Racial/ethnic minority
• Family history of kidney disease
• Low income or education
• Systemic inflammation
• Dyslipidemia
Initiation
• Diabetes mellitus
• Hypertension
• Autoimmune disease
• Polycystic kidney disease
• Drug toxicity
• Urinary tract abnormalities (infections, obstruction, stones)
Progression
• Hyperglycemia: Poor blood glucose control (in patients with diabetes)
• Hypertension: Elevated blood pressure
• Proteinuria
• Tobacco smoking

Minority and low socioeconomic communities may be targets for more widespread CKD screening programs. Other factors, such as hyperlipidemia, are not directly proven to cause CKD, but can be modified by drug therapies.

Hyperlipidemia

Patients with CKD have a higher prevalence of dyslipidemia compared to the general population. The dyslipidemia in CKD is manifested as an elevation in total cholesterol (TC) levels, low-density lipoprotein cholesterol (LDL-C) levels, triglycerides, and lipoprotein(a) levels, and decreases in high-density lipoprotein cholesterol (HDL-C) levels. The prevalence within the CKD population appears to be related somewhat to the degree of **proteinuria**. In nephrotic syndrome, with urine protein excretion rates that exceed 3 g/24 hours, almost all patients have some degree of dyslipidemia.[3] Mounting evidence suggests that hyperlipidemia can promote renal injury and subsequent progression of CKD. The mechanism is similar to that of atherosclerosis, whereby lipid deposition causes activation of macrophages and monocytes, which secrete growth factors that stimulate cell proliferation and oxidation of lipoproteins. These lead to endothelial dysfunction, cellular injury, and fibrosis in the kidney.[4]

Initiation Factors

The three most common causes of CKD in the United States are diabetes mellitus, hypertension, and **glomerulonephritis**. Together these account for about 75% of the cases of CKD (37% for diabetes, 24% for hypertension, and 14% for glomerulonephritis).[2] These are discussed in further detail below.

Diabetes

Diabetes mellitus (DM) is the most common cause of CKD.[2] The risk of developing nephropathy associated with DM is closely linked to hyperglycemia and is similar for both type 1 and type 2, although it is slightly higher in patients with type 2 DM.[5] An estimated 3% of patients with DM will develop ESRD, which is 12 times greater than those without DM.[6]

Hypertension

The second most common cause of CKD is hypertension.[2] It is more difficult to determine the true risk of developing CKD in patients with hypertension because the two are so closely linked, with CKD also being a cause of hypertension. The prevalence of hypertension is correlated with the degree of renal dysfunction (decreased GFR) with 40% of patients with CKD stage 1, 55% of patients with CKD stage 2, and over 75% of patients with CKD stage 3 presenting with hypertension.[1] The risk of developing ESRD is linked to both systolic and diastolic blood pressure.[7] A blood pressure greater than 210/110 mm Hg is associated with a 22% increased relative risk of developing ESRD, compared with a blood pressure less than 120/80 mm Hg.[7]

Glomerulonephritis

The etiologic and pathophysiologic features of glomerular diseases vary with the specific disease, making it difficult to extrapolate the risk for developing CKD in patients affected by glomerular diseases. Certain glomerular diseases are known to rapidly progress to ESRD, while others progress more slowly or may be reversible.

Progression Factors

Progression factors can be used as predictors of CKD. The most important predictors of CKD include proteinuria, elevated blood pressure, hyperglycemia, and tobacco smoking.

Proteinuria

The presence of protein in the urine is a marker of glomerular and tubular dysfunction and is recognized as an independent risk factor for the progression of CKD.[8] Furthermore, the degree of proteinuria correlates with the risk for progression of CKD. An increase of 1 g of protein excretion per day is associated with a five-fold increase in the risk of progression of CKD, regardless of the cause of CKD.[9] The mechanisms by which proteinuria potentiates CKD are discussed later. **Microalbuminuria** is also linked with vascular injury and increased cardiovascular mortality.[10]

Elevated Blood Pressure

Systemic blood pressure correlates with glomerular pressure and elevations in both systemic blood pressure and glomerular pressure contribute to glomerular damage. The rate of GFR decline is related to elevated systolic blood pressure and mean arterial pressure. The decline in GFR is estimated to be 14 mL/minute per year with a systolic blood pressure of 180 mm Hg. Conversely, the decline in GFR decreases to 2 mL/minute per year with a systolic blood pressure of 135 mm Hg.[11]

Elevated Blood Glucose

The reaction between glucose and protein in the blood produces advanced glycosylation end-products (AGEs), which are metabolized in the proximal tubules. Hyperglycemia increases the synthesis of AGEs in patients with diabetes and the corresponding increase in metabolism is suspected to be a cause of nephropathy associated with diabetes.[12]

Tobacco Smoking

Smoking is an independent risk factor for the development of microalbuminuria in primary hypertension. In patients with CKD, smoking is also an independent risk factor for progression to ESRD, with a relative risk ratio of up to 1.69 in heavy smokers, independent of other risk factors for the development and progression of CKD.[13] Patients with DM who smoke have more than a two- to three-fold increased risk of developing diabetic nephropathy compared to non-smokers.[13] In patients with CKD, smoking increases the risk of developing microalbuminuria, and increases the rate of progression to ESRD.[13]

The effects of smoking on the kidney are multifactorial and occur in both healthy individuals and those with CKD. Smoking induces glomerular hyperfiltration, produces an antidiuretic action that increases blood pressure, and can damage the proximal tubule, resulting in impaired cationic transport. Furthermore, systemic complications correlated with tobacco abuse, including increases in blood pressure, platelet activity, and thromboxane A_2 production, can also negatively impact kidney function.[13] These effects are related to the amount of cigarettes smoked, in terms of pack years.[13]

PATHOPHYSIOLOGY OF CKD

A number of factors can cause initial damage to the kidney. The resulting sequelae, however, follow a common pathway that promotes progression of CKD and results in irreversible damage leading to ESRD (Fig. 23–1).

The initial damage to the kidney can result from any of the initiation factors listed in Table 23–2. Regardless of the cause, however, the damage results in loss of nephron mass. The resultant effect is hypertrophy of the remaining nephrons to compensate for the loss of renal function and nephron mass. These adaptive changes result in an increase in glomerular filtration and tubular function, both reabsorption and secretion, in the remaining nephrons. Initially, these adaptive changes preserve many of the clinical parameters of renal function, including creatinine and electrolyte excretion. However, as time progresses, glomerular capillary pressure is increased, mediated by angiotensin II, to maintain the hyperfiltration state of the functioning nephrons. Angiotensin II is a potent vasoconstrictor of both the afferent and efferent arterioles, but has a preferential effect to constrict the efferent arteriole, thereby increasing the pressure in the glomerular capillaries. Increased glomerular capillary pressure expands the pores in the glomerular basement membrane, altering the size-selective barrier and allowing proteins to be filtered through the glomerulus.[14]

Protein excretion through the nephron, or proteinuria, increases nephron loss through various complex mechanisms. Filtered proteins are reabsorbed in the renal tubules, which activates the tubular cells to produce inflammatory and vasoactive cytokines and triggers complement activation.[14] These in turn cause interstitial damage and scarring within the renal tubules, leading to damage and loss of more nephrons. Ultimately, the process leads to progressive loss of nephron mass to the point where the remaining nephrons are no longer able to maintain clinical stability and renal function declines.

ASSESSMENT FOR CKD

Because CKD often presents without symptoms, assessment for CKD relies on appropriate screening strategies in all

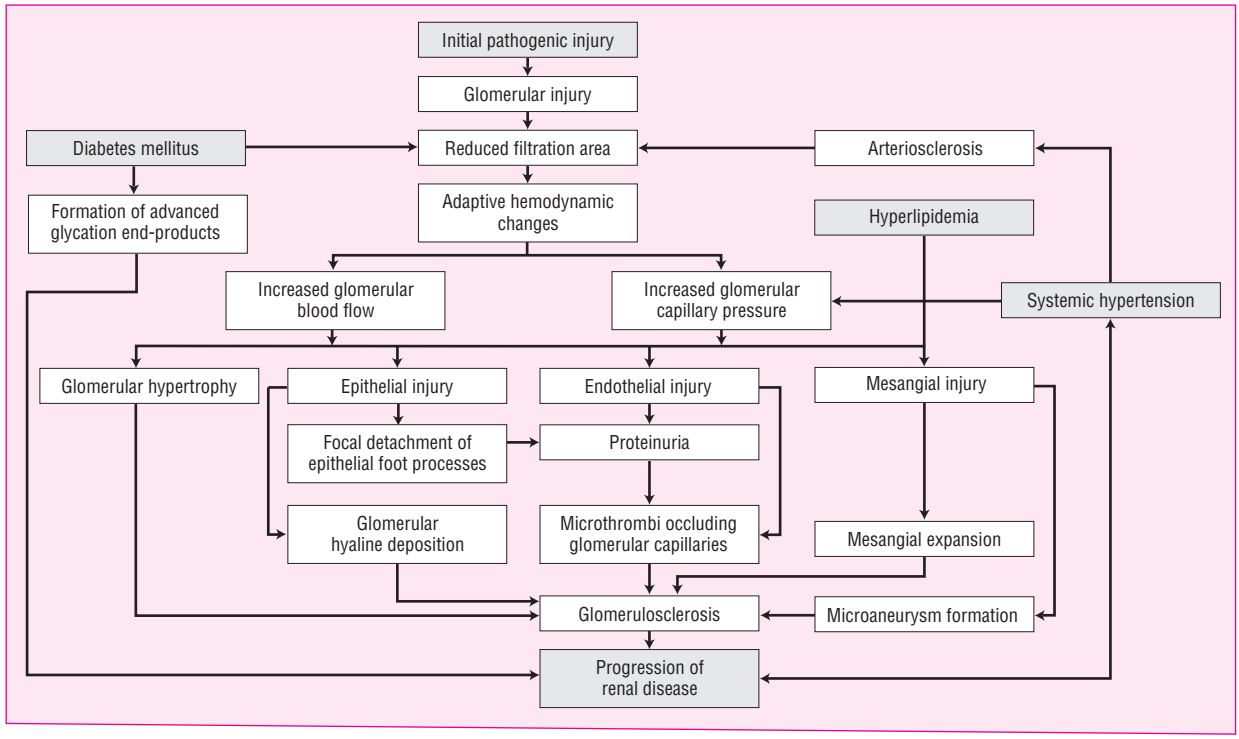


FIGURE 23–1. Proposed mechanisms for progression of renal disease. (From Joy MS, Kshirsagar A, Paparello J. Chronic kidney disease: Progression-modifying therapies. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 803, with permission.)

patients with risk factors for developing CKD (Table 23–2). Evaluation for CKD and the subsequent treatment strategies are dependent on the diagnosis, comorbid conditions, severity and complications of disease, and risk factors for the progression of CKD. ❷ *Early treatment of CKD and the associated complications of CKD are the most important factors to decrease morbidity and mortality associated with CKD.* However, the probability of patients not diagnosed with CKD to have an assessment of serum creatinine or urine protein excretion ranges from 0.01 to 0.04, depending on insurance coverage.[2] Screening for CKD should be performed in all people with an increased risk for developing CKD, including patients with DM, hypertension, genitourinary abnormalities, autoimmune disease, increased age, or a family history of kidney disease. The assessment for CKD should include measurement of serum creatinine, urinalysis, blood pressure, serum electrolytes, and/or imaging studies.

The primary marker of structural kidney damage is proteinuria, even in patients with normal GFR. Clinically significant proteinuria is defined as urinary protein excretion greater than 300 mg/day or greater than 20 mcg/minute in a timed urine collection. Significant proteinuria can also be determined by a spot urine dipstick greater than 30 mg/dL or a urine protein/creatinine ratio greater than 200 mg/g.[1] Microalbuminuria is defined as 30 to 300 mg of albumin excreted in the urine per day or a urine albumin/creatinine ratio greater than 30 mg/day.[1] The NKF recommends routine assessment of proteinuria to detect CKD. A urine dipstick positive for the presence of protein warrants quantification of proteinuria. Patients with a urine protein/creatinine ratio greater than 200 mg/g or urine albumin/creatinine ratio greater than 30 mg/g should undergo diagnostic evaluation; patients with values below these levels should be reevaluated routinely.[1]

Other markers for structural kidney damage that can be used in place of proteinuria include abnormalities in urinary sediment, such as hematuria, or abnormalities in imaging studies or kidney biopsy.[1]

Complications of CKD

❸ *The decline in renal function is associated with a number of complications, which will be discussed later in the chapter, including:*

- *Fluid and electrolyte disorders*
- *Anemia*
- *Metabolic bone disease*



Clinical Presentation of Chronic Kidney Disease

General
The development of CKD is usually subtle in onset, often with no noticeable symptoms.

Symptoms
Stages 1 and 2 CKD are generally asymptomatic.
Stages 3 and 4 CKD may be associated with minimal symptoms.
Typical symptoms associated with stage 5 CKD include pruritus, dysgeusia, nausea, vomiting, constipation, muscle pain, fatigue, and bleeding abnormalities.

Signs
Cardiovascular: Worsening hypertension, edema, dyslipidemia, left ventricular hypertrophy, electrocardiographic changes and chronic heart failure.

Musculoskeletal: Cramping.

Neuropsychiatric: Depression, anxiety, impaired mental cognition.

Gastrointestinal: Gastroesophageal reflux disease, gastrointestinal (GI) bleeding, and abdominal distention.

Genitourinary: Changes in urine volume and consistency, "foaming" of urine (indicative of proteinuria), and sexual dysfunction.

Laboratory Tests
Stages 1 and 2 CKD: Increased **blood urea nitrogen** (BUN) and serum **creatinine** (SCr) and decreased GFR
Stages 3, 4, and 5 CKD: Increased BUN and SCr; decreased GFR.

Advanced stages: Increased potassium, phosphorus, and magnesium; decreased bicarbonate (metabolic acidosis); calcium levels are generally low in earlier stages of CKD and may be elevated in stage 5 CKD, secondary to the use of calcium-containing phosphate binders.
Decreased albumin, if inadequate nutrition intake in advanced stages.
Decreased red blood cell (RBC) count, hemoglobin (Hgb) and hematocrit (Hct); iron metabolism may also be altered [iron level, total iron binding capacity (TIBC), serum ferritin level, and transferrin saturation (TSAT)]. Erythropoietin levels are not routinely monitored and are generally normal to low.
Urine positive for albumin or protein.
Increased parathyroid hormone (PTH) level; decreased vitamin D levels (stages 4 or 5 CKD).
Stool may be Hemoccult-positive if GI bleeding occurs from uremia.

Other Diagnostic Tests
Structural abnormalities of kidney may be present on diagnostic exams.

TREATMENT OF CHRONIC KIDNEY DISEASE

Desired Outcomes
The primary goal is to slow and prevent the progression of CKD. This requires early identification of patients at risk for CKD to initiate interventions early in the course of the disease.

Nonpharmacologic Therapy

Nutritional Management
Reduction in dietary protein intake has been shown to slow the progression of kidney disease.[8] However, protein restriction must be balanced with the risk of malnutrition in patients with CKD. Patients with a GFR less than 25 mL/minute/ 1.73 m^2 received the most benefit from protein restriction;[8] therefore, patients with a GFR above this level should not restrict protein intake. The NKF recommends that patients who have a GFR less than 25 mL/minute/1.73 m^2 who are not receiving dialysis, however, should restrict protein intake to 0.6 g/kg per day. If patients are not able to maintain adequate dietary energy intake, protein intake may be increased up to 0.75 g/kg per day.[15] Malnutrition is common in patients with ESRD for various reasons, including decreased appetite, hypercatabolism, and nutrient losses through dialysis. For this reason, patients receiving dialysis should maintain protein intake of 1.2 g/kg per day to 1.3 g/kg per day.

Pharmacologic Therapy

Intensive Blood Glucose Control (for Patients with Diabetes)
Intensive insulin therapy, the administration of insulin three or more times daily to maintain preprandial blood glucose levels between 70 and 120 g/dL and postprandial blood glucose levels less than 180 g/dL, has been shown to decrease the incidence of proteinuria and albuminuria in patients with diabetes, both with and without documented nephropathy. The development and progression of nephropathy is also delayed in patients with type 1 DM receiving intensive insulin therapy. Continued benefits of intensive insulin therapy have been demonstrated up to 8 years after the study.[16]

Optimal Blood Pressure Control
Reductions in blood pressure are associated with a decrease in proteinuria, leading to a decrease in the rate of progression of kidney disease. The NKF recommends a goal blood pressure of less than 130/80 mm Hg in patients with stages 1 through 4 CKD.[17] Stage 5 CKD patients who are receiving hemodialysis should achieve a goal blood pressure of less than 140/90 mm Hg before hemodialysis and less than 130/80 after hemodialysis.[17] Because hypertension and kidney dysfunction are linked, blood pressure control can be more difficult to attain in patients with

CKD compared to patients with normal kidney function. All antihypertensive agents have similar effects on reducing blood pressure. However, three or more agents are generally required to achieve the blood pressure goal of less than130/80 mm Hg in CKD patients.

Reduction in Proteinuria

The ability of antihypertensive agents to preserve kidney function differs. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) decrease glomerular capillary pressure and volume because of their effects on angiotensin II. This, in turn, reduces the amount of protein filtered through the glomerulus, independent of the reduction in blood pressure,[18] which ultimately decreases the progression of CKD. ❹ *The ability of ACEIs and ARBs to reduce proteinuria is greater than that of other antihypertensives, up to 35% to 40%,[17] making ACEIs and ARBs the antihypertensive agents of choice for all patients with CKD.* All patients with documented proteinuria should receive an ACE-I or ARB, regardless of blood pressure.[17] Because diabetes is associated with an early onset of microalbuminuria, all patients with diabetes should also receive an ACE-I or ARB, regardless of blood pressure.[17] When initiating ACE-I or ARB therapy, the dose should be titrated to the maximum tolerated dose, even if the blood pressure is less than130/80 mm Hg. Patients who do not achieve adequate reductions in blood pressure or protein excretion may benefit from combination therapy with an ACE-I and an ARB.[17] Figure 23–2 depicts an algorithm for the treatment of hypertension in patients with CKD.

The nondihydropyridine calcium channel blockers have been shown to also decrease protein excretion in patients with diabetes,[20] but the reduction in proteinuria appears to be related to the reductions in blood pressure. The maximal effect of nondihydropyridine calcium channel blockers on proteinuria is seen with a blood pressure reduction to less than 130/80 mm Hg and no additional benefit is seen with increased doses. Dihydropyridine calcium channel blockers, however, do not have the same effects on protein excretion, and may actually worsen protein excretion.[17]

Other Interventions to Limit Progression of Chronic Kidney Disease

Hyperlipidemia Treatment

Hyperlipidemia plays a role in the development of cardiovascular disease (CVD) in patients with CKD. The primary goal of treatment of dyslipidemias is to decrease the risk of atherosclerotic cardiovascular disease. A secondary goal in patients with CKD is to reduce proteinuria and decline in kidney function. Treatment of hyperlipidemia in patients with CKD has been demonstrated to slow the decline in GFR by 1.9 mL/minute per year of treatment with antihyperlipidemic agents.[21]

The NKF suggests that CKD should be classified as a coronary heart disease (CHD) risk equivalent and the goal LDL-C level should be below 100 mg/dL in all patients with CKD.[22] The most frequently used agents for the treatment of dyslipidemias in patients with CKD are the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors ("statins") and the fibric acid derivatives. However, other treatments have been studied in patients with CKD and should be considered if first-line therapies are contraindicated.

Another important consideration in treating lipid disorders in patients with CKD is management of proteinuria. Protein excretion in the nephrotic range (greater than 3 g/day) is associated with an increase in both total and LDL-C levels.[23] Triglyceride levels can also be elevated in patients with severe proteinuria. Results from clinical trials suggest that the use of ACEIs to reduce proteinuria can decrease total cholesterol levels.[24] While the use of ACEIs is unlikely to decrease cholesterol to goal levels, reducing proteinuria can aid in cholesterol reduction, particularly in patients with nephrotic syndrome or severe proteinuria. Conversely, treatment of hyperlipidemia can reduce protein excretion and subsequent progression of CKD.[4]

Smoking Cessation

While the effects of smoking on renal hemodynamics are well established, as discussed previously, the effect of smoking cessation on CKD progression has not been studied. Data are emerging that suggest that smoking cessation may be a practical approach to slow the progression of CKD. However, smoking cessation does not reverse existing renal dysfunction in former smokers.

Anemia Treatment

Anemia decreases oxygen delivery to the renal tubules, promoting the release of inflammatory and vasoactive cytokines, which contribute to the progression of CKD. Treatment of anemia in patients with CKD reduces the cardiovascular effects of anemia and has been demonstrated to decrease morbidity and mortality by as much as 20%.[25] Studies have demonstrated that treatment of anemia may slow the progression of CKD.[26] The management of anemia will be discussed later.

Outcome Evaluation

Monitor serum creatinine and potassium levels and blood pressure within 1 week after initiating angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker therapy. Discontinue the medication and switch to another agent if a sudden increase in serum creatinine greater than 30% occurs, hyperkalemia develops, or the patient becomes hypotensive. Titrate the dose of the ACE-I or ARB every 1 to 3 months to the maximum tolerable dose. If blood pressure is not reduced to less than 130/80 mm Hg, add another agent to the regimen.

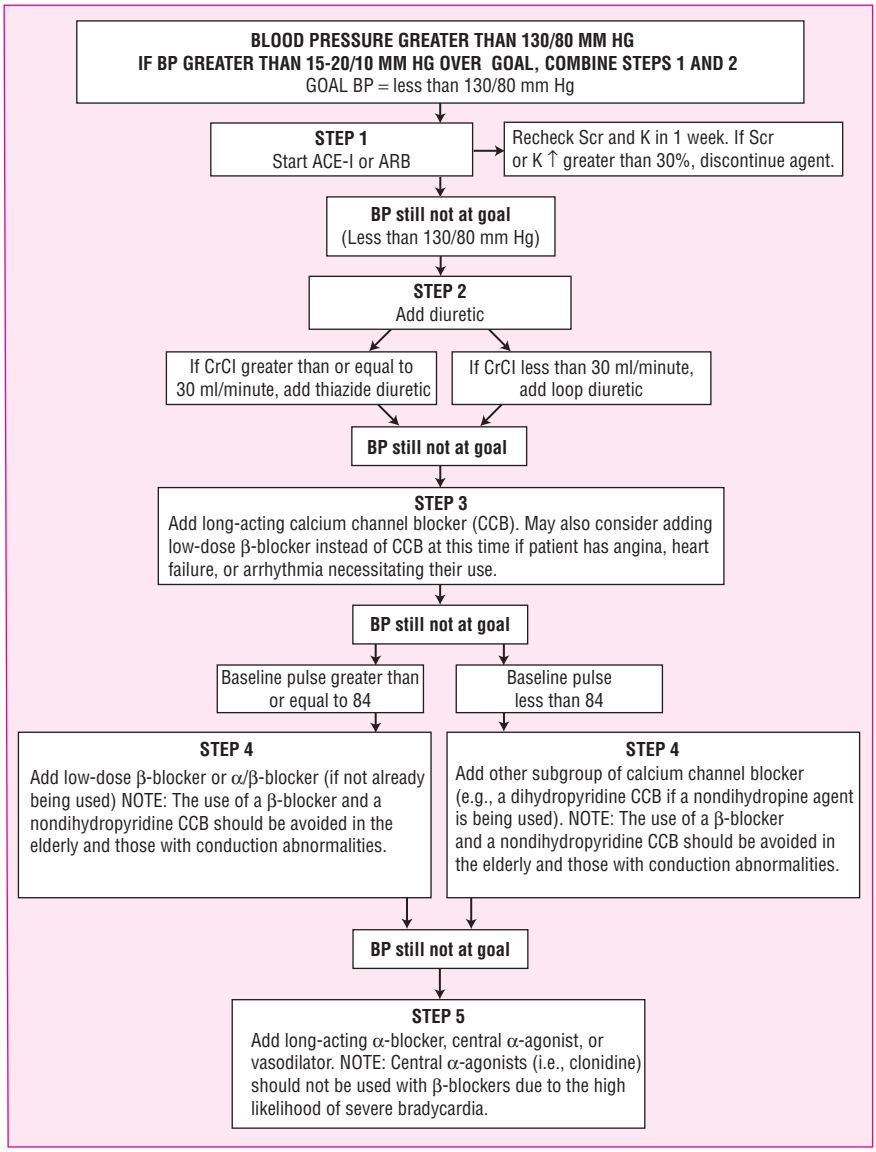


FIGURE 23–2. Hypertension management algorithm for patients with CKD. Dosage adjustments should be made every 2 to 4 weeks as needed. The dose of one agent should be maximized before another is added. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CrCl, creatinine clearance; K, potassium; Scr, serum creatinine. (From Joy MS, Kshirsagar A, Paparello J. Chronic kidney disease: Progression-modifying therapies. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 808, with permission.)

Refer the patient to a nephrologist to manage complications associated with CKD. As CKD progresses to stage 4, begin discussion to prepare the patient for renal replacement therapy.

CONSEQUENCES OF CHRONIC AND END-STAGE KIDNEY DISEASE

Impaired Sodium and Water Homeostasis

Sodium and water balance are primarily regulated by the kidney. Reductions in nephron mass decrease glomerular filtration and subsequent reabsorption of sodium and water, leading to edema.

Pathophysiology

Sodium and water balance can be maintained despite wide variations in intake with normal kidney function. The fractional excretion of sodium (FE_{Na}) is approximately 1% to 3% with normal kidney function, allowing sodium balance to be maintained with a sodium intake of 120 to 150 mEq (120 to 150 mmol) per day. Urine osmolality can range from 50 to 1200 mOsm/L (50 to 1200 mmol/L) with normal kidney function, allowing for water balance to be maintained with a wide range of fluid intake. As nephron mass decreases, the remaining nephrons increase sodium excretion and FE_{Na} may increase up to 10% to 20%.[27] This produces an osmotic diuresis which impairs the ability of the kidneys to concentrate and dilute urine and the urine becomes fixed at an osmolality close to that of the plasma, approximately 300 mOsm/L (300 mmol/L). The inability of the kidney to concentrate the urine results in nocturia in patients with CKD, usually presenting as early as stage 3 CKD.

As nephron mass continues to decline, the sodium load overwhelms the remaining nephrons and total sodium excretion is decreased, despite the increase in sodium excretion by



Clinical Presentation of Impaired Sodium and Water Homeostasis

General
Alterations in sodium and water balance in CKD manifests as increased edema.

Symptoms
Nocturia can present in stage 3 CKD.
Edema generally presents in stage 4 CKD or later.

Signs
Cardiovascular: Worsening hypertension, edema.
Genitourinary: Change in urine volume and consistency.

Laboratory Tests
Increased blood pressure
Sodium levels remain within the normal range
Urine osmolality is generally fixed at 300 mOsm/L (300 mmol/L)

the functioning nephrons. Sodium retention causes fluid retention that manifests as systemic hypertension resulting from increased intravascular volume. Severe volume overload can lead to pulmonary edema.

Treatment

Nonpharmacologic Therapy

The kidney is unable to adjust to abrupt changes in sodium intake in patients with severe CKD. Therefore, patients should be advised to refrain from adding salt to their diet, but should not restrict sodium intake. Changes in sodium intake should occur slowly over a period of several days to allow adequate time for the kidney to adjust urinary sodium content. Sodium restriction produces a negative sodium balance, which causes fluid excretion to restore sodium balance. The resulting volume contraction can decrease perfusion of the kidney and hasten the decline in GFR. Saline-containing intravenous (IV) solutions should be used cautiously in patients with CKD because the salt load may precipitate volume overload.

Fluid restriction is generally unnecessary as long as sodium intake is controlled. The thirst mechanism remains intact in CKD to maintain total body water and plasma osmolality near normal levels. Fluid intake should be maintained at the rate of urine output to replace urine losses, usually fixed at approximately 2 L/day as urine concentrating ability is lost. Significant increases in free water intake orally or intravenously can precipitate volume overload and hyponatremia. Patients with stage 5 CKD require renal replacement therapy to maintain normal volume status. Fluid intake is often limited in patients receiving hemodialysis to prevent fluid overload between dialysis sessions.

Pharmacologic Therapy

Diuretic therapy is often necessary to prevent volume overload in patients with CKD. Loop diuretics are most frequently used to increase sodium and water excretion. Thiazide diuretics are ineffective when used alone in patients with a GFR less than 30 mL/minute/1.73 m^2. As CKD progresses, higher doses or continuous infusion of loop diuretics may be needed, or combination therapy with loop and thiazide diuretics to increase sodium and water excretion.

Outcome Evaluation

Monitor edema after initiation of diuretic therapy. Monitor fluid intake to ensure obligatory losses are being met and avoid dehydration. If adequate diuresis is not attained with a single agent, consider combination therapy with another diuretic.

Impaired Potassium Homeostasis

Potassium balance is also primarily regulated by the kidney via the distal tubular cells. Reduction in nephron mass decreases tubular secretion of potassium, leading to hyperkalemia. Hyperkalemia is estimated to affect more than 50% of patients with stage 5 CKD.[28]

Pathophysiology

The distal tubules secrete 90% to 95% of the daily dietary intake of potassium. The fractional excretion of potassium (FE_K) is approximately 25% with normal kidney function.[29] The GI tract excretes the remaining 5% to 10% of dietary potassium intake. Following a large potassium load, extracellular potassium is shifted intracellularly to maintain stable extracellular levels.

As nephron mass decreases, both the distal tubular secretion and GI excretion are increased because of aldosterone stimulation. Functioning nephrons increase FE_K up to 100% and GI excretion increases as much as 30% to 70% in CKD,[30] as a result of aldosterone secretion in response to increased potassium levels.[30] This maintains serum potassium concentrations within the normal range through stages 1 to 4 CKD. Hyperkalemia begins to develop when GFR falls below 20% of normal, when nephron mass and renal potassium secretion is so low that the capacity of the GI tract to excrete potassium has been exceeded.[30]

Medications can increase the risk of hyperkalemia in patients with CKD, including angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, used for the treatment of proteinuria and hypertension. Potassium-sparing diuretics, used for the treatment of edema and chronic heart failure, can also exacerbate the development of hyperkalemia, and should be used with caution in patients with stage 3 CKD or higher.

Treatment

Nonpharmacologic Therapy

Patients with CKD should avoid abrupt increases in dietary intake of potassium because the kidney is unable to increase potassium excretion with an acute potassium load, particularly in latter stages of the disease. Hyperkalemia resulting



Clinical Presentation of Hyperkalemia

General
Hyperkalemia is generally asymptomatic in patients with CKD until serum potassium levels are greater than 5.5 mEq/L (5.5 mmol/L), when cardiac abnormalities present.

Symptoms
Mild hyperkalemia is generally not associated with overt symptoms.

Signs
Cardiovascular: Electrocardiogram (ECG) changes

Laboratory Tests
Increased serum potassium levels

from an acute increase in potassium intake can be more severe and prolonged. Patients who develop hyperkalemia should restrict dietary intake of potassium to 50 to 80 mEq (50 to 80 mmol) per day. Dialysate potassium concentrations can also be altered in patients receiving hemodialysis and peritoneal dialysis to manage hyperkalemia. Because GI excretion of potassium plays a large role in potassium homeostasis in patients with stage 5 CKD, a good bowel regimen is essential to minimize constipation, which can occur in 40% of patients receiving hemodialysis.[29] Severe hyperkalemia is most effectively managed by hemodialysis.

Pharmacologic Therapy

Patients with acute hyperkalemia usually require other therapies to manage hyperkalemia until dialysis can be initiated. Patients who present with cardiac abnormalities caused by hyperkalemia should receive calcium gluconate or chloride (1 g intravenously) to reverse the cardiac effects. Temporary measures can be employed to shift extracellular potassium into the intracellular compartment to stabilize cellular membrane effects of excessive serum potassium levels. Such measures include the use of regular insulin (5 to 10 units intravenously) and dextrose (5% to 50% intravenously), or nebulized albuterol (10 to 20 mg). Sodium bicarbonate should not be used to shift extracellular potassium intracellularly in patients with CKD unless severe metabolic acidosis (pH less than 7.2) is present. These measures will decrease serum potassium levels within 30 to 60 minutes after treatment, but potassium must still be removed from the body. Shifting potassium to the intracellular compartment, however, decreases potassium removal by dialysis. Often, multiple dialysis sessions are required to remove potassium that is redistributed from the intracellular space back into the serum.

Sodium polystyrene sulfonate (SPS, 15 to 30 g orally), a sodium-potassium exchange resin, promotes potassium excretion from the GI tract. The onset of action is within 2 hours after administration of SPS, but the maximum effect on potassium levels may not be seen for up to 6 hours, which limits the utility in patients with severe hyperkalemia. Of note, loop diuretics are often used to decrease potassium levels in patients with normal or mildly decreased kidney function, but are not useful in patients with stage 5 CKD to decrease potassium concentrations. Fludrocortisone is a mineralocorticoid that mimics the effects of aldosterone and increases potassium excretion in the distal tubules and through the GI tract. However, fludrocortisone causes significant sodium and water retention, which exacerbates edema and hypertension, and may not be tolerated by many CKD patients.

Outcome Evaluation

Monitor electrocardiogram continuously in patients with cardiac abnormalities until serum potassium levels drop below 5 mEq/L (5 mmol/L) or cardiac abnormalities resolve. Evaluate serum potassium and glucose levels within 1 hour in patients who receive insulin and dextrose therapy. Evaluate serum potassium levels within 2 to 4 hours after treatment with SPS or diuretics. Repeat doses of diuretics or SPS if necessary until serum potassium levels fall below 5 mEq/L (5 mmol/L). Monitor blood pressure and serum potassium levels in 1 week in patients who receive fludrocortisone.

Anemia of CKD

The progenitor cells of the kidney produce 90% of the hormone erythropoietin (EPO), which stimulates red blood cell (RBC) production. ❺ *Reduction in nephron mass decreases renal production of EPO, which is the primary cause of anemia in patients with CKD. The development of* ***anemia of CKD*** *results in decreased oxygen delivery and utilization, leading to increased cardiac output and left ventricular hypertrophy (LVH), which increase the cardiovascular risk and mortality in patients with CKD.*

Epidemiology and Etiology

Current NKF guidelines define anemia as a hemoglobin (Hgb) level less than 11 g/dL (6.8 mmol/L).[31] A number of factors can contribute to the development of anemia, including deficiencies in vitamin B_{12} or folate, hemolysis, bleeding, or bone marrow suppression. Many of these can be detected by alterations in RBC indices, which should be included in the evaluation for anemia. A complete blood cell count is also helpful in evaluating anemia to determine overall bone marrow function.

The prevalence of anemia is correlated with the degree of renal dysfunction. More than 26% of patients with a GFR greater than 60 mL/minute/1.73 m^2 are estimated to have anemia, and the number increases to 75% in patients with a GFR less than 15 mL/minute/1.73 m^2.[32] The risk of developing anemia also increases as GFR declines, doubling for patients with stage 3 CKD, increasing to 3.8-fold in patients with stage 4 CKD, and



Patient Encounter, Part 2

The patient returns to your clinic 2 years later with complaints of "feeling tired all of the time." She had been trying to exercise more, but has not had enough energy to exercise for the past 6 months or so. She also complains that she feels cold all of the time, despite increasing the temperature in her house.

Current Meds
Furosemide 80 mg orally daily
Lisinopril 40 mg orally daily
Metoprolol 50 mg orally twice daily
Insulin glargine 25 units subcutaneously at bedtime
Insulin lispro subcutaneously per sliding scale with meals

ROS
Slightly pale skin color; fatigue daily in the afternoon; otherwise unremarkable

PE
VS: Blood pressure 135/85 mm Hg, pulse 72 beats per minute, temperature 35.9°C (96.6°F); Wt 175 lb (79.5 kg)
Chest: Regular rate and rhythm, normal S_1, S_3 present.
Abd: Obese; no organomegaly, bruits or tenderness, (+) bowel sounds; heme (–) stool
Exts: 1+ pedal edema bilaterally; decreased sensation in feet; small lesion on left ankle that appears to be healing slowly

Labs
Sodium 142 mEq/L (142 mmol/L); potassium 4.8 mEq/L (4.8 mmol/L); chloride 103 mEq/L (103 mmol/L); carbon dioxide 20 mEq/L (20 mmol/L); BUN 58 mg/dL (20.71 mmol/L urea); SCr 3.2 mg/dL (282.88 µmol/L); glucose 130 mg/dL (7.28 mmol/L); WBC 4.8×10^3 cells/m^3 (4.8×10^9/L); RBC 2.5×10^3 cells/m^3 (2.5×10^{12}/L); Hgb 8.0 g/dL (4.96 mmol/L); Hct 25% (0.25); mean corpuscular volume (MCV) 88 fL; mean corpuscular hemoglobin concentration (MCHC) 35 g/dL (350 g/L); platelets 250×10^3 cells/m^3 (250×10^9/L); iron 35 mcg/dL (6.26 mmol/L); TIBC 150 mcg/dL (26.85 µmol/L); ferritin 75 ng/mL (168 pmol/L); TSAT 15% (0.15); Hb_{A1c} 7.5% (0.075)

- What signs and symptoms are consistent with anemia of CKD?
- What additional information could you request to determine other causes of anemia in this patient?
- What treatment would you recommend for this patient for treatment of anemia?
- How would you evaluate the effectiveness of treatment of anemia?

to 10.5-fold for patients with stage 5 CKD, compared to stages 1 and 2 CKD.[32]

Pathophysiology

The primary cause of anemia in patients with CKD is a decrease in EPO production. With normal kidney function, as Hgb, hematocrit (Hct), and tissue oxygenation decrease, the plasma concentration of EPO increases exponentially. As nephron mass decreases, EPO production also decreases. Thus, as Hgb, Hct, and tissue oxygenation decrease in patients with CKD, plasma EPO levels remain constant within the normal range, but low relative to the degree of hypoxia present. The result is a normochromic, normocytic anemia.

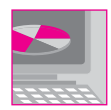
Several other factors also contribute to the development of anemia in patients with CKD. **Uremia**, a result of declining renal function, decreases the lifespan of RBCs from a normal of 120 days to as low as 60 days in patients with stage 5 CKD. Iron deficiency and blood loss from regular laboratory testing and hemodialysis also contribute to the development of anemia in patients with CKD.

Treatment

General Approach to Therapy

Studies have demonstrated that initiation of treatment for anemia before stage 5 CKD decreases mortality in patients with ESRD receiving dialysis, particularly in the elderly.[33] The treatment of anemia can decrease morbidity, increase exercise capacity and tolerance, and slow the progression of CKD if target Hgb levels are achieved.[34]

Patients with CKD should be evaluated for anemia when the GFR falls below 60 mL/minute or if the serum creatinine rises above 2 mg/dL (176.8 mmol/L). If the Hgb is less than 11 g/dL (6.8 mmol/L), an anemia work-up should be performed. The work-up for anemia should rule out other potential causes for anemia (see Chapter 63). Abnormalities found during the anemia work-up should be corrected before initiating **erythropoiesis-stimulating agents** (ESA),



Clinical Presentation of Anemia of CKD

General
Anemia of CKD generally presents with fatigue and decreased quality of life.

Symptoms
Anemia of CKD is associated with symptoms of cold intolerance, shortness of breath, and decreased exercise capacity.

Signs
Cardiovascular: Left ventricular hypertrophy, ECG changes, congestive heart failure
Neurologic: Impaired mental cognition
Genitourinary: Sexual dysfunction

Laboratory Tests
Decreased RBC count, Hgb, and Hct
Decreased serum iron level, TIBC, serum ferritin, and TSAT
Decreased erythropoietin levels relative to the degree of hypoxia that is present

particularly iron deficiency, as iron is an essential component of RBC production. If Hgb is still below the goal level when all other causes of anemia have been corrected, EPO deficiency should be assumed. EPO levels are not routinely measured and have little clinical significance in monitoring progression and treatment of anemia in patients with CKD.

❻ *Generally, treatment requires a combination of ESA and iron supplementation. The goal of treatment for anemia of CKD is to increase Hgb levels greater than 11 g/dL (6.8 mmol/L).* The goal for iron supplementation is to maintain serum ferritin levels between 100 and 500 ng/mL (225 to 1123.5 pmol/L) in patients not receiving hemodialysis and between 200 and 500 ng/mL (449.4 to 1123.5 pmol/L) in patients receiving hemodialysis and TSAT greater than 20% (0.2).[31] The approach to the management of anemia of CKD with ESA and iron supplementation is illustrated in Figs. 23–3 and 23–4.

Nonpharmacologic Therapy

Sufficient dietary iron intake must be maintained in patients with anemia of CKD. Approximately 1 to 2 mg of iron is

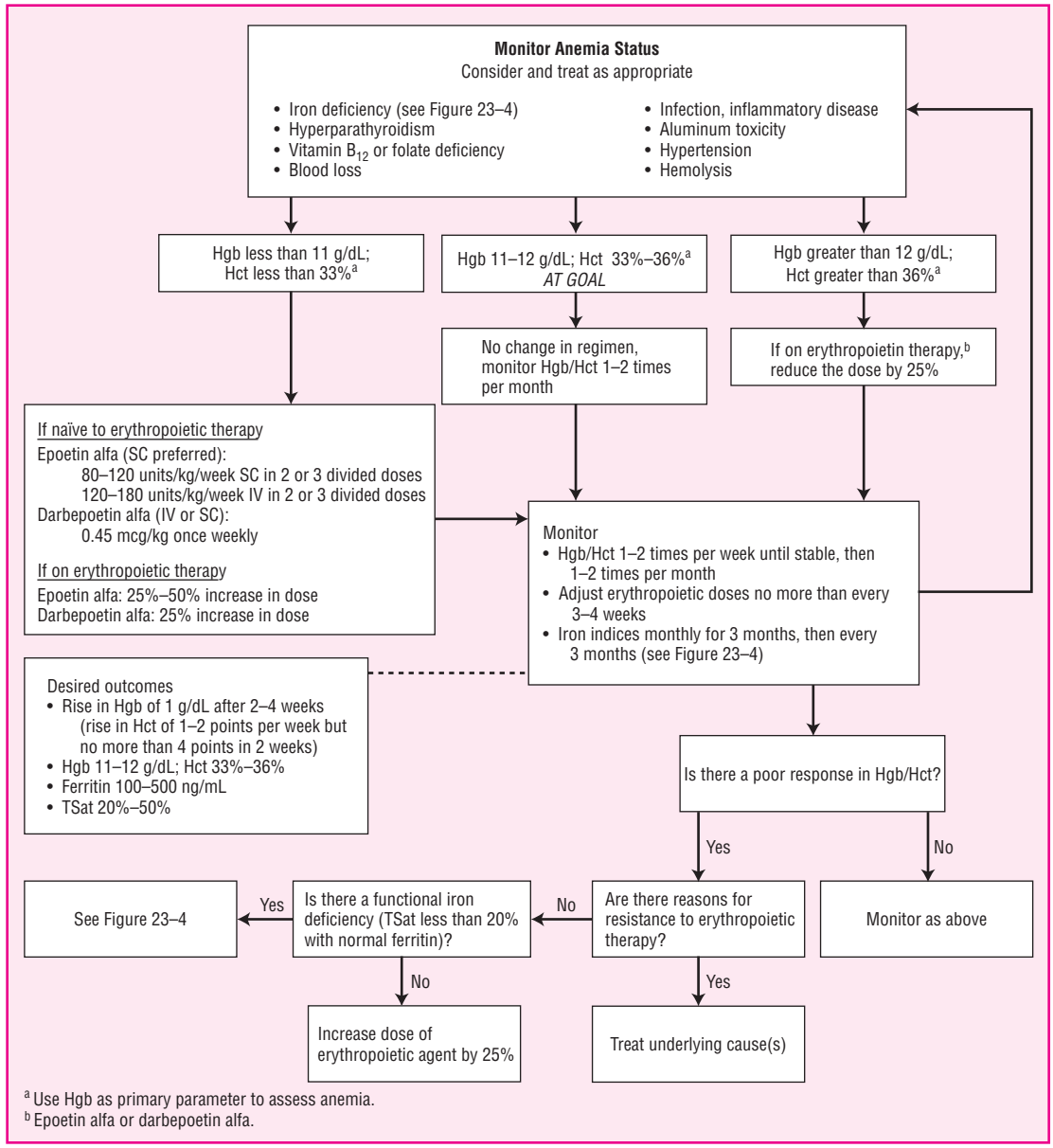


FIGURE 23–3. Guidelines for erythropoietic therapy in the management of anemia of CKD. (Adapted from Joy MS, Kshirsagar A, Paparello J. Chronic kidney disease: Progression-modifying therapies. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 828, with permission.)

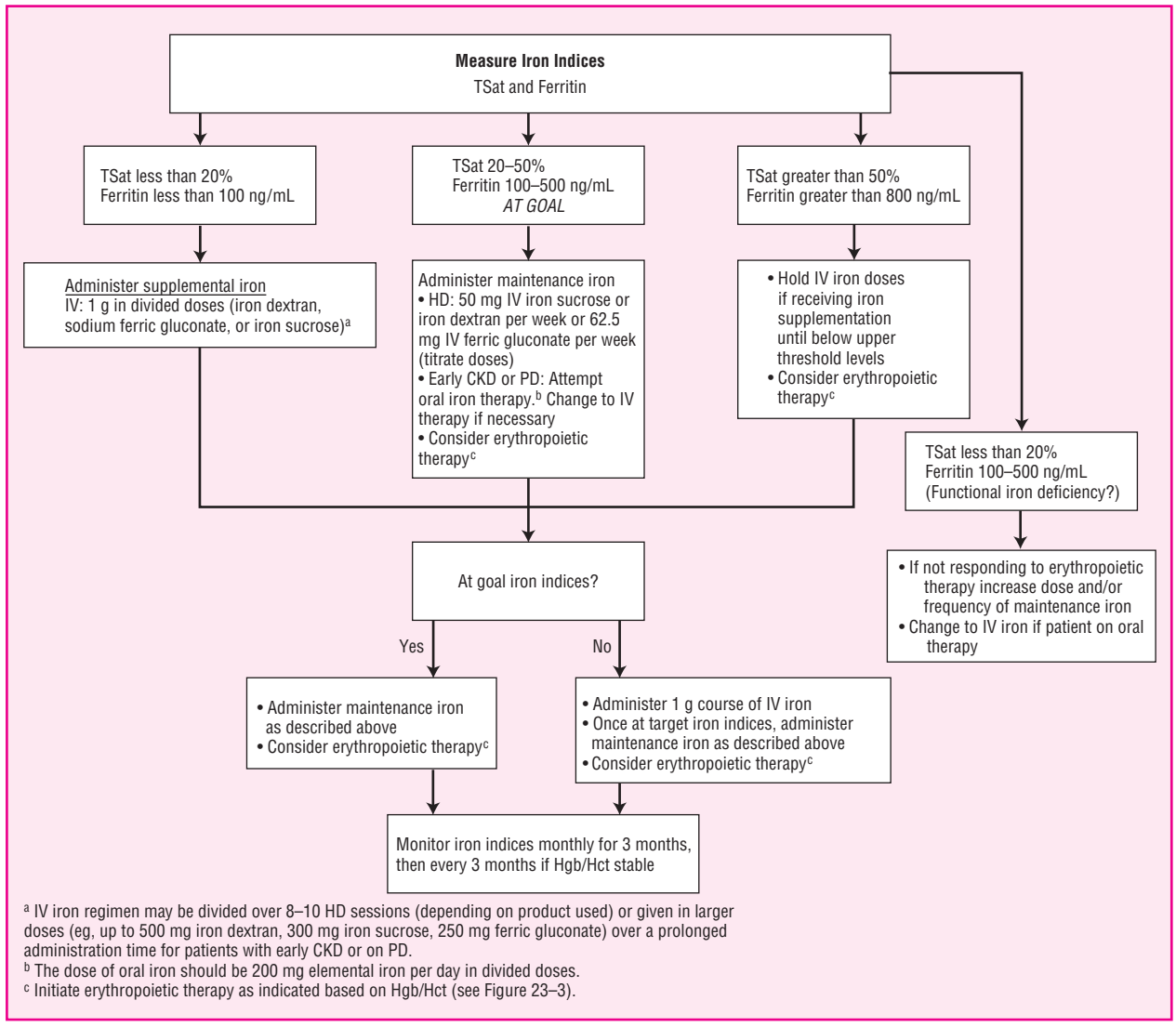


FIGURE 23–4. Guidelines for iron therapy in the management of anemia of CKD. (Adapted from Joy MS, Kshirsagar A, Paparello J. Chronic kidney disease: Progression-modifying therapies. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 827, with permission.)

absorbed daily from the diet. This small amount is generally not adequate to preserve adequate iron stores to promote RBC production. RBC transfusions have been used in the past as the primary means to maintain Hgb and Hct levels in patients with anemia of CKD. This treatment is still utilized today in patients with severe anemia, but is considered a third-line therapy for anemia of CKD.

Pharmacologic Therapy

The first-line treatment for anemia of CKD involves replacement of erythropoietin with erythropoiesis-stimulating agents (ESAs). Use of ESAs increases the iron demand for RBC production and iron deficiency is common, requiring iron supplementation to correct and maintain adequate iron stores to promote RBC production. Androgens were used extensively before the availability of ESAs, but are now reserved as third-line agents because of toxicity; namely, hepatotoxicity.

Erythropoiesis-Stimulating Agents (ESAs) Erythropoietin is a growth factor that acts on erythroblasts formed from stem cells in the bone marrow, stimulating proliferation and differentiation into normoblasts, then reticulocytes, which are released into the bloodstream to eventually mature into erythrocytes (mature RBCs). The ESAs currently available in the United States are: epoetin alfa (distributed as Epogen® by Amgen, Inc., Thousand Oaks, CA; and Procrit® by Ortho Biotech, Johnson & Johnson, Raritan, NJ) and darbepoetin alfa (Aranesp® by Amgen, Inc.). Epoetin alfa and epoetin beta, which is available outside the United States, have the same biological activity as endogenous EPO. Darbepoetin alfa

differs from epoetin alfa by the addition of carbohydrate side chains that increase the half-life of darbepoetin alfa compared to epoetin alfa and endogenous EPO, allowing for less frequent dosing than that of epoetin alfa. All ESAs are equivalent in their efficacy and have a similar adverse-effect profile.

The most common adverse effect seen with ESA is increased blood pressure, which can occur in up to 23% of patients.[31] Antihypertensive agents may be required to control blood pressure in patients receiving ESAs. Caution should be used when initiating an ESA in patients with very high blood pressures (greater than 180/100 mm Hg). If blood pressures are refractory to antihypertensive agents, ESAs may need to be withheld.

Subcutaneous (SC) administration of ESA produces a more predictable and sustained response than IV administration, and is therefore the preferred route of administration for both agents. Intravenous administration is often utilized in patients who have established IV access or are receiving hemodialysis. Starting doses of ESAs depend on the patient's Hgb level, the target Hgb level, the rate of Hgb increase and clinical circumstances.[31] The initial increase in Hgb should be 1–2 g/dL (0.6206–1.2404 mmol/L) per month. The starting doses of epoetin alfa previously recommended are 80 to 120 units/kg per week for SC administration and 120 to 180 units/kg per week for IV administration, divided two to three times per week. The starting dose of darbepoetin alfa is 0.45 mcg/kg administered SC or IV once weekly (Table 23–3).

Iron Supplementation Use of ESAs can lead to iron deficiency if iron stores are not adequately maintained. If serum ferritin and TSAT fall below the goal levels, iron supplementation is required. Oral iron supplements are less costly than IV supplements and are generally the first-line treatment for iron supplementation. When administering iron by the oral route, 200 mg of elemental iron should be delivered daily to maintain adequate iron stores.

Oral iron supplementation is generally not effective in maintaining adequate iron stores in patients receiving ESAs because of poor absorption and an increased need for iron with ESA therapy, making the IV route necessary for iron supplementation. The IV iron products currently available are: iron dextran (distributed as INFeD® by Watson Pharmaceuticals, Inc., Morristown, NJ, and Dexferrum® by American Reagent, Inc., Shirley, NY); sodium ferric gluconate (Ferrlecit® by Watson Pharmaceuticals, Inc., Corona, CA); and iron sucrose (Venofer® by American Reagent, Inc., Shirley, NY). Initiation of IV iron should be based on evaluation of iron stores. A serum ferritin level less than 100 ng/mL in conjunction with a TSAT level less than 20% indicates absolute iron deficiency and is a clear indication for the need for iron replacement.[31] When TSAT is less than 20% in conjunction with normal or elevated serum ferritin levels, treatment should be based on the clinical picture of the patient, as serum ferritin is an acute phase reactant, which may become elevated with inflammation and stress. Iron supplementation may be indicated if Hgb levels are below the goal level.

When replacing iron stores in patients receiving ESA therapy, the general approach to treatment is to give a total of 1 g of IV iron, administered in smaller, sequential doses. Because iron stores deplete quickly in patients who do not receive iron supplementation, maintenance doses are often used, particularly in patients receiving hemodialysis. Maintenance doses consist of smaller doses of iron administered weekly or with each dialysis session (e.g., iron dextran or iron sucrose 20 to 100 mg per week; sodium ferric gluconate 62.5 to 125 mg per week).

Intravenous iron preparations are equally effective in increasing iron stores. Iron dextran has been associated with side effects, including anaphylactic reactions and delayed reactions, such as arthralgias and myalgias. A test dose of 25 mg iron dextran should be administered 30 minutes before the full dose to monitor for potential anaphylactic reactions. However, patients should be monitored closely when receiving iron dextran, as anaphylactic reactions can occur in patients who safely received prior doses of iron dextran. For this reason, use of iron dextran has decreased dramatically in CKD patients in favor of the newer iron preparations, sodium ferric gluconate and iron sucrose, which are associated with fewer severe reactions. The most common side effects seen with these preparations include hypotension, flushing, nausea, and injection site reactions. A test dose is not required prior to the administration of either sodium ferric gluconate or iron sucrose.

TABLE 23–3. Estimated Starting Doses of Darbepoetin Alfa Based on Previous Epoetin Alfa Dose

Previous Epoetin Alfa Dose (units/week)	Weekly Darbepoetin Alfa Dose (mcg/week)
Less than 2500	6.25
2500–4999	12.5
5000–10,999	25
11,000–17,999	40
18,000–33,999	60
34,000–59,999	100
60,000–89,999	150
Greater than or equal to 90,000	200

Outcome Evaluation

Evaluate Hgb every 1 to 2 weeks when ESA therapy is initiated or the dose is adjusted until Hgb is greater than 11 g/dL (6.82 mmol/L). Once goal Hgb is attained, evaluate Hgb every 2 to 4 weeks thereafter. While the patient is receiving ESA therapy, monitor iron stores monthly in patients who are not receiving iron supplements or every 3 months in patients who are receiving iron supplements. When the goal Hgb is reached, monitor iron stores every 3 months.

Secondary Hyperparathyroidism and Renal Osteodystrophy

Epidemiology and Etiology

Increases in parathyroid hormone (PTH) occur early as renal function begins to decline. The actions of PTH on bone



Patient Encounter, Part 3

The patient returns to your clinic 1 year later for routine follow-up. She has no complaints at this time.

Current Meds

Furosemide 80 mg orally daily
Lisinopril 40 mg orally daily
Metoprolol 75 mg orally twice daily
Insulin glargine 28 units subcutaneously at bedtime
Insulin lispro subcutaneously per sliding scale with meals
Darbepoetin 60 mcg subcutaneously weekly

ROS

Unremarkable

PE

VS: Blood pressure 128/75 mm Hg, pulse 68 beats per minute, temperature 36.5°C (97.9°F); Wt 170 lb (77.3 kg)
Chest: Regular rate and rhythm, normal S_1, S_3 present
Abd: Obese; no organomegaly, bruits, tenderness, (+) bowel sounds; heme (–) stool
Exts: 2+ edema bilaterally; decreased sensation to light touch in feet; no lesions

Labs

Sodium 144 mEq/L (144 mmol/L); potassium 5.0 mEq/L (5.0 mmol.L); chloride 105 mEq/L (105 mmol/L); carbon dioxide 18 mEq/L (18 mmol/L); BUN 75 mg/dL (26.78 mmol/L urea); SCr 4.8 mg/dL (424.32 µmol/L); glucose 115 mg/dL (6.38 mmol/L); calcium 8.6 mg/dL (2.15 mmol/L); phosphate 7.8 mg/dL (2.52 mmol/L); albumin 3.0 mg/dL (30 g/L); intact parathyroid hormone (iPTH) 538 pg/mL (538 ng/L); WBC 6.0×10^3 cells/mm^3 (6.0×10^9/L); RBC 3.5×10^3 cells/mm^3 (3.5×10^{12}/L); Hgb 10.5 g/dL (6.51 mmol/L); Hct 32% (0.32); platelets 350×10^3 cells/mm^3 (350×10^9/L)

- What signs are consistent with secondary hyperparathyroidism?
- What information would you request to determine if the patient has renal osteodystrophy?
- How would you determine whether treatment is necessary for this patient?
- What treatment would you recommend for secondary hyperparathyroidism?

turnover lead to **renal osteodystrophy** (ROD). As many as 75% to 100% of patients with stage 3 CKD have ROD.[35] The type of bone disease can vary based on the degree of bone turnover. High bone turnover is the most common cause of bone abnormalities in patients with CKD, present in as many as 75% of patients receiving dialysis,[35] and is generally mediated by high levels of PTH. Adynamic bone disease, characterized by low bone turnover, is less common, although the prevalence appears to be increasing,[35] which may be related to more aggressive treatment of hyperparathyroidism. The development of ROD can dramatically affect morbidity in patients with CKD.

Pathophysiology

As renal function declines in patients with CKD, decreased phosphorus excretion disrupts the balance of calcium and phosphorus homeostasis. ❼ *The parathyroid glands release PTH in response to decreased serum calcium and increased serum phosphorus levels. The actions of PTH include:*

- *Increasing calcium resorption from bone*
- *Increasing calcium reabsorption from the proximal tubules in the kidney*
- *Decreasing phosphorus reabsorption in the proximal tubules in the kidney*
- *Stimulating activation of vitamin D by 1-α-hydroxylase to calcitriol (1,25-dihydroxyvitmin D_3) to promote calcium absorption in the GI tract and increased calcium mobilization from bone*

All of these actions are directed at increasing serum calcium levels and decreasing serum phosphorus levels, although the activity of calcitriol also increases phosphorus absorption in the GI tract and mobilization from the bone, which can worsen hyperphosphatemia. Calcitriol also decreases PTH levels through a negative feedback loop. These measures are sufficient to correct serum calcium levels in the earlier stages of CKD.

As kidney function continues to decline and the GFR falls less than 60 mL/minute/1.73 m^2, phosphorus excretion continues to decrease and calcitriol production decreases, causing PTH levels to begin to rise significantly, leading to **secondary hyperparathyroidism** (sHPT). The excessive production of PTH leads to hyperplasia of the parathyroid glands, which decreases the sensitivity of the parathyroid glands to serum calcium levels and calcitriol feedback, further promoting sHPT.

The most dramatic consequence of sHPT is alterations in bone turnover and the development of ROD. Other complications of CKD can also promote ROD. Metabolic acidosis decreases bone formation and aluminum toxicity causes aluminum uptake into bone in place of calcium, weakening the bone structure. The pathogenesis of sHPT and ROD are depicted in Fig. 23–5.

The increased serum phosphorus binds to calcium in the serum, which leads to deposition of hydroxyapatite crystals throughout the body. The calcium-phosphorus (Ca-P) product reflects serum solubility. A Ca-P product greater than 75 mg^2/dL^2 promotes crystal deposition in the joints and eye, leading to arthritis and conjunctivitis, respectively. Soft tissue deposition primarily affects the coronary arteries of the heart, lungs, and vascular tissue and is associated with a Ca-P product greater than 55 mg^2/dL^2.[36] The Ca-P product has been associated with increased mortality[37] and is a risk factor for calcification of vascular and soft tissues.[35]

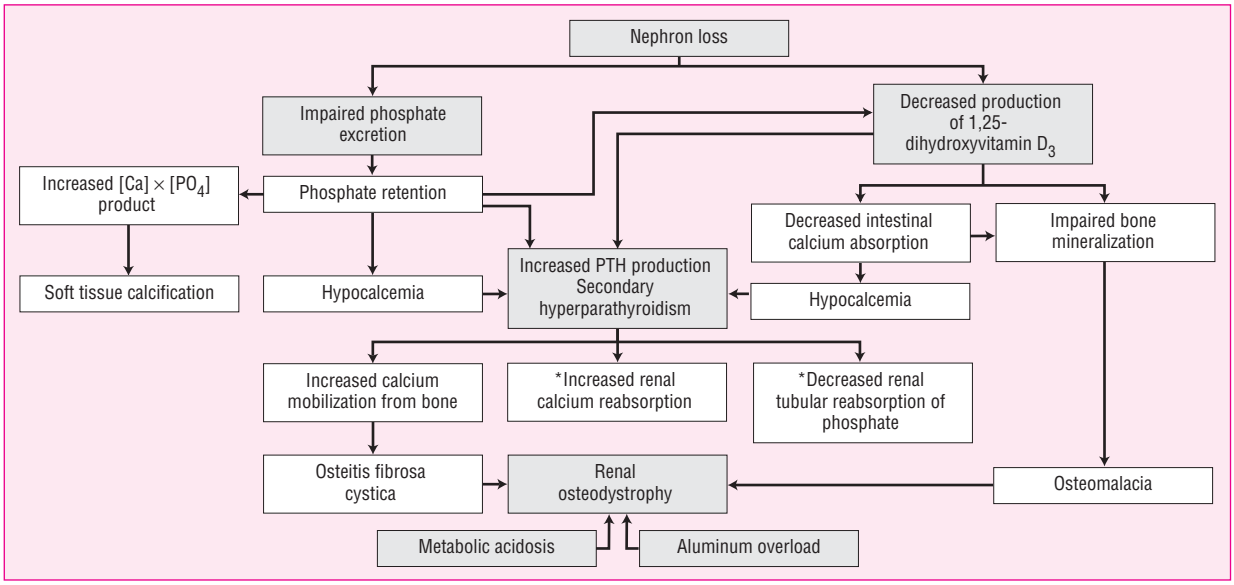


FIGURE 23–5. Pathogenesis of secondary hyperparathyroidism and renal osteodystrophy in patients with CKD. *These adaptations are lost as renal failure progresses. [Ca] × [PO_4] calcium-phosphorus product. (From Joy MS, Kshirsagar A, Paparello J. Chronic kidney disease: Progression-modifying therapies. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 834, with permission.)



Clinical Presentation of Secondary Hyperparathyroidism and Renal Osteodystrophy

General
Onset of sHPT and ROD is subtle and may not be associated with symptoms.

Symptoms
sHPT and ROD are usually asymptomatic in early disease.
Calcification in the joints can be associated with decreased range of motion.
Conjunctival calcifications are associated with a gritty sensation in the eyes, redness, and inflammation.

Signs
Cardiovascular: Increased stroke index, heart rate, and diastolic and mean arterial pressures
Musculoskeletal: Bone pain, muscle weakness
Dermatologic: Pruritus

Laboratory Tests
Increased serum phosphorus levels
Low to normal serum calcium levels
Increased Ca-P product
Increased PTH levels
Decreased vitamin D levels

Diagnostic Tests
Radiographic studies show calcium-phosphate deposits in joints and/or cardiovascular system
Bone biopsy of the iliac crest

Metabolic acidosis, a common complication of CKD, also contributes to ROD by altering the solubility of hydroxyapatite, promoting bone dissolution. Additionally, metabolic acidosis inhibits the activity of osteoblasts, which promote bone formation, while stimulating osteoclasts to promote bone resorption. Finally, metabolic acidosis can worsen sHPT by reducing the sensitivity of the parathyroid gland to serum calcium levels.[38]

Treatment

General Approach

℞ *Diagnosis and management of bone disease in CKD is based on corrected serum levels of calcium and phosphorus, the Ca-P (using corrected calcium levels), and intact PTH levels (iPTH).*[39] The target levels of each vary with the stage of CKD and are listed in Table 23–4. The primary target for treatment is control of serum phosphorus levels, as this is the initial parameter that disrupts homeostasis. However, serum phosphorus can be difficult to control, particularly in the latter stages of CKD. Management of sHPT often requires supplemental treatment in addition to phosphorus management.

Nonpharmacologic Therapy

The first-line treatment for the management of hyperphosphatemia is dietary phosphorus restriction to 800 to 1000 mg per day in patients with stage 3 CKD or higher who have phosphorus levels at the upper limit of the normal range or elevated iPTH levels.[39] Foods high in phosphorus are also high in protein, which can make it difficult to restrict phosphorus intake while maintaining adequate protein intake to avoid

TABLE 23–4. Target Levels for Calcium, Phosphorus, Calcium-Phosphorus Product, and Intact Parathyroid Hormone

Parameter	Stage 3 CKD	Stage 4 CKD	Stage 5 CKD
Corrected calcium	"Normal"	"Normal"	8.4–9.5 mg/dL (2.1–2.37 mmol/L)
Phosphorus	2.7–4.6 mg/dL (0.87–1.49 mmol/L)	2.7–4.6 mg/dL (0.87–1.49 mmol/L)	3.5–5.5 mg/dL (1.13–1.78 mmol/L)
Ca-P product	Less than 55 mg^2/dL^2	Less than 55 mg^2/dL^2	Less than 55 mg^2/dL^2
Intact PTH	35–70 pg/mL (35–70 ng/L)	70–110 pg/mL (70–110 ng/L)	150–300 pg/mL (150–300 ng/L)

Ca-P, calcium-phosphorus product; CKD, chronic kidney disease; PTH, parathyroid hormone.

malnutrition. Hemodialysis and peritoneal dialysis can remove up to 2 to 3 g of phosphorus per week. However, this is insufficient to control hyperphosphatemia and pharmacologic therapy is necessary in addition to dialysis treatment.

Other nonpharmacologic strategies to manage sHPT and ROD in patients with CKD include restriction of aluminum exposure and parathyroidectomy. Ingestion of aluminum-containing antacids and other aluminum-containing products should be avoided in patients with stage 4 CKD or higher (GFR less than 30 mL/minute/1.73m^2) because of the risk of aluminum toxicity and potential uptake into the bone. Purification techniques for dialysate solutions also minimize the risk of exposure to aluminum.

Parathyroidectomy is a treatment of last resort for sHPT, but should be considered in patients with persistently elevated iPTH levels above 800 pg/mL (800 ng/L) that is refractory to medical therapy to lower serum calcium and/or phosphorus levels.[39] A portion or all of the parathyroid tissue may be removed, and in some cases a portion of the parathyroid tissue may be transplanted into another site, usually the forearm. Bone turnover can be disrupted in patients undergoing parathyroidectomy whereby bone production outweighs bone resorption. The syndrome, known as "hungry bone syndrome," is characterized by excessive uptake of calcium, phosphorus, and magnesium for bone production, leading to hypocalcemia, hypophosphatemia, and hypomagnesemia. Serum ionized calcium levels should be monitored frequently (every 4 to 6 hours for the first 48 to 72 hours) in patients receiving a parathyroidectomy. Calcium supplementation is usually necessary, administered IV initially, then orally (with vitamin D supplementation) once normal calcium levels are attained for several weeks to months after the procedure.

Pharmacologic Therapy

Phosphate-Binding Agents When serum phosphorus levels cannot be controlled by restriction of dietary intake, phosphate-binding agents are used to bind dietary phosphate in the GI tract to form an insoluble complex that is excreted in the feces. Phosphorus absorption is decreased, thereby decreasing serum phosphorus levels. The drugs used for binding dietary phosphate are listed in Table 23–5. These agents should be administered with each meal and can be tailored to the amount of phosphorus that is typically ingested during each meal. For example, patients can take a smaller dose with smaller meals or snacks, and a larger dose with larger meals.

Calcium-based phosphate binders, including calcium carbonate and calcium acetate, are effective in decreasing serum phosphate levels, as well as increasing serum calcium levels. Calcium acetate binds more phosphorus than the carbonate salt, making it a more potent agent for binding dietary phosphate. Calcium citrate is usually not used as a phosphate-binding agent because the citrate salt can increase aluminum absorption. The calcium-containing phosphate binders also aid in the correction of metabolic acidosis, another complication of renal failure. Caution should be used with these agents if serum calcium levels are near the upper end of the normal range or are elevated because of the risk of increasing the Ca-P product and potentiating vascular and soft tissue calcifications. The dose of calcium-based phosphate binders should not provide more than 1500 mg of elemental calcium per day, and the total elemental calcium intake per day should not exceed 2000 mg, including medication and dietary intake.[39] The most common adverse effects of calcium-containing phosphate binders are constipation and hypercalcemia.

Phosphate-binding agents that do not contain calcium, magnesium, or aluminum include sevelamer hydrochloride and lanthanum carbonate. These agents are particularly useful in patients with hyperphosphatemia who have elevated serum calcium levels or who have vascular or soft tissue calcifications. Sevelamer is a cationic polymer that is not systemically absorbed and binds to phosphate in the GI tract, and prevents absorption and promotes excretion of phosphate through the GI tract via the feces. Sevelamer has an added benefit of reducing LDL-C by up to 30% and increasing HDL-C levels.[39] The most common side effects of sevelamer are GI complaints, including nausea, constipation, and diarrhea. The cost of sevelamer is significantly higher compared to calcium-containing phosphate binders, however, which often makes sevelamer a second-line agent for controlling phosphorus levels.

TABLE 23–5. Phosphate-Binding Agents Used in the Treatment of Hyperphosphatemia in CKD

Compound	Trade Name	Compound Content (mg)	Elemental Calcium Content (mg)	Starting Dose	Comments
Calcium carbonate (40% elemental calcium)	Tums	500, 750, 1000, 1250	200, 300, 400, 500	0.5–1 g (elemental calcium) three times a day with meals	First-line agent; dissolution characteristics and phosphorus-binding effect may vary from product to product; try to limit daily intake of elemental calcium to 1500 mg/day Approximately 39 mg phosphorus bound per 1 g calcium carbonate
	Oscal-500	1250	500		
	Caltrate 600	1500	600		
	Nephro-Calci	1500	600		
	LiquiCal	1200	480		
	CalciChew	1250	500		
Calcium acetate (25% elemental calcium)	Phos-Lo	667	167	0.5–1 g (elemental calcium) three times a day with meals	First-line agent; comparable efficacy to calcium carbonate with one-half the dose of elemental calcium; do not exceed 1500 mg elemental calcium intake per day Approximately 45 mg phosphorus bound per 1 g calcium acetate By prescription only
Sevelamer	Renagel	400, 800	—	800 mg three times a day with meals	First-line agent; lowers LDL-C More expensive than calcium products; preferred in patients at risk for extraskeletal calcification May require large doses to control phosphorus levels
Lanthanum	Fosrenol	250, 500 chewable tablets	—	750–1500 mg three times a day with meals	Second-line agent; more expensive than calcium products; preferred in patients at risk for extraskeletal calcification Most patients require 1500–3000 mg per day to control phosphorus
Aluminum hydroxide	Alterna GEL	600 mg/5 mL	—	300–600 mg three times a day with meals	Third-line agents; do not use concurrently with citrate-containing products Reserve for short-term use (4 weeks) in patients with hyperphosphatemia not responding to other binders
	Amphojel	300, 600 (tablet) 320 mg/5 mL (suspension)			
	Alu-Cap	400			
Aluminum carbonate	Basaljel	500 (tablet, capsule) 400 mg/5 mL (suspension)	—	450–500 mg three times a day with meals	Same as for aluminum hydroxide
Magnesium carbonate	Mag-Carb	70 (capsule)	—	70 mg three times a day with meals	Third-line agent; diarrhea common; monitor serum magnesium
Magnesium hydroxide	Milk of Magnesia	300, 600 (tablet) 400 mg/5 mL, 800 mg/5 mL (suspension)	—	300–400 mg three times a day with meals	Same as for magnesium carbonate
Magnesium carbonate/calcium carbonate	MagneBind 200	200 mg (elemental magnesium)	160	200 mg three times a day with meals	Same as for calcium carbonate and magnesium carbonate

LDL-C, low-density lipoprotein cholesterol.

Lanthanum is a naturally occurring trivalent rare earth element (atomic number 57). Lanthanum carbonate quickly dissociates in the acidic environment of the stomach, where the lanthanum ion binds to dietary phosphorus, forming an insoluble compound that is excreted in the feces. Lanthanum has been shown to remove more than 97% of dietary phosphorus from the GI tract.[40] Side effects of lanthanum include nausea, peripheral edema, and myalgias.

Aluminum- and magnesium-containing phosphate-binding agents are not recommended for chronic use in patients with CKD to minimize the risk of aluminum and magnesium accumulation. Aluminum-containing agents may be used for

a short course of therapy (less than 4 weeks) if phosphorus levels are significantly elevated greater than 7 mg/dL (2.26 mmol/L), but should be replaced by other phosphate-binding agents after no more than 4 weeks.[39] In addition to the risk of magnesium accumulation, the use of magnesium-containing agents is also limited by the GI side effects, primarily diarrhea.

Vitamin D Therapy Exogenous vitamin D compounds that mimic the activity of calcitriol act directly on the parathyroid gland to decrease PTH secretion. This is particularly useful when reduction of serum phosphorus levels does not sufficiently reduce PTH levels. The most active form of vitamin D is calcitriol (1,25-dihydroxyvitamin D_3), which is available commercially as an oral formulation (Rocaltrol® by Roche Laboratories, Inc., Nutley, NJ) and an injectable formulation (Calcijex® by Abbott Laboratories, North Chicago, IL). The effects of calcitriol are mediated by upregulation of the vitamin D receptor in the parathyroid gland, which decreases parathyroid gland hyperplasia and PTH synthesis and secretion. However, vitamin D receptor upregulation also occurs in the intestines, which increases calcium and phosphorus absorption, increasing the risk of hypercalcemia and hyperphosphatemia. It is important that serum calcium and phosphorus levels are within the normal range for the stage of CKD and the Ca-P product is less than 55 mg^2/dL^2 prior to starting calcitriol therapy.

Other vitamin D analogs available in the United States include paricalcitol (19-nor-1,25-dihydroxyvitamin D_2, Zemplar® by Abbott Laboratories, North Chicago, IL) and doxercalciferol (1-α-hydroxyvitamin D_2, Hectoral® by Bone Care International, Middleton, WI). Alfacalcidiol (1-α-hydroxyvitamin D_3) is only available outside the United States. Paricalcitol has less effect on vitamin D receptors in the intestines, decreasing the effects on intestinal calcium and phosphorus absorption, while retaining the effects on parathyroid gland hyperplasia and PTH synthesis and secretion.[41] This makes paricalcitol more useful in patients with an elevated Ca-P product. Doxercalciferol, on the other hand, has similar effects as calcitriol on vitamin D receptors in the parathyroid glands and intestines. Like calcitriol, calcium and phosphorus levels and the Ca-P product should be within the normal range for the stage of CKD prior to starting doxercalciferol. Recommendations for vitamin D analog therapy depend on the stage of CKD (Table 23–6).[39]

It is important to monitor vitamin D therapy aggressively to assure that PTH levels are not oversuppressed. Oversuppression of PTH levels can induce adynamic bone disease, which manifests as decreased osteoblast and osteoclast activity, decreased bone formation, and low bone turnover.

Calcimimetics

Cinacalcet is a calcimimetic that increases the sensitivity of receptors on the parathyroid gland to serum calcium levels to reduce PTH secretion. Cinacalcet may be beneficial in patients with an increased Ca-P product who have elevated PTH levels and cannot use vitamin D therapy. Because the effects of cinacalcet on PTH can reduce serum calcium levels and result in hypocalcemia, cinacalcet should not be used if serum calcium levels are below normal.

Reversal of Metabolic Acidosis

Studies have demonstrated that reversal of metabolic acidosis can improve bone disease associated with CKD.[38] Serum bicarbonate levels should be maintained at 22 mEq/L (22 mmol/L) in patients with bone disease associated with CKD.[39] The treatment of metabolic acidosis is described below.

TABLE 23–6. Dosing Recommendations for Vitamin D in Patients with CKD

Serum PTH (pg/mL)	Calcitriol Dose	Paricalcitol Dose	Doxercalciferol Dose
Stage 3 or 4 CKD			
70–300[a]	0.25 mcg orally daily	Not recommended	2.5 mg orally 3 times weekly
Stage 5 CKD on hemodialysis			
300–600[b]	0.5–1.5 mcg PO or intravenously per HD	2.5–5 mcg intravenously per HD	5 mcg orally per HD 2 mcg intravenously per HD
600–1000[b]	1–4 mcg orally per HD 1–3 mcg intravenously per HD	6–10 mcg intravenously per HD	5–10 mcg orally per HD 2–4 mcg intravenously per HD
Greater than 1000[c]	3–7 mcg orally per HD 3–5 mcg intravenously per HD	10–15 mcg intravenously per HD	10–20 mcg orally per HD 4–8 mcg intravenously per HD
Stage 5 CKD on peritoneal dialysis			
Greater than 300[b]	0.25 mcg orally daily 0.5–1 mcg orally 2–3 times weekly	Not recommended	2.5–5 mcg orally 2–3 times weekly

[a]If serum calcium less than 9.5 mg/dL (2.37 mmol/L), phosphorus less than 4.6 mg/dL (1.49 mmol/L), and Ca-P product less than 55 mg^2/dL^2
[b]If serum calcium less than 9.5 mg/dL (2.37 mmol/L), phosphorus less than 5.5 mg/dL (1.78 mmol/L), and Ca-P product less than 55 mg^2/dL^2
[c]If serum calcium less than 10 mg/dL (2.5 mmol/L), phosphorus less than 5.5 mg/dL (1.78 mmol/L), and Ca-P product less than 55 mg^2/dL^2
CKD, chronic kidney disease; HD, hemodialysis; PO, orally; PTH, parathyroid hormone.

Outcome Evaluation

Monitor serum calcium and phosphorus levels regularly in patients receiving phosphate-binding agents. When initiating therapy, monitor serum levels every 1 to 4 weeks, depending on the severity of hyperphosphatemia. Titrate doses of phosphate binders to achieve the target levels of serum calcium and phosphorus and the Ca-P product (Table 23–4). Once target levels are achieved, monitor serum calcium and phosphorus levels every 1 to 3 months. Monitor intact PTH levels monthly while initiating vitamin D therapy, then every 3 months once stable iPTH levels are achieved. When starting or increasing the dose of cinacalcet, monitor serum calcium and phosphorus levels within 1 week and iPTH levels should be monitored within 1 to 4 weeks. Once target levels are achieved, decrease monitoring to every 3 months.

Metabolic Acidosis

Epidemiology and Etiology

Approximately 80% of patients with a GFR less than 20 to 30 mL/minute develop metabolic acidosis.[38] Metabolic acidosis can increase protein catabolism and decrease albumin synthesis, which promote muscle wasting, and alter bone metabolism. Other consequences associated with metabolic acidosis in CKD include worsening cardiac disease, impaired glucose tolerance, altered growth hormone and thyroid function, and inflammation.[38]

Pathophysiology

The kidneys play a key role in the management of acid-base homeostasis in the body by regulating excretion of hydrogen ions. With normal kidney function, bicarbonate that is freely filtered through the glomerulus is completely reabsorbed via the renal tubules. Hydrogen ions are generated at a rate of 1 mEq/kg (1 mmol/kg) per day during metabolism of ingested food and are excreted at the same rate by the kidney via buffers in the urine created by ammonia generation and phosphate excretion. As a result, the pH of body fluids is maintained within a very narrow range.

As kidney function declines, bicarbonate reabsorption is maintained, but hydrogen excretion is decreased because the ability of the kidney to generate ammonia is impaired. The positive hydrogen balance leads to metabolic acidosis, which is characterized by a serum bicarbonate level of 15 to 20 mEq/L (15 to 20 mmol/L). This picture is generally seen when the GFR declines below 20 to 30 mL/minute.[38]

Treatment

Serum electrolytes should be monitored in patients with CKD for the development of metabolic acidosis. Metabolic acidosis in patients with CKD is generally characterized by an elevated anion gap greater than 17 mEq/L (17 mmol/L), due to the accumulation of phosphate, sulfate, and other organic anions.

Nonpharmacologic Therapy

Treatment of metabolic acidosis in CKD requires pharmacologic therapy. Other disorders that may contribute to metabolic acidosis should also be addressed. Altering bicarbonate levels in the dialysate fluid in patients receiving dialysis may assist with the treatment of metabolic acidosis, although pharmacologic therapy may still be required.

Pharmacologic Therapy

Pharmacologic therapy with sodium bicarbonate or citrate/citric acid preparations may be needed in patients with stage 3 CKD or higher to replenish body stores of bicarbonate. Calcium carbonate and calcium acetate, used to bind phosphorus in sHPT, also aid in increasing serum bicarbonate levels, in conjunction with other agents.

Sodium bicarbonate tablets are administered in increments of 325 and 650 mg tablets. A 650 mg tablet of sodium bicarbonate contains 7.7 mEq (7.7 mmol) each of sodium and bicarbonate. Sodium retention associated with sodium bicarbonate can cause volume overload, which can exacerbate hypertension and chronic heart failure. Patient tolerability of sodium bicarbonate is low because of carbon dioxide production in the GI tract that occurs during dissolution.

Solutions that contain sodium citrate/citric acid (Shohl's solution and Bicitra) provide 1 mEq/L (1 mmol/L) each of sodium and bicarbonate. Polycitra is a sodium/potassium citrate solution that provides 2 mEq/L (2 mmol/L) of bicarbonate, but contains 1 mEq/L (1 mmol/L) each of sodium and potassium, which can promote hyperkalemia in patients with severe CKD. The citrate portion of these preparations is metabolized in the liver to bicarbonate, while the citric acid portion is metabolized to CO_2 and water, increasing tolerability compared to sodium bicarbonate. Sodium retention is also decreased with these preparations. However, these products are liquid preparations, which may not be palatable to some patients. Citrate can also promote aluminum toxicity by augmenting aluminum absorption in the GI tract.

When determining the dose of bicarbonate replacement, the goal for therapy is to achieve a normal serum bicarbonate level of 24 mEq/L (24 mmol/L). The dose is usually determined by calculating the base deficit: [0.5 L/kg × (body weight)] × [(normal CO_2) – (measured CO_2)]. Because of the risk of volume overload resulting from the sodium load administered with bicarbonate replacement, the total base deficit should be administered over several days. Once the goal serum bicarbonate level is attained, a maintenance dose of bicarbonate is necessary and should be titrated to maintain serum bicarbonate levels.

Outcome Evaluation

Monitor serum electrolytes and arterial blood gases regularly. Correct metabolic acidosis slowly to prevent the development of metabolic alkalosis or other electrolyte abnormalities.

Other Therapeutic Considerations in CKD

Uremic Bleeding

Uremia can lead to a number of alterations in clotting ability, resulting in hemorrhage. Bleeding complications associated with CKD include ecchymoses, prolonged bleeding from mucous membranes and puncture sites used for blood collection and hemodialysis, GI bleeding, intramuscular bleeding, and others. Most bleeding complications associated with CKD are mild. However, serious bleeding events, including GI bleeds and intracranial hemorrhage, can occur.

Pathophysiology

Uremia alters a number of mechanisms that contribute to bleeding. Platelet function and aggregation is altered through decreased production of thromboxane.[42] Platelet–vessel wall interactions are also altered in patients with uremia because of decreased activity of von Willebrand factor.[42] and are exacerbated by anemia in CKD patients. With a normal RBC count in the plasma, platelets skim the surface of the endothelial tissue in the blood vessels. In patients with anemia, RBC count is decreased and platelets circulate closer to the center of the vessels, which decreases the interaction with the vessel wall. The risk of bleeding is increased in patients receiving hemodialysis. Anticoagulants administered to prevent or treat clotting during hemodialysis or in vascular access sites, including heparin, warfarin, aspirin, and clopidogrel, exacerbate the risk of bleeding in these patients.

Treatment

Nonpharmacologic Therapy The incidence and severity of bleeding associated with uremia has decreased since dialysis has become the mainstay of treatment for ESRD. Dialysis initiation improves platelet function and reduces bleeding time.[42] Improved care of the patient with ESRD, with anemia treatment and improvement in nutritional status, are also likely contributors to decreased uremic bleeding.

Pharmacologic Therapy Treatments used to decrease bleeding time in patients with uremic bleeding include cryoprecipitate, which contains various components important in platelet aggregation and clotting, such as von Willebrand factor and fibrinogen. Cryoprecipitate decreases bleeding time within 1 hour in 50% of patients. However, cost and the risk of infection have limited the use of cryoprecipitate.

Desmopressin (DDAVP) increases the release of factor VIII (von Willebrand factor) from endothelial tissue in the vessel wall. Bleeding time is promptly reduced, within 1 hour of administration, and is sustained for 4 to 8 hours.[42] Doses used for uremic bleeding are 0.3 to 0.4 mcg/kg intravenously over 20 to 30 minutes, 0.3 mcg/kg subcutaneously, or 2 to 3 mcg/kg intranasally. Repeated doses can cause tachyphylaxis by depleting stores of von Willebrand factor. Side effects of DDAVP include flushing, dizziness, and headache.

Estrogens have also been used to decrease bleeding time. The onset of action is slower than that of DDAVP, but more sustained, and depends on the route of administration. Intravenous doses of 0.6 mg/kg per day for 4 to 5 days decreases bleeding time within 6 hours of administration, and produces an effect that lasts up to 2 weeks after stopping therapy. The onset of action with oral doses of 50 mg/kg daily is within 2 days of treatment and is sustained for 4 to 5 days after stopping therapy. Transdermal patches providing 50 to 100 mcg per day have also been shown to be effective in decreasing bleeding time.[42] Side effects of estrogen use include hot flashes, fluid retention, and hypertension.

Pruritus

Pruritus can affect 25% to 86% of patients with advanced stages of CKD, and is not related to the cause of renal failure.[43] Pruritus can be significant and has been linked to mortality in patients receiving hemodialysis.[43]

Pathophysiology

The cause of pruritus is unknown, although several mechanisms have been proposed. Vitamin A is known to accumulate in the skin and serum of patients with CKD, but a definite correlation with pruritus has not been established. Histamine may also play a role in the development of pruritus, which may be linked to mast cell proliferation in patients receiving hemodialysis. Hyperparathyroidism has also been suggested as a contributor to pruritus, despite the fact that serum PTH levels do not correlate with itching. Accumulation of divalent ions, specifically magnesium and aluminum, may also play a role in pruritus in patients with CKD. Other theories that have been proposed include inadequate dialysis, dry skin, peripheral neuropathy, and opiate accumulation.[43]

Treatment

Nonpharmacologic Therapy Pruritus associated with CKD is difficult to alleviate. It is important to evaluate other potential dermatologic causes of pruritus to maximize the potential for relief. Adequate dialysis is generally the first line of treatment in patients with pruritus. However, this has not been shown to decrease the incidence of pruritus significantly. Maintaining proper nutritional intake, especially with regard to dietary phosphorus and protein intake, may lessen the degree or occurrence of pruritus. Patients who do not attain relief from other measures may benefit from ultraviolet B phototherapy.

Pharmacologic Therapy Topical emollients have been used as treatment for pruritus in patients with dry skin, but are often not effective in relieving pruritus associated with CKD. Antihistamines, such as hydroxyzine 25 to 50 mg or diphenhydramine 25 to 50 mg orally or intravenously, are used as

first-line oral agents used to treat pruritus. Cholestyramine has also been used at doses of 5 g twice daily. Oral activated charcoal has also been used in doses of 1 to 1.5 g four times daily with some demonstrated efficacy. Other therapies that are often used in combination with other agents include oral ondansetron or naltrexone and topical capsaicin. Each has been reported to have efficacy in the treatment of pruritus associated with CKD.

Vitamin Replacement

Water-soluble vitamins removed by hemodialysis (HD) contribute to malnutrition and vitamin deficiency syndromes. Patients receiving HD often require replacement of water-soluble vitamins to prevent adverse effects. The vitamins that may require replacement are ascorbic acid, thiamine, biotin, folic acid, riboflavin, and pyridoxine. Patients receiving HD should receive a multivitamin B complex with vitamin C supplement, but should not take supplements that include fat-soluble vitamins, such as vitamins A, E, or K, which can accumulate in patients with renal failure.

RENAL REPLACEMENT THERAPY

Patients who progress to ESRD require renal replacement therapy (RRT). The modalities that are used for RRT are dialysis, including HD and peritoneal dialysis (PD), and kidney transplantation. The United States Renal Data Service (USRDS) reported that the number of patients with ESRD was 452,957, with 102,567 new cases being diagnosed in 2003.[2] The most common form of RRT is dialysis, accounting for 72% of all patients with ESRD. The principles and complications associated with dialysis are discussed below. Chapter 52 discusses the principles of kidney transplantation.

Indications for Dialysis

❾ *Planning for dialysis should begin when creatinine clearance falls* less than *30 mL/minute/1.73 m^2 (stage 4 CKD),*[1] *when progression to ESRD is inevitable, to allow time to educate the patient and family on the treatment modalities and establish the appropriate access for the modality of choice.* Ideally, initiation of dialysis should be done at a point when the patient is ready to undergo treatment, rather than when the patient is in emergent need of dialysis.

Initiation of dialysis is dependent on the patient's clinical status. Symptoms that may indicate the need for dialysis include persistent anorexia, nausea, vomiting, fatigue, and pruritus. Other criteria that indicate the need for dialysis include declining nutritional status, declining serum albumin levels, uncontrolled hypertension, and volume overload, which may manifest as chronic heart failure, and electrolyte abnormalities, particularly hyperkalemia. Blood urea nitrogen (BUN) and serum creatinine (SCr) levels may be used as a guide for the initiation of dialysis, but should not be the absolute indicator. Dialysis is initiated in most patients when the GFR falls below 15 mL/minute/1.73 m^2.[1] Patient should determine which modality of dialysis to use based on their own preferences. Advantages and disadvantages of hemodialysis and peritoneal dialysis are listed in Tables 23–7 and 23–8, respectively.



Patient Encounter, Part 4

The patient presents to clinic several years later and complains that she "feels lousy." She states that she doesn't feel like eating and has lost 20 pounds (9 kg) in the last 6 months.

Current Meds
Furosemide 80 mg orally twice daily
Metolazone 5 mg orally twice daily
Lisinopril 40 mg orally daily
Metoprolol 75 mg orally twice daily
Insulin glargine 30 units subcutaneously at bedtime
Insulin lispro subcutaneously per sliding scale with meals
Darbepoetin 100 mcg subcutaneously weekly
Iron polysaccharide 150 mg orally daily
Sevelamer 800 mg orally three times daily with meals
Calcitriol 0.25 mcg orally daily
Sodium bicarbonate 1300 mg orally three times daily

ROS
Unremarkable

PE
VS: Blood pressure 160/85 mm Hg, pulse 70 beats per minute, temperature 36.8°C (98.2°F), Wt 150 lb (68.2 kg)
Chest: Regular rate and rhythm, normal S_1, S_3 and S_4 both present; slight pericardial friction rub
Exts: 3+ bilateral lower extremity edema which is present half-way up her calf

Labs
Sodium 142 mEq/L (142 mmol/L); potassium 5.8 mEq/L (5.8 mmol/L); chloride 102 mEq/L (102 mmol/L); carbon dioxide 16 mEq/L (16 mmol/L); BUN 85 mg/dL (30.34 mmol/L urea); SCr 9.5 mg/dL (839.8 µmol/L); glucose 112 mg/dL (6.22 mmol/L); calcium 8.2 mg/dL (2.05 mmol/L); phosphate 5.8 mg/dL (1.87 mmol/L); iPTH 438 pg/mL (1.87 ng/L); WBC 5.3 × 10^3 cells/mm^3 (5.3 × 10^9/L); RBC 3.2 × 10^3 cells/mm^3 (3.2 × 10^{12}/L); Hgb 9.8 g/dL (6.08 mmol/L); Hct 29% (0.29); platelets 390 × 10^3 cells/mm^3 (390 × 10^9/L)

- What indications does the patient have for dialysis?
- What alternatives for renal replacement therapy exist for the patient?
- What are the advantages and disadvantages of each modality for renal replacement?

TABLE 23–7. Advantages and Disadvantages of Hemodialysis

Advantages

1. Higher solute clearance allows intermittent treatment.
2. Parameters of adequacy of dialysis are better defined and therefore underdialysis can be detected early.
3. The technique's failure rate is low.
4. Even though intermittent heparinization is required, hemostasis parameters are better corrected with hemodialysis than peritoneal dialysis.
5. In-center hemodialysis enables closer monitoring of the patient.

Disadvantages

1. Requires multiple visits each week to the hemodialysis center, which translates into loss of control by the patient.
2. Dysequilibrium, dialysis, hypotension, and muscle cramps are common. May require months before patient adjusts to hemodialysis.
3. Infections in hemodialysis patients may be related to the choice of membranes, the complement-activating membranes being more deleterious.
4. Vascular access is frequently associated with infection and thrombosis.
5. Decline of residual renal function is more rapid compared to peritoneal dialysis.

From Elwell RJ, Foote EF. Hemodialysis and peritoneal dialysis. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 852, with permission.

TABLE 23–8. Advantages and Disadvantages of Peritoneal Dialysis

Advantages

1. More hemodynamic stability (blood pressure) due to slow ultrafiltration rate.
2. Increased clearance of larger solutes, which may explain good clinical status in spite of lower urea clearance.
3. Better preservation of residual renal function.
4. Convenient intraperitoneal route of administration of drugs such as antibiotics and insulin.
5. Suitable for elderly and very young patients who may not tolerate hemodialysis well.
6. Freedom from the "machine" gives the patient a sense of independence (for continuous ambulatory peritoneal dialysis).
7. Less blood loss and iron deficiency, resulting in easier management of anemia or reduced requirements for erythropoietin and parenteral iron.
8. No systemic heparinization requirement.
9. Subcutaneous versus intravenous erythropoietin or darbepoetin is usual, which may reduce overall doses and be more physiologic.

Disadvantages

1. Protein and amino acid losses through the peritoneum and reduced appetite owing to continuous glucose load and sense of abdominal fullness predispose to malnutrition.
2. Risk of peritonitis.
3. Catheter malfunction, and exit site and tunnel infection.
4. Inadequate ultrafiltration and solute dialysis in patients with a large body size, unless large volumes and frequent exchanges are employed.
5. Patient burnout and high rate of technique failure.
6. Risk of obesity with excessive glucose absorption.
7. Mechanical problems such as hernias, dialysate leaks, hemorrhoids, or back pain may occur.
8. Extensive abdominal surgery may preclude peritoneal dialysis.
9. No convenient access for intravenous iron administration.

From Elwell RJ, Foote EF. Hemodialysis and peritoneal dialysis. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 853, with permission.

The goals of dialysis are to remove toxic metabolites to decrease uremic symptoms, correct electrolyte abnormalities, restore acid-base status, and maintain volume status to ultimately improve quality of life and decrease the morbidity and mortality associated with ESRD.

Hemodialysis

Principles of Hemodialysis

⓾ *Hemodialysis (HD) involves the exposure of blood to a semipermeable membrane (dialyzer) against which a physiologic solution (dialysate) is flowing.* The dialyzer is composed of thousands of capillary fibers made up of the semipermeable membrane, which are enclosed in the dialyzer, to increase the surface area of blood exposure to maximize the efficiency of removing substances. The dialysate is composed of purified water and electrolytes, and is run through the dialyzer countercurrent to the blood on the other side of the semipermeable membrane. The process allows for the removal of several substances from the bloodstream, including water, urea, creatinine, uremic toxins, and drugs. Although the dialysate is not sterilized, the membrane prevents bacteria from entering into the bloodstream. However, if the membrane ruptures during hemodialysis, infection becomes a major concern for the patient.

Three types of membranes used for dialysis are classified by the size of the pores and the ability to remove solutes from the bloodstream. Conventional (standard) membranes have small pores, which limit solute removal to relatively small molecules, such as creatinine and urea. High-efficiency membranes also have small pores, but have a higher surface area that increases removal of small molecules, such as water, urea, and creatinine from the blood. High-flux membranes have larger pores that allow for the removal of high-molecular-weight substances, including some drugs, such as vancomycin.

Three primary processes are utilized for the removal of substances from the blood. Diffusion is the movement of a solute across the dialyzer membrane from an area of higher concentration (usually the blood) to a lower concentration (usually the dialysate). This process is the primary means for small molecules to be removed from the bloodstream, such as electrolytes. At times, solutes can be added to the dialysate that are diffused into the bloodstream. Changing the composition of the dialysate allows for control of the amount of electrolytes

that are being removed. Ultrafiltration is the movement of solvent (plasma water) across the dialyzer membrane by applying hydrostatic or osmotic pressure, and is the primary means for removing water from the bloodstream. Changing the hydrostatic pressure applied to the dialyzer or the osmotic concentration of the dialysate allows for control of the amount of water being removed. Convection is the movement of dissolved solutes across the dialyzer membrane by "dragging" the solutes along a pressure gradient with a fluid transport and is the primary means for larger molecules to be removed from the bloodstream, such as urea. Changing the pore size of the dialyzer membrane alters the efficiency of convection and allows for control of the amount of water removed in relation to the amount of solute being removed.

Vascular Access

Long-term permanent access to the bloodstream is a key component of HD. There are three primary techniques used to obtain permanent vascular access in patients receiving HD. Arteriovenous fistula (AVF) is the preferred access method because it has the longest survival rate and the fewest complications.[44] An AVF is made by creating an anastomosis between an artery and a vein, usually in the forearm of the non-dominant arm. An arteriovenous graft (AVG) results in a similar access site, but uses a synthetic graft, usually made of polytetrafluoroethylene, to connect the artery and vein in the forearm. The advantages of the AVG is that it is able to be used within 2 to 3 weeks, compared to 2 to 3 months for an AVF. However, AVGs are complicated by stenosis, thrombosis, and infections, which lead to a shorter survival time of the graft. Double-lumen venous catheters, placed in the femoral, subclavian, or jugular vein, are often used as temporary access while waiting for the AVF or AVG to mature. The catheters are tunneled beneath the skin to an exit site to reduce the risk of infection. Venous catheters can also be used as permanent access in patients in whom arteriovenous access cannot be established.

Complications of Hemodialysis

Complications associated with HD include hypotension, myalgia, thrombosis, and infection.

Hypotension

Hypotension is the most common complication seen during hemodialysis. It has been reported to occur with approximately 10% to 30% of dialysis sessions, but may be as frequent as 50% of sessions in some patients.[46]

Pathophysiology Hypotension associated with hemodialysis manifests as a symptomatic sudden drop of more than 30 mm Hg in mean arterial or systolic pressure or a systolic pressure drop to less than 90 mm Hg during the dialysis session. The primary cause is fluid removal from the bloodstream. Ultrafiltration removes fluid from the plasma, which promotes redistribution of fluids from extracellular spaces into the plasma. However, decreased serum albumin levels and removal of solutes from the bloodstream decrease the osmotic pressure of the plasma relative to the extracellular spaces, slowing redistribution during hemodialysis.[45] The decreased plasma volume causes hypotension. Other factors that can contribute to hypotension include antihypertensive medications prior to HD, a target dry weight that is too low, diastolic or autonomic dysfunction, low dialysate calcium or sodium, high dialysate temperature, or ingesting meals prior to HD.

Risk factors that may increase the potential for hypotension include elderly age, diabetes, autonomic neuropathy, uremia, and cardiac disease.[46] The symptoms associated with hypotension during dialysis include dizziness, nausea, vomiting, sweating, and chest pain.

Treatment Nonpharmacologic management of acute hypotension that occurs during dialysis involves placing the patient in the Trendelenburg position (with the head lower than the feet) and decreasing the ultrafiltration rate. Pharmacologic management of acute hypotension during dialysis includes administration of normal saline (100 to 200 mL), hypertonic saline (23.4%, 10 to 20 mL), or mannitol (12.5 g) to restore intravascular volume.

Preventive measures for patients who may be prone to hypotension include accurate determination of the "dry weight" and maintaining a constant ultrafiltration rate. Midodrine is an α-adrenergic agonist that is effective in reducing hypotension in patients with autonomic dysfunction that is taken with each dialysis session or as chronic therapy. Midodrine can be administered at doses of 2.5 to 10 mg prior to HD or 5 mg twice daily for chronic hypotension. Side effects of midodrine include pruritus and paresthesias.

Hypotension may be related to alterations in levocarnitine levels during dialysis. Patients who have low levels of levocarnitine may benefit from supplementation. Levocarnitine is administered as doses of 20 mg/kg intravenously at the end of each dialysis session. However, levocarnitine should not be used as a first-line agent for the treatment of hypotension because of the significant cost associated with the treatment. Patients receiving levocarnitine should be evaluated every 3 months for response to therapy.[47] Other preventive measures that have not been well studied include caffeine, sertraline, or fludrocortisone.

Muscle Cramps

Pathophysiology Muscle cramps can occur with up to 20% of dialysis sessions.[48] The cause is often related to excessive ultrafiltration, which causes hypoperfusion of the muscles. Other contributing factors to the development of muscle cramps include hypotension and electrolyte and acid-base imbalances that occur during hemodialysis sessions.

Treatment Nonpharmacologic treatments of muscle cramping that occurs during hemodialysis include decreasing the ultrafiltration rate and accurately determining the "dry weight." Pharmacologic measures include vitamin E, which is administered at doses of 400 IU daily. Other options that are not as well studied include oxazepam and prazosin.

Thrombosis

Thrombosis associated with hemodialysis most commonly occurs in patients with venous catheter access for dialysis and is a common cause of catheter failure. However, thrombosis can occur in synthetic grafts and less frequently in AV fistulas.

Nonpharmacologic management of thrombosis in a hemodialysis catheter involves saline flushes. Smaller clots may be managed by balloon angioplasty to mechanically open the catheter. In severe cases in whom clots cannot be removed by either mechanical or pharmacologic therapy, the catheter may require replacement.

Pharmacologic management of thrombosis includes local administration of thrombolytic agents. Alteplase (2 mg per port) and reteplase (0.5 unit per port) are the two most commonly used agents today. Urokinase has been used in the past, but after its reintroduction to the United States market, the larger dosed vial size makes it less cost effective than the newer agents.

Infection

Infections are an important cause of morbidity and mortality in patients receiving hemodialysis. The cause of infection is usually related to organisms found on the skin, namely *Staphylococcus epidermidis* and *S. aureus*. Other organisms have also been found to cause access-related infections. The greatest risk to patients receiving hemodialysis is the development of bacteremia. As with thrombosis, venous catheters are most commonly infected, followed by synthetic AV grafts, and finally AV fistulas.

Blood cultures should be obtained for any patient receiving hemodialysis who develops a fever. Nonpharmacologic management of infections involves preventive measures with sterile technique, proper disinfection, and minimizing the use and duration of venous catheters for hemodialysis access.

Pharmacologic management of infections should cover the gram-positive organisms that most frequently cause access-related infections. Patients who have positive blood cultures should receive treatment tailored to the organism isolated. Preventive measures for access-related infections include mupirocin at the exit site and povidone-iodine ointment. The recommendations of the NKF for treatment of infections associated with hemodialysis are listed in Table 23–9.

Peritoneal Dialysis

Principles of Peritoneal Dialysis

Peritoneal dialysis (PD) utilizes similar principles as hemodialysis in that blood is exposed to a semipermeable membrane against which a physiologic solution is placed. In the case of PD, however, the semipermeable membrane is the peritoneal membrane, and a sterile dialysate is instilled into the peritoneal cavity. The peritoneal membrane is composed of a continuous single layer of mesothelial cells that covers the abdominal and pelvic walls on one side of the peritoneal cavity, and the visceral organs, including the GI tract, liver, spleen, and diaphragm on the other side. The mesothelial cells are covered by microvilli that increase the surface area of the peritoneal membrane to approximate body surface area (1 to 2 m^2).

TABLE 23–9. Management of Hemodialysis Access Infections

AV fistula	Treat as subacute bacterial endocarditis for 6 weeks Initial antibiotic choice should always cover gram-positive organisms (e.g., vancomycin 20 mg/kg intravenously with serum concentration monitoring or cefazolin 20 mg/kg intravenously 3 times per week) Gram-negative coverage is indicated for patients with diabetes, HIV infection, prosthetic valves, or those receiving immunosuppressive agents (gentamicin 2 mg/kg intravenously with serum concentration monitoring).
Synthetic Grafts (AVG)	
Local infection	Empiric antibiotic coverage for gram-positive, gram-negative, and *Enterococcus* (e.g., gentamicin plus vancomycin, then individualize after culture results become available); continue for 2–4 weeks
Extensive infection	Antibiotics as above plus total resection
Access less than 1 month old	Antibiotics as above plus removal of the graft
Tunneled Cuffed Catheters (Internal Jugular, Subclavian)	
Infection localized to catheter exit site	No drainage: topical antibiotics (e.g., mupirocin ointment) Drainage present: gram-positive coverage (e.g., cefazolin 20 mg/kg IV 3 times per week)
Bacteremia with or without systemic signs or symptoms	Gram-positive coverage as above If stable and asymptomatic, change catheter and provide culture-specific antibiotic coverage for a minimum of 3 weeks.

AV, arteriovenous; HIV, human immunodeficiency virus; IV, intravenous.

Blood vessels that supply the abdominal organs, muscle, and mesentery serve as the blood component of the system.

The gaps between the mesothelial cells allow for large solutes to pass through into the bloodstream. Both the interstitium and endothelial cells of the blood vessels provide resistance to limit the solute size that is removed from the blood. Diffusion is the most important component of solute transport in PD, which is enhanced by the large surface area and volume of dialysate, as well as contact time with the peritoneal membrane. Ultrafiltration is achieved in PD by creating an osmotic pressure gradient between the dialysate and the blood. Traditionally, glucose has been used to create the osmotic gradient, but the solutions are not biocompatible with the peritoneal membrane, resulting in cytotoxicity of the cells. More recently, polymeric glucose derivatives, such as icodextrin, have been used to create a colloid-driven osmosis that results in ultrafiltration and convection of solute removal.

In PD, prewarmed dialysate is instilled into the peritoneal cavity where it "dwells" for a specified length of time (usually one to several hours, depending on the type of PD) to adequately clear metabolic waste products. At the end of the dwell time, the dialysate is drained and replaced with fresh dialysate. The continuous nature of PD provides for a more physiologic removal of waste products from the bloodstream, which mimics endogenous renal function by decreasing the fluctuations seen in serum concentrations of the waste products. Similarly, water is removed at a more constant rate, lessening the fluctuations in intravascular fluid balance and providing for more hemodynamic stability.

There are several types of PD that are used. The most common is continuous ambulatory peritoneal dialysis (CAPD), which requires the patient to exchange 1 to 3 L of dialysate four to six times per day. Exchanges are generally done every 4 to 6 hours throughout the day with a longer dwell time overnight. Automated peritoneal dialysis (APD) procedures involve the use of a cycler machine that performs sequential exchanges overnight while the patient is sleeping. Continuous cycling PD (CCPD) performs three to five exchanges throughout the night. The final exchange remains in the peritoneal cavity to dwell for the duration of the day. Nightly intermittent PD (NIPD) performs six to eight exchanges throughout the night. The final exchange of dialysate is drained in the morning and the peritoneal cavity remains empty throughout the day. Nocturnal tidal PD (NTPD) is similar to NIPD, with the exception that only a portion of the dialysate is exchanged throughout the night. The final exchange is drained in the morning and the peritoneal cavity remains empty throughout the day.

Peritoneal Access

Access to the peritoneal cavity requires placement of an indwelling catheter. There are several types of indwelling catheters available, but all require placement of the distal end into the peritoneal cavity. The central portion of the catheter is generally tunneled under the abdominal wall and subcutaneous tissue where it is held in place by cuffs that provide stability and mechanical support to the catheter. The proximal portion of the catheter exits the abdomen near the umbilicus. Placement and handling of the catheter during PD exchanges requires a sterile environment to minimize the risk of infectious complications.

Complications of Peritoneal Dialysis

Complications associated with PD include mechanical problems related to the PD catheter, metabolic problems associated with the components of the dialysate fluid, damage to the peritoneal membrane, and infections (Table 23–10). Strategies to manage infectious complications of PD are discussed below.

Peritonitis

Peritonitis is a leading cause of morbidity in PD patients, which often leads to loss of the catheter and subsequent change to HD as the treatment modality. However, recent advances with connectors used during instillation and drainage of dialysate and delivery systems have dramatically decreased the incidence of peritonitis. Peritonitis can be caused by chemical irritation or microorganisms.

TABLE 23–10. Common Complications during Peritoneal Dialysis

Mechanical Complications
Kinking in catheter
Catheter migration
Catheter adherence to peritoneal tissue
Excessive movement of catheter at exit site
Peritoneal Damage
Alterations in permeability of the peritoneal membrane
Sclerosis of the peritoneal membrane
Pain
Impingement of the catheter tip on visceral organs
Instillation pain
Rapid inflow of dialysate
Acidic pH of dialysate
Chemical irritation from dialysate additives (e.g., antibiotics)
Low dialysate temperature
Infections
Peritonitis
Exit-site infections
Tunnel infections
Metabolic Complications
Exacerbation of diabetes mellitus from glucose load
Fluid overload
Exacerbation of chronic heart failure
Edema
Pulmonary congestion
Electrolyte abnormalities
Malnutrition
Albumin and amino acid loss
Muscle wasting
Increased adipose tissue
Fibrin formation in dialysate

Pathophysiology Gram-positive organisms, namely *S. epidermidis*, are the most common cause of peritonitis. Other pathologic organisms include *S. aureus*, streptococcal species, enterococcus species, gram-negative organisms including *Escherichia coli* and *Pseudomonas* species, and fungal organisms. Peritonitis should be presumed if cloudy fluid is drained from the peritoneal cavity and the fluid should be evaluated by cultures. Antibiotic treatment should be initiated immediately, until cell counts and cultures prove otherwise.[49] Patients with peritonitis may also complain of abdominal pain, although pain may be absent in some cases.

Treatment The International Society of Peritoneal Dialysis (ISPD) revised the recommendations for the treatment of PD-related infections in 2005.[49] Drug selection for empiric treatment of peritonitis should cover both gram-positive and gram-negative organisms specific to the dialysis center and be based on the protocols and sensitivity patterns of organisms known to cause peritonitis, as well as the history of infections in the patient. First-generation cephalosporins, such as cefazolin, or vancomycin are recommended for empiric coverage of gram-positive organisms. Appropriate coverage for gram-negative organisms includes third- or fourth-generation cephalosporins, such as ceftazidime or cefepime, or aminoglycosides. Alternatives for gram-negative coverage include amikacin and oral fluoroquinolones. An example of an appropriate empiric treatment for peritonitis includes cefazolin in combination with ceftazidime, cefepime, or an aminoglycoside. If the patient has a cephalosporin allergy, vancomycin in combination with an aminoglycoside is an alternative empiric treatment.[49]

The preferred route of administration is intraperitoneal (IP) rather than IV to achieve maximum concentrations at the site of infection. Antibiotics can be administered IP intermittently as a single large dose in one exchange per day or continuously as multiple smaller doses with each exchange. Intermittent administration requires at least 6 hours of dwell time in the peritoneal cavity to allow for adequate systemic absorption and provides adequate levels to cover the 24-hour period. However, continuous administration is better suited for PD modalities that require more frequent exchanges (less than 6-hour dwell time). The reader should refer to the ISPD guidelines for dosing recommendations for IP antibiotics in CAPD and automated PD patients.[49] The dose of the antibiotics should be increased by 25% for patients with residual renal function who are able to produce more than 100 mL urine output per day.

Once the organism has been identified and sensitivities are known, drug selection should be adjusted to reflect the susceptibilities of the organism. Streptococcal, staphylococcal, and enterococcal species sensitive to β-lactam antibiotics should be treated with continuous IP dosing to increase efficacy and minimize resistance.[49] Peritonitis caused by *S. aureus* or *P. aeruginosa* are often associated with catheter-related infections, which are difficult to treat and often require removal of the catheter. Rifampin 600 mg orally daily (in a single or divided dose) may be added to IP vancomycin for the treatment of methicillin-resistant *S. aureus* (MRSA), but should be limited to duration of 1 week to minimize the development of resistance. Two antibiotics are required for treatment of *P. aeruginosa* peritonitis.[49] If multiple organisms are cultured, treatment should cover all of the organisms, including anaerobic organisms, and the patient should be evaluated for other intra-abdominal pathologies.[49]

Peritonitis caused by fungal organisms is associated with mortality in 25% of patients,[49] which can be reduced by removing the catheter after fungal organisms are identified. Empiric treatment should include amphotericin B and flucytosine.[49] Although amphotericin penetration into the peritoneal cavity is poor with IV administration, IP administration is associated with chemical irritation and pain. Fluconazole, voriconazole, or caspofungin may be suitable alternatives, depending on culture results.

Catheter-Related Infections

Catheter-related infections generally occur at the exit site or the portion of the catheter that is tunneled in the subcutaneous tissue. Previous infections increase the risk and incidence of catheter-related infections.

Pathophysiology The major pathologic organisms responsible for causing catheter-related infections are *S. aureus* and *P. aeruginosa*. These organisms also cause the most serious catheter-related infections. *S. epidermidis* is found in less than 20% of catheter-related infections. Other organisms include diphtheroids, anaerobic bacteria, *Legionella*, and fungi.[49]

Exit-site infections present with purulent drainage at the site. Erythema may or may not be present with an exit-site infection. Tunnel infections are generally an extension of the exit-site infection and rarely occur alone. Symptoms of a tunnel infection may include tenderness, edema, and erythema over the tunnel pathway, but are often asymptomatic. Ultrasound can be used to detect tunnel infections in asymptomatic patients. Exit-site infections caused by *S. aureus* and *P. aeruginosa* often spread to tunnel infections and are the most common causes of catheter-infection–related peritonitis.

Treatment Exit-site infections may be treated immediately with empiric coverage, or treatment may be delayed until cultures return. Empiric treatment of catheter-related infections should cover *S. aureus*. Coverage for *P. aeruginosa* should also be included if the patient has a history of infections with this organism.[49] Cultures and sensitivity testing are particularly important in tailoring antibiotic therapy for catheter-related infections to ensure eradication of the organism and prevent recurrence or related peritonitis.

Less severe infections may be treated with topical antibiotic cream, although this practice is controversial. Oral antibiotics

are also effective for treatment of catheter-related infections. Empiric or routine use of vancomycin for gram-positive infections should be avoided unless the infection is caused by MRSA. Rifampin may be added to therapy for severe infections or slowly-resolving *S. aureus* infections, but monotherapy is not recommended.[49] Oral fluoroquinolones are used as first-line agents to treat *P. aeruginosa*, which can be difficult to treat and require prolonged treatment. If the infection is slow to resolve or if it recurs, IP ceftazidime or a second agent should be added.[49] Treatment of catheter-related infections should be continued until the exit site appears normal with no erythema or drainage. Generally, at least 2 weeks of therapy or longer are required to ensure complete eradication of the organism and prevent future recurrence, which is common with *S. aureus* and *P. aeruginosa*. Infections that do not resolve may require replacement of the PD catheter. Catheter-related infections that present in conjunction with or progress to peritonitis with the same organism require removal of the PD catheter until the peritonitis is resolved.[49]

Prophylaxis of Peritonitis and Catheter-Related Infections

Prevention of peritonitis and catheter-related infections starts when the catheter is placed. The exit site should be properly cared for until it is well healed before it can be used for PD. Patients should receive proper instructions for care of the catheter during this time period, which can last up to 2 weeks. Patients should also be instructed on the proper techniques to use for dialysate exchanges to minimize the risk of infections during exchanges, which is the most common cause of peritonitis.

Intranasal *S. aureus* increases the risk of *S. aureus* exit-site infections, tunnel infections, peritonitis, and subsequent catheter loss.[49] Several measures have been used to decrease the risk of peritonitis caused by *S. aureus*, including mupirocin cream applied daily around the exit site, intranasal mupirocin cream twice daily for 5 days each month, or rifampin 300 mg orally twice daily for 5 days, repeated every 3 months.[49] Mupirocin use is preferred over rifampin to prevent the development of resistance to rifampin, although mupirocin resistance has also been reported.[49] Other measures that have been used to decrease both *S. aureus* and *P. aeruginosa* infections include gentamicin cream applied twice daily and ciprofloxacin otic solution applied daily to the exit site.[49]

Outcome Evaluation

Clinical improvement should be seen within 48 hours of initiating treatment for peritonitis or catheter-related infections. Perform daily inspections of peritoneal fluid or the exit site to determine clinical improvement. Peritoneal fluid should become clear with improvement of peritonitis and erythema and discharge should remit with improvement of catheter-related infections. If no improvement is seen within 48 hours, obtain additional cultures and cell counts to determine the appropriate alterations in therapy.



Patient Care and Monitoring

1. Assess the patient to determine if the patient should be evaluated for CKD. Does the patient have any risk factors for CKD?
2. Review any available laboratory data to determine the staging of CKD.
3. Obtain a thorough medical and medication history from the patient. Does the patient have any concomitant diseases, such as diabetes or hypertension, that should be treated to prevent the progression of CKD?
4. Determine if an ACE-I or ARB is appropriate for the patient. Does the patient have proteinuria?
5. Develop a plan to assess and optimize treatment of CKD.
6. Determine if the patient requires medical treatment for electrolyte imbalances. Does the patient have edema? Does the patient have an arrhythmia?
7. Educate the patient on dietary changes to manage electrolyte imbalances associated with CKD.
8. Assess the patient for the presence of anemia. Do the laboratory tests suggest the patient requires medical treatment?
9. Develop a plan to assess and optimize treatment for anemia.
10. Determine if the patient requires medical intervention to prevent the development of or treatment for secondary hyperparathyroidism.
11. Develop a plan to assess and optimize treatment for secondary hyperparathyroidism.
12. Establish if the patient requires renal replacement therapy.
13. Evaluate the patient for complications associated with dialysis. Does the patient develop hypotension or cramps during hemodialysis? Does the patient have symptoms consistent with peritonitis or a catheter infection?
14. Develop a plan to assess and optimize treatment for complications associated with dialysis.
15. Stress the importance of adherence with the treatments for CKD and associated complications, including lifestyle modifications and medications. Recommend a therapeutic regimen that is easy for the patient to accomplish.
16. Provide patient education with regard to CKD and the associated complications, lifestyle modifications, and drug therapy:

    - What causes CKD and what things to avoid.
    - Possible complications of CKD and symptoms associated with the complications.
    - When to take medications.
    - What potential adverse effects may occur.
    - Which drugs may interact with therapy.
    - Warning signs to report to the physician (edema, irregular heart beat, fatigue, unusual bleeding).

ABBREVIATIONS

ACE-I:	angiotensin-converting enzyme inhibitor
AGE:	advanced glycosylation end-product
APD:	automated peritoneal dialysis
ARB:	angiotensin receptor blocker
ARF:	acute renal failure
AVF:	arteriovenous fistula
AVG:	arteriovenous graft
BUN:	blood urea nitrogen
Ca-P:	calcium-phosphorus product
CAPD:	continuous ambulatory peritoneal dialysis
CCPD:	continuous cycling peritoneal dialysis
CHD:	coronary heart disease
CKD:	chronic kidney disease
CVD:	cardiovascular disease
DDAVP:	desmopressin
DM:	diabetes mellitus
ECG:	electrocardiogram
EPO:	erythropoietin
ESA:	erythropoiesis-stimulating agent
ESRD:	end-stage renal disease
FE_K:	fractional excretion of potassium
FE_{Na}:	fractional excretion of sodium
GFR:	glomerular filtration rate
GI:	gastrointestinal
Hb_{A1c}:	$hemoglobin_{A1c}$
Hct:	hematocrit
HD:	hemodialysis
HDL-C:	high-density lipoprotein cholesterol
Hgb:	hemoglobin
HMG-CoA:	3-hydroxy-3-methylglutaryl coenzyme A
IP:	intraperitoneal
iPTH:	intact parathyroid hormone
ISPD:	International Society of Peritoneal Dialysis
IV:	intravenous
LDL-C:	low-density lipoprotein cholesterol
LVH:	left ventricular hypertrophy
MCHC:	mean corpuscular hemoglobin concentration
MCV:	mean corpuscular volume
MDRD:	Modification of Diet in Renal Disease (study)
MRSA:	methicillin-resistant *Staphylococcus aureus*
NIPD:	nightly intermittent peritoneal dialysis
NKF:	National Kidney Foundation
NKF-DOQI:	National Kidney Foundation-Dialysis Outcome Quality Initiative
NTPD:	nocturnal tidal peritoneal dialysis
PD:	peritoneal dialysis
PTH:	parathyroid hormone
RBC:	red blood cell
ROD:	renal osteodystrophy
RRT:	renal replacement therapy
SC:	subcutaneous
SCr:	serum creatinine
sHPT:	secondary hyperparathyroidism
SPS:	sodium polystyrene sulfonate
TC:	total cholesterol
TIBC:	total iron binding capacity
TSAT:	transferrin saturation
USRDS:	United States Renal Data Service

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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24 Fluids and Electrolytes

Mark A. Malesker and Lee E. Morrow



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Estimate the volumes of various body fluid compartments.
2. Calculate the daily maintenance fluid requirement for patients given their age, weight, and gender.
3. Differentiate among currently available fluids for volume resuscitation.
4. Identify the electrolytes primarily found in the extracellular and intracellular fluid compartments.
5. Describe the unique relationship between serum sodium concentration and total body water.
6. Review the etiology, clinical presentation, and management for disorders of sodium, potassium, calcium, phosphorus, and magnesium.

Key Concepts

❶ Total body water (TBW) is approximately 50% of lean body weight in the normal female and 60% of lean body weight in males. TBW is comprised of the intracellular fluid (two-thirds of TBW) and the extracellular fluid (one-third of TBW). The extracellular fluid is made up of two major fluid subcompartments: the interstitial space and the intravascular space.

❷ Therapeutic fluids include crystalloid and colloid solutions. The most commonly used crystalloids include normal saline, hypertonic saline, and lactated Ringer's solution. Examples of colloids include albumin, the dextrans, hetastarch, and fresh frozen plasma.

❸ The calculated serum osmolality helps determine deviations in TBW content.

❹ Hyponatremia is a very common finding in hospitalized patients and is defined as a serum sodium level below 136 mEq/L (136 mmol/L).

❺ Intravenous potassium infusions running at rates of greater than 10 mEq/hour require cardiac monitoring.

❻ Calcium gluconate is the preferred peripherally infused calcium supplement because it is less irritating to the veins. Calcium chloride must be infused via a central line.

❼ In the critical care setting, hypophosphatemia can result in impaired diaphragmatic contractility and acute respiratory failure.

❽ Concentrated electrolytes (potassium chloride, potassium phosphate, and sodium chloride greater than 0.9%) should not be stored in patient care areas as a patient safety measure.

❾ Serum magnesium levels do not correlate well with total body magnesium stores. For this reason, magnesium supplementation is often given empirically to critically ill patients.

BODY FLUID COMPARTMENTS

A thorough understanding of the fundamentals of fluid and electrolyte homeostasis is essential given the frequency with which clinical disturbances are seen and the profound effects these disturbances can have on various aspects of patient care. However, the interplay of body fluids, serum electrolytes, and clinical monitoring is complex, and a thorough command of these issues is a challenging task even for advanced practitioners.[1] Practitioners must be familiar with the key concepts of body compartment volumes, calculation of daily fluid requirements, and the various types of fluid available for replacement. The management of disorders of sodium, potassium, calcium, phosphorus, and magnesium integrates these concepts with issues of dose recognition and patient safety.

The most fundamental concept to grasp is an assessment of total body water (TBW), which is directly related to body

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weight. ❶ *TBW constitutes approximately 50% of lean body weight in healthy females and 60% of lean body weight in males.* The percentage of TBW decreases as body fat increases and/or with age (75% to 85% of body weight is water for newborns). Unless the patient is obese (body weight greater than 120% of ideal body weight), clinicians typically use a patient's actual body weight when calculating TBW.[2] In this instance, it is customary to estimate TBW using lean body weight as calculated by the Devine-Devine method: males' lean body weight = 50 kg + [2.3 kg/inch × (height in inches – 60)] and females' lean body weight = 45.5 kg + [2.3 kg/inch × (height in inches – 60)].[3–5] Note that 1 kg is equivalent to 2.2 pounds and 1 inch is equivalent to 2.54 cm. One liter of water weighs 1 kg (2.2 lb).

The intracellular fluid (ICF) represents the water contained within cells and is rich in electrolytes such as potassium, magnesium, phosphates, and proteins. ❶ *The ICF is approximately two-thirds of TBW regardless of gender.* For a 70-kg man, this would mean that the TBW is 42 L and the ICF is approximately 28 L. For a 70-kg woman, these values would be 35 L and 24 L, respectively. Note that ICF represents approximately 40% of total body weight in men and approximately 33% of total body weight in women.

The extracellular fluid (ECF) is the fluid outside the cell and is rich in sodium, chloride, and bicarbonate. ❶ *The ECF is approximately one-third of TBW (14 L in a 70-kg man or 12 L in a 70-kg woman) and is subdivided into two compartments: the interstitial fluid and the intravascular fluid.* The interstitial fluid (also known as lymphatic fluid) represents the fluid occupying the spaces between cells, and is about 25% of TBW (10.5 L in a 70-kg man or 8.8 L in a 70-kg woman). The intravascular fluid (also known as plasma) represents the fluid within the blood vessels and is about 8% of TBW (3.4 L in a 70-kg man or 2.8 L in a 70-kg woman). The ECF is approximately one-third of TBW or 14 L in a 70-kg male. Because the exact percentages are cumbersome to recall, many clinicians accept that the ECF represents roughly 20% of body weight (regardless of gender) with 15% in the interstitial space and 5% in the intravascular space.[6] Note that serum electrolytes are routinely measured from the ECF.

The transcellular fluid includes the viscous components of the peritoneum, pleural space, and pericardium, as well as the cerebrospinal fluid, joint space fluid, and the gastrointestinal (GI) digestive juices. Although the transcellular fluid normally accounts for about 1% of TBW, this amount can increase significantly during various illnesses favoring fluid collection in one of these spaces (e.g., pleural effusions or ascites in the peritoneum). The accumulation of fluid in the transcellular space is often referred to as "third spacing." To review the calculations of the body fluid compartments in a representative patient, see Patient Encounter 1.

To maintain fluid balance, the total amount of fluid gained throughout the day (input, or "ins") must equal the total amount of fluid lost (output, or "outs"). Although most forms of the body's input and output can be measured, several cannot. For a normal adult on an average diet, ingested fluids are easily measured and average 1400 mL per day. Other fluid inputs, such as those from ingested foods and the water by-product of oxidation, are not directly measurable. Fluid outputs such as urinary and stool losses are also easily measured and are referred to as sensible losses. Other sources of fluid loss, such as evaporation of fluid through the skin and/or lungs, are not readily measured and are called insensible losses. Table 24–1 shows the estimated ins and outs (I&Os) for a healthy 150-lb (68-kg) man.[6] The measurable ins and outs are routinely measured in hospitalized patients and are used to estimate total fluid balance for each 24-hour period. It is important to realize that in hospitalized patients, multiple other forms of fluid loss must be considered. These include losses from enteric suctioning [most commonly, nasogastric (NG) tubes], from surgical drains (e.g., chest tubes, nephrostomy tubes, and pancreatic drains), via fistulous tracts, and enhanced evaporative losses (burns and fever).

ECF depletion tends to occur acutely. In this setting, rapid and aggressive fluid replacement is required to maintain adequate organ perfusion. Because ECF depletion is generally due to the loss of isotonic fluid (proportional losses of sodium and water), major disturbances of plasma **osmolality**



Patient Encounter 1, Body Fluid Compartments

Calculate the TBW, ICF, and ECF in a 70-kg male.
TBW = 0.5 × body weight (kg) for females and 0.6 × body weight (kg) for males
ICF = $^2/_3$ TBW
ECF = $^1/_3$ TBW

Example
TBW = 0.6 × 70 kg = 42 L
ICF = $^2/_3$ TBW = 0.67 × 42 L = 28 L
ECF = $^1/_3$ TBW = .33 × 42 L = 14 L
Interstitial fluid = $^3/_4$ ECF or 25% TBW = .25 × 42 L = 11 L
Plasma fluid = $^1/_4$ ECF or 8% TBW = .08 × 42 L = 3 L
TBW, total body water; ICF, intracellular fluid; ECF, extracellular fluid.

TABLE 24–1. Ins and Outs for a Healthy 150-lb (68-kg) Man

Input	mL/day	Output	mL/day
Ingested fluid[a]	1400	Urine[a]	1500
Fluid in food	850	Skin losses	500
Water of oxidation	350	Respiratory tract losses	400
		Stool	200
Total	**2600**	**Total**	**2600**

[a]Readily quantifiable.

are not common. ECF depletion manifests clinically as signs and symptoms associated with decreased tissue perfusion: dizziness, orthostasis, tachycardia, decreased urine output, increased hematocrit, decreased central venous pressure, and/or hypovolemic shock. Common causes of ECF depletion include external fluid losses (burns, hemorrhage, diuresis, GI losses, and adrenal insufficiency) and third-spacing of fluids (septic shock, anaphylactic shock, or abdominal ascites).

TBW depletion (often referred to as "dehydration") is typically a more gradual, chronic problem compared to ECF depletion. Because TBW depletion represents a loss of hypotonic fluid (proportionally more water is lost than sodium) from all body compartments, a primary disturbance of osmolality is usually seen. The signs and symptoms of TBW depletion include CNS disturbances (mental status changes, seizures, and coma), excessive thirst, dry mucous membranes, decreased skin turgor, elevated serum sodium, increased plasma osmolality, concentrated urine, and acute weight loss. Common causes of TBW depletion include insufficient oral intake, excessive insensible losses, diabetes insipidus, excessive osmotic diuresis, and impaired renal concentrating mechanisms. Long-term care residents are frequently admitted to the acute care hospital with TBW depletion secondary to lack of adequate oral intake, often with concurrent excessive insensible losses.

The volume of fluid required to correct TBW depletion equals the basal fluid requirement plus ongoing exceptional losses plus the fluid deficit. Basal daily fluid requirements are calculated using the formulas in Table 24–2. For an adult, this represents 1500 mL for the first 20 kg of body weight plus 20 mL for each additional kg. The volume of replacement fluids required for a given patient (the fluid deficit) can be estimated by the acute weight change in the patient (1 kg = 1 L of fluid). Because the precise weight change is not typically known, it is often calculated as follows: fluid deficit = normal TBW – present TBW. Normal TBW is estimated based on the patient's height using the formulas in Table 24–2, and the present TBW is estimated based on the patient's current body weight.

Once TBW has been restored, the volume of "maintenance" fluid equals the basal fluid requirement plus ongoing exceptional losses. If the pathophysiologic process leading to TBW depletion has not been identified and corrected (or accounted for in the calculation of maintenance fluid requirements), TBW depletion will quickly recur. To review the concepts involved in the calculation of replacement fluids for a representative patient (see Patient Encounter 2).

TABLE 24–2. Useful Calculations for the Estimate of Patient Maintenance Fluid Requirements

Neonate (1–10 kg) = 100 mL/kg
Child (10–20 kg) = 1000 mL + 50 mL for each kg greater than 10
Adult (greater than 20 kg) = 1500 mL + 20 mL for each kg greater than 20



Patient Encounter 2, Fluid Requirements

Calculate the daily fluid requirement for a 70-kg adult male. Use the equation from Table 24–2: Adult fluid requirement = 1500 mL + 20 mL for each kg greater than 20 The fluid requirements for a 70-kg adult would be 1500 mL + 20 mL (50 kg) = 2500 mL

Therapeutic Fluids

❷ *Therapeutic intravenous (IV) fluids include crystalloid solutions, colloidal solutions, and oxygen-carrying resuscitation solutions.* Crystalloids are composed of water and electrolytes, all of which pass freely through semipermeable membranes and remain in the intravascular space for shorter periods of time. As such, these solutions are very useful for correcting electrolyte imbalances but result in smaller hemodynamic changes for a given unit of volume.

Fluids can be classified further according to their tonicity. Isotonic solutions (i.e., normal saline or 0.9% sodium chloride [NaCl]) have a tonicity equal to that of the ICF (approximately 310 mEq/L or 310 mmol/L) and do not shift the distribution of water between the ECF and the ICF. Because hypertonic solutions (i.e., hypertonic saline or 3% NaCl) have greater tonicity than the ICF (greater than 376 mEq/L or 376 mmol/L), they draw water from the ICF into the ECF. In contrast, hypotonic solutions (i.e., 0.45% NaCl) have less tonicity than the ICF (less than 250 mEq/L or 250 mmol/L) leading to an osmotic pressure gradient that pulls water from the ECF into the ICF. The tonicity, electrolyte content, and glucose content of selected fluids are shown in Table 24–3.

The tonicity of crystalloid solutions is directly related to their sodium concentration. The most commonly used crystalloids include normal saline, hypertonic saline, and lactated Ringer's solution. Excessive administration of any fluid replacement therapy, regardless of tonicity, can lead to fluid overload, particularly in patients with cardiac or renal insufficiency.

Normal Saline (0.9% NaCl)

Normal saline is an isotonic fluid composed of water, sodium, and chloride. It provides primarily ECF replacement and can be used for virtually any cause of TBW depletion. Common uses of normal saline include: perioperative fluid administration; volume resuscitation of shock, hemorrhage, or burn patients; fluid challenges in hypotensive or oliguric patients; and hyponatremia.

Half-Normal Saline (0.45% NaCl)

Half-normal saline is a hypotonic fluid that provides free water in relative excess when compared to the sodium concentration. This crystalloid is typically used to treat patients

TABLE 24–3. Electrolyte and Dextrose Content of Selected Crystalloid Fluids

IV Solution	Osmolarity (mOsm)	Dextrose (g/L) (mmol/L)	Sodium (mEq/L) (mmol/L)	Potassium (mEq/L) (mmol/L)	Calcium (mEq/L) (mmol/L)	Chloride (mEq/L) (mmol/L)	Lactate (mEq/L) (mmol/L)
5% Dextrose	250	50 / 2.78					
10% Dextrose	505	100 / 5.55					
0.9% NaCl	308		154			154	
0.45% NaCl	154		77			77	
3% NaCl	1025		513			513	
D5% and 0.45% NaCl	405	50 / 2.78	77			77	
D5% and 0.2% NaCl	329	50 / 2.78	34			34	
Ringer's injection	310		147	4	5 / 2.5	156	
Lactated Ringer's	274		130	4	3 / 1.5	109	28
Lactated Ringer's and D5%	525	50 / 2.78	130	4	5 / 2.5	109	28

D, dextrose; NaCl, sodium chloride.

who are hypertonic with primary depletion of the ECF. Because half-normal saline is hypotonic, serum sodium must be closely monitored during administration.

Hypertonic Saline (3% NaCl)

Hypertonic saline is obviously hypertonic and provides a significant sodium load to the intravascular space. This solution is utilized very infrequently given the potential to cause significant shifts in the water balance between the ECF and the ICF. It is typically considered to treat patients with severe hyponatremia who have symptoms attributable to low serum sodium.

Ringer's Lactate

This isotonic volume expander contains sodium, potassium, chloride, and lactate that approximates the fluid and electrolyte composition of the blood. Ringer's lactate (also known as "lactated Ringer's" or LR) provides ECF replacement and is most often used in the perioperative setting, and for patients with lower GI fluid losses, burns, or dehydration. The lactate component of LR works as a buffer to increase the pH. Large volumes of LR may cause metabolic alkalosis. Because patients with significant liver disease are unable to metabolize lactate sufficiently, Ringer's lactate administration in this population may lead to accumulation of lactate with iatrogenic lactic acidosis. The lactate is not metabolized to bicarbonate in the presence of liver disease and lactic acid can result.

5% Dextrose in Water (D5W)

D5W is a solution of free water and dextrose that provides a modest amount of calories but no electrolytes. Although it is technically isotonic, it acts as a hypotonic solution in the body. It is commonly used to treat severe hypernatremia. D5W is used in small volumes (100 mL) to dilute many IV medications or at a low infusion rate (10 to 15 mL/hour) to "keep the vein open" (KVO) for IV medications.

Colloids do not dissolve into a true solution, and therefore do not pass readily across semipermeable membranes. As such, colloids effectively remain in the intravascular space and increase the oncotic pressure of the plasma. This effectively shifts fluid from the interstitial compartment to the plasma compartment. In clinical practice, these theoretical benefits are generally short lived and for most patients there is little therapeutic advantage of colloids over crystalloids or vice-versa. Examples of colloids include 5% albumin, 25% albumin, the dextrans, hetastarch, and fresh frozen plasma. Note that each of these agents contains a substance (proteins and complex sugars) that will ultimately be metabolized. When this ultimately occurs, the oncotic agent will be lost and only the remaining hypotonic fluid delivery agent will remain. As such, use of large volumes of colloidal agents is more likely to induce fluid overload compared to crystalloids. Although smaller volumes of colloids have equal efficacy as larger volumes of crystalloids, they generally must be infused more slowly. Often the net result is that the time to clinical benefit is the same regardless of which class of fluid is utilized. For example, 500 mL of normal saline is required to increase the systolic blood pressure to the same degree as seen with approximately 250 mL of albumin; however, the normal saline can be administered twice as fast.

Albumin

Albumin is a protein derived from fractionating human plasma. Because albumin infusion is expensive and may be associated with adverse events, it should be used for acute

volume expansion and *not* as a supplemental source of protein calories. Historically, albumin was used indiscriminately in the intensive care unit until anecdotal publications suggested that albumin may cause immunosuppression. However, the recently completed Safety After Fifty Evaluation (SAFE) trial randomized nearly 7000 hypovolemic patients to either albumin or normal saline therapy and found that the mortality for those who received albumin was the same as for those who received normal saline.[7] This finding confirmed the results of several previous reviews and meta-analyses of studies using human albumin versus normal saline therapy for resuscitation of critically ill patients.[8–10] Albumin combined with furosemide has been demonstrated to improve fluid balance, oxygenation, and hemodynamics in the subset of patients with acute lung injury who have low serum protein.[11]

While albumin is the most commonly used colloid, the other products are not without their own risks and benefits. Hetastarch (various manufacturers) contains 6% starch and 0.9% sodium chloride. This product has no oxygen-carrying capacity and is administered intravenously as a plasma expander. Limitations of this product include acquisition cost, hypersensitivity reactions, and bleeding. Dosing should be reduced in the presence of renal dysfunction. Low-molecular-weight dextran (various manufacturers) and high-molecular-weight dextran (various manufacturers) are polysaccharide plasma expanders. Anaphylactic reactions and prolonged bleeding times have historically limited the use of these products. Fresh frozen plasma (FFP) has been used in cases of excessive blood loss (surgery or trauma) and to prevent bleeding in the presence of abnormal coagulation studies. Fresh frozen plasma is now rarely used for volume expansion. Risks of fresh frozen plasma include anaphylaxis, the potential for viral transmission through plasma, hepatitis, and an increased nosocomial infection rate in the intensive care setting.

Fluid Management Strategies

Classic indications for IV fluid include maintenance of blood pressure, restoring the ICF volume, replacing ongoing renal or insensible losses when oral intake is inadequate, and the need for glucose as a fuel for the brain.[12] Although large volumes of fluid are given during the resuscitation of most trauma patients, a recent analysis reported uncertainty about the use of early large-volume fluid replacement in patients with active bleeding, calling into question our understanding of the need for fluids in various patient populations.[13]

When determining the appropriate fluid to be utilized, it is important to first determine the type of fluid problem (TBW versus ECF depletion), and start therapy accordingly. For patients demonstrating signs of impaired tissue perfusion, the immediate therapeutic goal is to increase the intravascular volume and restore tissue perfusion. The standard therapy is normal saline given at 150 to 500 mL/hour until perfusion is optimized. Although LR is a therapeutic alternative, lactic acidosis may arise with massive or prolonged infusions. In severe cases, a colloid or blood product may be indicated to increase oncotic pressure within the vascular space. Once isovolemia is achieved, patients may be switched to a more hypotonic solution (0.45% NaCl) at a rate that delivers estimated daily needs.

The clinical scenario and the severity of the volume abnormality dictate monitoring parameters during fluid replacement therapy. These may include a subjective sense of thirst, mental status, skin turgor, orthostatic vital signs, pulse rate, weight changes, blood chemistries, fluid input and output, central venous pressure, pulmonary capillary wedge pressure, and cardiac output. Fluid replacement requires particular caution in patient populations at risk of fluid overload, such as those with renal failure, cardiac failure, hepatic failure, or the elderly. Other complications of IV fluid therapy include infiltration, infection, phlebitis, thrombophlebitis, and extravasation.

In summary, the settings in which fluid replacement is used are: hypovolemic patients (e.g., sepsis or pneumonia); hypervolemic patients [e.g., congestive heart failure (CHF), cirrhosis, or renal failure]; euvolemic patients who are unable to take oral fluids in proportion to insensible losses (e.g., the perioperative period); and patients with electrolyte abnormalities (see below).

ELECTROLYTES

Normally, the number of anions and cations in each fluid compartment are equal. Cell membranes play the critical role of maintaining distinct ICF and ECF spaces which are biochemically distinct. Serum electrolyte concentrations reflect the stores of ECF electrolytes rather than that of ICF electrolytes. Table 24–4 lists the chief cations and anions along with their normal concentrations in the ECF and ICF. The principal cations are sodium, potassium, calcium, and magnesium, while the key anions are chloride, bicarbonate, and phosphate. In the ECF, sodium is the most common cation and chloride is the most abundant anion; while in the ICF, potassium is the primary cation and phosphate is the main anion. Normal serum electrolyte values are listed in Table 24–5.

Osmolality is a measure of the number of osmotically active particles per unit of solution, independent of the weight or nature of the particle. Equimolar concentrations of all substances in the undissociated state exert the same osmotic pressure. Although the normal serum osmolality is 280 to 300 mOsm/kg (280 to 300 mmol/kg), multiple scenarios exist where this value becomes markedly abnormal. ❸ *The calculated serum osmolality helps determine deviations in TBW content.* As such, it is often useful to calculate the serum osmolality as follows:

$$\text{Serum osmolality (mOsm/L)} = 2\,[Na^+] + [\text{glucose (mg/dL)}]/18 + [\text{blood urea nitrogen}]/2.8$$

TABLE 24–4. Normal Cation and Anion Concentrations in the ECF and ICF

ECF			ICF	
Ion Species	Plasma (mEq/L)	Interstitial Fluid (mEq/L)	Ion Species	mEq/L
Cations			**Cations**	
Na^+	142	144	K^+	135
K^+	4	4	Mg^{2+}	43
Ca^{2+}	5	2.5		
Mg^{2+}	3	1.5		
Total	154	152	Total	178
Anions			**Anions**	
Cl^-	103	114	$PO4^{2-}$	90
HCO_3^-	27	30	Protein	70
PO_4^{2-}	2	2	$SO4^{2-}$	18
SO_4^{2-}	1	1		
Organic acid	5	5		
Protein	16	0		
Total	154	152	Total	178

ECF, extracellular fluid; ICF, intracellular fluid.

Note: For glucose, multiply by a factor of 0.055 to convert conventional glucose units (mg/dL) to SI glucose units (mmol/L).

Because the body regulates water to maintain osmolality, deviations in serum osmolality are used to estimate TBW stores. Water moves freely across all cell membranes, making serum osmolality an accurate reflection of the osmolality within all body compartments. An increase in osmolality is equated with a loss of water greater than the loss of solute (TBW depletion). A decrease in serum osmolality is seen when water is retained in excess of solute (congestive heart failure or hepatic cirrhosis). The difference between the measured serum osmolality and the calculated serum osmolality, using the equation above, is referred to as the **osmolar gap.** Under normal circumstances the osmolar gap should be 10 mOsm/L or less. An increased osmolar gap suggests the presence of a small, osmotically active agent and is most commonly seen with the ingestion of alcohols (ethanol, methanol, ethylene glycol, or isopropyl alcohol) or during mannitol therapy. Patient Encounter 3 illustrates the utility of serum osmolality in a clinical setting.

Many of the electrolyte disturbances discussed in the remainder of this chapter represent medical emergencies that call for aggressive interventions including the use of concentrated electrolytes. However, these solutions are a frequent source of medical errors with significant potential for patient harm. *As such, the 2005 National Patient Safety Goals published by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) recommends that concentrated electrolyte solutions (potassium chloride, potassium phosphate, and sodium chloride greater than 0.9%) be removed from patient care areas.* In addition, JCAHO recommends standardizing and limiting the number of drug concentrations available in each institution so as to further reduce the risk of medication errors and improve outcomes.[14]

TABLE 24–5. Normal Ranges for Serum Electrolyte Concentrations

Sodium	136–145 mEq/L or 136–145 mmol/L
Potassium	3.5–5.0 mEq/L or 3.5–5.0 mmol/L
Chloride	98–106 mEq/L or 98–106 mmol/L
Bicarbonate	21–30 mEq/L or 21–30 mmol/L
Magnesium	1.4–1.8 mEq/L or 0.7–0.9 mmol/L
Calcium	
Total	4.4–5.2 mEq/L (9–10.5 mg/dL) or 2.25–2.5 mmol/L
Ionized	2.2–2.8 mEq/L (4.5–5.6 mg/dL) or 1.1–1.4 mmol/L
Phosphorus	3–4.5 mg/dL (1.0–1.4 mmol/L)



Patient Encounter 3, Calculate the Plasma Osmolality

A 50-year-old homeless man is brought to the emergency department staggering and smelling like beer. Rapid respiration, tachycardia, and a BP of 90/60 mm Hg were noted. The sodium is 142 mEq/L (142 mmol/L), potassium 3.6 mEq/L (3.6 mmol/L), chloride 100 mEq/L (100 mmol/L), bicarbonate 12 mEq/L (12 mmol/L), glucose 180 mg/dL (9.99 mmol/L), and BUN 28 mg/dL (9.99 mol/L). The measured osmolarity is 360 mOsm/L.

Calculate the osmolality.

$(2 \times Na) + (glucose/18) + (BUN/2.8) = (2 \times 142) + (180/18) + (28/2.8) = 304$ mOsm/L

Calculate the osmolar gap.

360 – 304 = 56 mOsm/L for gap

- What is the likely cause of an increased gap in this patient?
- Ethanol content of the ingested beer

Sodium

The body's normal daily sodium requirement is 1.0 to 1.5 mEq/kg (80 to 130 mEq, which is 80 to 130 mmol) to maintain a normal serum sodium concentration of 136 to 145 mEq/L (136 to 145 mmol/L).[15] Sodium is the predominant cation of the ECF and largely determines ECF volume. Sodium is also the primary factor in establishing the osmotic pressure relationship between the ICF and ECF. All body fluids are in osmotic equilibrium and changes in serum sodium concentration are associated with shifts of water into and out of body fluid compartments. When sodium is added to the intravascular fluid compartment, fluid is pulled intravascularly from the interstitial fluid and the ICF until osmotic balance is restored. As such, a patient's measured sodium level should *not* be viewed as an index of sodium need because this parameter reflects the balance between total body sodium content and TBW. Disturbances in the sodium level most often represent disturbances of TBW. Sodium imbalances cannot be properly assessed without first assessing the body fluid status.

❹ *Hyponatremia is very common in hospitalized patients and is defined as a serum sodium concentration below 136 mEq/L (136 mmol/L).* Clinical signs and symptoms appear at concentrations below 120 mEq/L (120 mmol/L) and typically consist of agitation, fatigue, headache, muscle cramps, and nausea. With profound hyponatremia (less than 110 mEq/L [110 mmol/L]), confusion, seizures, and coma may be seen. Because therapy is also influenced by volume status, hyponatremia is further defined as: (1) hypertonic hyponatremia; (2) hypotonic hyponatremia with an increased ECF volume; (3) hypotonic hyponatremia with a normal ECF volume; and (4) hypotonic hyponatremia with a decreased ECF volume.[16]

Hypertonic hyponatremia is usually associated with significant hyperglycemia. Glucose is an osmotically active agent that leads to an increase in TBW with little change in total body sodium. For every 60 mg/dL (3.33 mmol/L) increase in serum glucose above 200 mg/dL (11.1 mmol/L), the sodium is expected to decrease by approximately 1 mEq/L (1 mmol/L). Appropriate treatment of the hyperglycemia will return the serum sodium to normal.[15]

Hypotonic hyponatremia with an increase in ECF is also known as dilutional hyponatremia. In this scenario, patients have an excess of total body sodium and TBW; however, the excess in TBW is greater than the excess in total body sodium. Common causes include CHF, hepatic cirrhosis, and nephrotic syndrome. Treatment includes sodium and fluid restriction in conjunction with treatment of the underlying disorder—for example, salt and water restrictions are used in the setting of CHF along with loop diuretics, angiotensin-converting enzyme inhibitors, and spironolactone.[15]

In hypotonic hyponatremia with a decreased ECF volume, patients usually have a deficit of both total body sodium and TBW, but the sodium deficit exceeds the TBW deficit. Common causes include diuretic use, profuse sweating, wound drainage, burns, GI losses (vomiting or diarrhea), hypoadrenalism (low cortisol and low aldosterone), and renal tubular acidosis. Treatment includes the administration of sodium to correct the sodium deficit and water to correct the TBW deficit. The sodium deficit can be calculated with the following equation:[2]

$$\text{Sodium deficit (mEq)} = (\text{TBW})(\text{desired } Na^+ \text{ concentration} - \text{current } Na^+ \text{ concentration})$$

Although both water and sodium are required in this instance, sodium needs to be provided in excess of water to fully correct this abnormality. As such, hypertonic saline (3% NaCl) is often used. One can estimate the change in serum sodium concentration after 1 L of 3% NaCl infusion using the following equation:[16]

$$\text{Change in serum } Na^+ = (\text{infusate } Na^+ - \text{serum } Na^+)/(\text{TBW} + 1)$$

In this formula, TBW is increased by 1 to account for the addition of the liter of 3% NaCl. Patient Encounters 4 and 5 illustrate the concepts of calculating and correcting the sodium deficit.

Depending on the severity of the hyponatremia, 0.9%, 3%, or 5% NaCl can be utilized. Most patients can be adequately managed with normal saline rehydration, which is generally the safest agent. Hypertonic saline (3% or 5% NaCl) is generally reserved for patients with severe hyponatremia (less than 120 mEq/L [120 mmol/L]) accompanied by coma, seizures, or high urinary sodium losses. Roughly one-third of the sodium deficit can be replaced over the first 12 hours as long as the replacement rate is less than 0.5 mEq/hour (0.5 mmol/L). The remaining two-thirds of the deficit can be administered over several days. Overly aggressive correction of symptomatic hyponatremia (greater than 12 mEq/L [12 mmol/L] per day) can result in central pontine myelinolysis.[17] Given the potential



Patient Encounter 4, Calculation of Sodium Deficit

Calculate the sodium deficit for a 75-kg male with a serum sodium of 123 mEq/L (123 mmol/L).

Sodium deficit (mEq) = (TBW) (desired – current Na concentration)

TBW = 0.6 × 75 kg = 45 L

Desired sodium = 140 mEq/L (140 mmol/L)

Current sodium = 123 mEq/L (123 mmol/L)

Example

Sodium deficit = (45 L)(140 mEq/L – 123 mEq/L)
= 765 mEq (or 765 mmol)



Patient Encounter 5, Estimate the Anticipated Change in Serum Sodium

Estimate the anticipated change in serum sodium concentrations after the infusion of 1 L of 3% sodium chloride in a 75-kg male with a serum sodium of 123 mEq/L (123 mmol/L).

$$\text{Change in serum } Na^+ = \frac{(\text{Infusate sodium} - \text{serum sodium})}{\text{TBW} + 1}$$

Example

$$\text{Change in serum } Na^+ = \frac{512 - 123}{(0.6\ \text{L/kg})(75\ \text{kg}) + 1} = \frac{389}{46}$$

$$= 8.45\ \text{mEq (or 8.45 mmol)}$$

for irreversible neurologic damage if untreated or if improperly treated, acute hyponatremia is an urgent condition that should be promptly treated with careful attention to monitoring serial sodium values and adjusting therapeutic infusions accordingly.[18]

In hypotonic hyponatremia with a normal ECF volume, patients have an excess of TBW with relatively normal sodium content. In essence, there is a presence of excess free water. This is most frequently seen in patients with the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Common causes of SIADH include carcinomas (e.g., lung or pancreas), pulmonary disorders (e.g., pneumonias or tuberculosis), central nervous system disorders (e.g., meningitis, stroke, tumor, or trauma), and medications (e.g., sulfonylureas, antineoplastic agents, barbiturates, morphine, antipsychotics, tricyclics, non-steroidal anti-inflammatory agents, selective serotonin reuptake inhibitors, dopamine agonists, and general anesthetics). These types of medications can stimulate the release of antidiuretic hormone from the pituitary gland. When antidiuretic hormone is released, the body retains water and the sodium concentration drops. Treatment generally consists of fluid restriction alone. Hypertonic saline is used only when the sodium concentration is less than 110 mEq/L (110 mmol/L) and/or severe symptoms (e.g., seizures) are present. Refractory SIADH may respond to demeclocycline (Declomycin®, ESP Pharma) dosed at 900 to 1200 mg/day.

Hypernatremia is a serum sodium concentration greater than 145 mEq/L (145 mmol/L) and can occur in the absence of a sodium deficit (pure water loss) or in its presence (hypotonic fluid loss).[19] The signs and symptoms of hypernatremia are the same as those found in TBW depletion. Symptoms of hypernatremia are evident with a serum concentration greater than 160 mEq/L (160 mmol/L) and usually consist of thirst, mental slowing, and dry mucous membranes. Signs and symptoms become more profound as hypernatremia worsens, with the patient demonstrating confusion, hallucinations, acute weight loss, decreased skin turgor, intracranial bleeding, or coma. Many coexisting disorders and medications may complicate the diagnosis.

The classic causes of hypernatremia are associated with TBW depletion. These include dehydration from loss of hypotonic fluid from the respiratory tract or skin, decreased water intake, osmotic diuresis (e.g., mannitol, available as generic), and diabetes insipidus (e.g., decreased ADH; phenytoin, available as generic; lithium, available as generic). Hypernatremia in hospitalized patients occurs secondary to inappropriate fluid management in patients at risk for increased free water losses and impaired thirst or restricted water intake.[20] Iatrogenic hypernatremia is occasionally caused by the administration of excessive hypertonic saline. Treatment of hypernatremia includes calculation of the TBW deficit followed by the administration of hypotonic fluids as previously described. The fluid volume should be replaced over 48 to 72 hours depending on the severity of symptoms and the degree of hypertonicity.[21] For asymptomatic patients, the rate of correction should not exceed 0.5 mEq/L per hour (0.5 mmol/L per hour). One rule of thumb is to replace half the calculated TBW deficit over 12 to 24 hours and the other half of the deficit over the next 24 to 48 hours.[2,19] Excessively rapid correction of hypernatremia may lead to cerebral edema and death. Patient Encounters 6 and 7 reinforce the concepts of calculating TBW deficit and expected changes in serum sodium concentration with therapy.

Potassium

The body's normal daily potassium requirement is 0.5 to 1 mEq/kg (0.5 to 1 mmol/kg) or 40 to 80 mEq (40 to 80 mmol) to maintain a serum potassium concentration of 3.5 to 5 mEq/L (3.5 to 5 mmol/L). Potassium is the most abundant cation in the ICF, balancing the sodium contained in the ECF and maintaining electroneutrality of bodily fluids. Because the majority of potassium is intracellular, serum potassium concentration is not a good measure of total body potassium; however, clinical manifestations of potassium disorders correlate well with serum potassium. The acid-base balance of the body affects serum potassium concentrations. Hyperkalemia is routinely seen in



Patient Encounter 6, Calculate Water Deficit

Calculate the water deficit in a 75-kg male with a serum sodium of 154 mEq/L (154 mmol/L).

Water deficit (L) = TBW × [(serum sodium/140) – 1]

Example

$$\text{Water deficit} = (0.6\ \text{L/kg})(75\ \text{kg})\ [154/140 - 1] = 45 \times 0.1$$

$$= 4.5\ \text{L}$$



Patient Encounter 7, Calculate the Anticipated Change in Serum Sodium

Calculate the anticipated change in serum sodium concentration after IV infusion of 1 L of 5% dextrose in a 75-kg male with a serum sodium of 156 mEq/L (156 mmol/L).

$$\text{Change in serum } Na^+ = \frac{(\text{Infusate Na} - \text{serum Na})}{\text{TBW} + 1}$$

Example

$$\text{Change in serum } Na^+ = \frac{0 - 156}{45 + 1} = \frac{-156}{46}$$

$$= -3.39 \text{ mEq (or } -3.39 \text{ mmol)}$$

patients with decreased pH (acidosis). Potassium regulation is primarily under the control of the kidneys with excess dietary potassium being excreted in the urine. Although mild abnormalities of serum potassium are considered a nuisance, severe hyperkalemia and hypokalemia can be life-threatening.[22,23,32]

Hypokalemia (serum potassium less than 3.5 mEq/L [3.5 mmol/L]) is a common clinical problem. Signs and symptoms of hypokalemia include cramps, muscle weakness, polyuria, electrocardiogram (ECG) changes (flattened T-waves and presence of U-waves), and cardiac arrhythmias (bradycardia, heart block, atrial flutter, premature ventricular contractions, and ventricular fibrillation). Causes of hypokalemia include GI losses (vomiting, diarrhea, or NG tube suction), renal losses (high aldosterone and low magnesium), inadequate potassium intake (in IV fluids or PO), or alkalosis. Many medications can precipitate hypokalemia. β_2-Agonists (albuterol available as generic) and insulin (multiple product formulations) lower potassium via cellular redistribution. The use of loop diuretics (furosemide [Lasix®], also available as generic), thiazide diuretics (hydrochlorothiazide, available as generic), high-dose antibiotics (penicillin, available as generic), and corticosteroids (prednisone, available as generic) cause a renal potassium wasting. In addition, amphotericin B (available as generic), cisplatin (available as generic), and foscarnet (Foscavir®, AstraZeneca) can also produce hypokalemia secondary to depletion of magnesium. Hypomagnesemia diminishes intracellular potassium concentration and produces potassium wasting. Given the potential for significant morbidity and mortality, serum potassium concentrations should be monitored closely for patients with known (or suspected) hypokalemia.[2,24,32] Hypokalemia is a risk factor for digitalis toxicity.

A 1 mEq/L (1 mmol/L) fall in serum potassium (i.e., from 4 mEq/L to 3 mEq/L [4 mmol/L to 3 mmol/L]) represents a loss of approximately 200 mEq (200 mmol) of potassium. However, when the serum potassium is below 3 mEq/L (3 mmol/L), each 1 mEq/L fall in serum potassium represents a 200 to 400 mEq (200 to 400 mmol) reduction in serum concentration. Potassium repletion should be guided by close monitoring of serum concentrations instead of using empirically chosen predefined amounts. Of the five potassium salts available, potassium acetate (10.2 mEq/K^+ per gram or 10.2 mmol/K^+ per gram) and potassium chloride (13.4 mEq/K^+ per gram or 13.4 mmol/K^+ per gram) are the most commonly used forms. When hypokalemia occurs in the setting of alkalosis, potassium chloride is the preferred agent; in acidosis, potassium should be provided in the form of acetate, citrate, bicarbonate, or gluconate salt. Table 24–6 outlines the potassium content of each potassium salt preparation, and Table 24–7 lists each of the oral potassium replacement products. Potassium acetate and chloride are available for IV infusions as premixed solutions. The usual dose of these agents is 10 to 20 mEq (10 to 20 mmol) diluted in 1000 mL of normal saline.[2,24,25]

Moderate hypokalemia is defined as a serum potassium of 2.5 to 3.5 mEq/L (2.5 to 3.5 mmol/L) without ECG changes. In this setting, potassium replacement can usually be given orally at a dose of 40 to 120 mEq/day (40 to 120 mmol/day). Anecdotally, oral potassium supplementation (see Table 24–7) is often more effective in repleting moderate hypokalemia. For patients with an ongoing source of potassium loss, chronic replacement therapy should be considered. The potassium

TABLE 24–6. Potassium Content in Various Potassium Salt Preparations

Potassium Salt	mEq/g (mmol/L)
Potassium gluconate	4.3
Potassium citrate	9.8
Potassium bicarbonate	10.0
Potassium acetate	10.2
Potassium chloride	13.4

Hypokalemia and alkalosis: Use potassium chloride
Hypokalemia and acidosis: Use potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate salts

TABLE 24–7. Oral Potassium Replacement Products[a]

Product	Salt	Strength
Extended/controlled-release tablets	Chloride	8 mEq (600 mg) 10 mEq (750 mg) 15 mEq (1125 mg) 20 mEq (1500 mg)
Effervescent tablets	Chloride and bicarbonate	20 mEq 25 mEq 50 mEq
Liquid	Chloride	20 mEq/15mL (10%) 30 mEq/15mL (15%) 40 mEq/15mL (20%)
Powder packets	Chloride	15 mEq 20 mEq 25 mEq

[a]For potassium, 1 mEq = 1 mmol.

deficit is a rough approximation of the amount of potassium needed to be replaced and can be estimated as follows:

$$\text{Potassium deficit(mEq)} = (4.0 - \text{current serum potassium}) \times 100$$

Severe hypokalemia is defined as a serum potassium less than 2.5 mEq/L (2.5 mmol/L) or hypokalemia of any severity that is associated with ECG changes (e.g., flattening of T wave or elevation of U wave) and cardiac arrhythmias. In these situations, IV replacement should be initiated urgently. ❺ *Potassium infusion at rates exceeding 10 mEq/hour requires cardiac monitoring given the potential for cardiac arrhythmias.* Although the maximally concentrated solution for potassium replacement is 80 mEq/L (80 mmol/L), the maximum infusion rate is 40 mEq/hour (40 mmol/hour), and must be administered via a central line. Table 24–8 outlines current IV potassium replacement guidelines.

Caution must be exercised when repleting potassium with IV agents given possible vein irritation and/or thrombophlebitis. The risk of these complications is minimized by using less concentrated solutions and by giving infusions via central access if possible. Administration of potassium in vehicles containing glucose is discouraged, as glucose facilitates the intracellular movement of potassium. Post-therapy improvements in serum potassium may be transient and continuous monitoring is required. Patients with a low serum magnesium will have exaggerated potassium losses from the kidneys and GI tract leading to refractory hypokalemia. In this situation, the magnesium deficit must be corrected in order to successfully treat the concurrent potassium deficiency. In the hypokalemic patient with concurrent acidosis, potassium is often given as acetate, which is metabolized to bicarbonate. In the patient with depleted phosphorus and potassium, therapy with potassium phosphate is the natural choice.[22,26,27]

Hyperkalemia is defined as a serum potassium concentration greater than 5 mEq/L (5 mmol/L). Manifestations of hyperkalemia include muscle weakness, paresthesias, hypotension, ECG changes (e.g., peaked T waves, shortened QT intervals, and wide QRS complexes), cardiac arrhythmias, and a decreased pH. Causes of hyperkalemia fall into three broad categories: (1) increased potassium intake; (2) decreased potassium excretion; and (3) potassium release from the intracellular space.

Increased potassium intake results from excessive dietary potassium (salt substitutes), excess potassium in IV fluids, and other select medications (potassium-sparing diuretics or cyclosporine, available as generic), angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory agents, pentamidine (available as generic), unfractionated heparin, and low-molecular-weight heparins. Decreased potassium excretion results from acute renal failure, chronic renal failure, or Addison's disease. Excess potassium release from cells results from tissue breakdown (surgery, trauma, hemolysis, or rhabdomyolysis), blood transfusions, and metabolic acidosis.

In addition to discontinuing all potassium supplements, potassium-sparing medications, and potassium-rich salt substitutes, management of hyperkalemia addresses three concurrent strategies: (1) agents to antagonize the pro-arrhythmic effects of hyperkalemia; (2) agents to drive potassium into the intracellular space and acutely lower the serum potassium; and (3) agents that will definitively (but more gradually) lower the total body potassium content.[28] If the serum potassium concentration is greater than 7 mEq/L (7 mmol/L) and/or ECG changes are present, IV calcium is provided to stabilize the myocardium. Depending on the acuity of the situation, 1 g of calcium chloride (13.5 mEq or 6.75 mmol) is administered by direct injection or diluted in 50 mL of D5W and delivered IV over 15 minutes. Clinical effects are seen within 1 to 2 minutes of infusion and persist for 10 to 30 minutes. Repeat doses may be administered as necessary. Because most patients with clinically significant hyperkalemia receive multiple boluses of calcium directed by electrocardiogram findings, iatrogenic hypercalcemia is a potential complication of hyperkalemia treatment. As such, total calcium concentration is commonly checked with each potassium concentration measurement. Ionized calcium measurements should be obtained in patients who have comorbid conditions that would lead to inconsistency between total serum calcium and free calcium (abnormal albumin, protein, or immunoglobulin concentrations).

Dextrose and insulin (with or without sodium bicarbonate) are typically given at the time of calcium therapy in order to redistribute potassium into the intracellular space. Dextrose 50% (25 g in 50 mL) can be given by slow IV push over 5 minutes or dextrose 10% with 20 units of regular insulin can be given by continuous IV infusion over 1 to 2 hours. The onset of action for this combination is 30 minutes and the duration of clinical effects

TABLE 24–8. Recommended Potassium Dosage/Infusion Rate Guidelines[a]

Clinical Scenario	Maximum Infusion Rate	Maximum Concentration	Maximum 24-hour Dose
K^+ greater than 2.5 mEq/L *AND* No ECG changes of hypokalemia	10 mEq/hour	40 mEq/L	200 mEq
K^+ less than 2.5 mEq/L *OR* ECG changes of hypokalemia	40 mEq/hour	80 mEq/L	400 mEq

[a]For potassium, 1 mEq = 1 mmol.

is 2 to 6 hours. High-dose inhaled β_2-agonists (e.g., albuterol, available as generic) may also be used to acutely drive potassium into the intracellular space.

It is critically important to recognize that the treatments of hyperkalemia discussed thus far are transient, temporizing measures. They are intended to provide time to institute definitive therapy aimed at removing excess potassium from the body. Agents that increase potassium excretion from the body include sodium polystyrene sulfonate, loop diuretics, and hemodialysis or hemofiltration (used only in patients with renal failure). Sodium polystyrene sulfonate (Kayexalate®, various manufacturers) can be given orally, via NG tube, or as a rectal retention enema and is dosed at 15 to 60 grams in four divided doses per day.

Calcium

More than 99% of total body calcium is found in bone; the remaining less than 1% is in the ECF and ICF. Calcium plays a critical role in the transmission of nerve impulses, skeletal muscle contraction, myocardial contractions, maintenance of normal cellular permeability, and the formation of bones and teeth. There is a reciprocal relationship between the serum calcium concentration (normally 8.6 to 10.2 mg/dL [2.15 to 2.55 mmol/L]) and the serum phosphate concentration that is regulated by a complex interaction between parathyroid hormone, vitamin D, and calcitonin. About one-half of the serum calcium is bound to plasma proteins; the other half is free ionized calcium. Given that the serum calcium has significant protein binding, the serum calcium concentration must be corrected in patients who have low albumin concentrations (the major serum protein). The most commonly used formula adds 0.8 mg/dL (0.2 mmol/L) of calcium for each gram of albumin deficiency as follows:

$$\text{Corrected [Ca]} = \text{Measured [Ca mg/dL]} + [0.8 \times (4 - \text{measured albumin})]$$ [29–31]

Note: To convert conventional units (mg/dL) to SI calcium units multiply by a factor of 0.25.

Hypocalcemia is caused by inadequate intake (vitamin deficiency, poor dietary calcium sources, and alcoholism) or excessive losses (hypoparathyroidism, renal failure, alkalosis, and pancreatitis). Clinical manifestations of hypocalcemia are seen with total serum concentrations less than 6.5 mg/dL (1.63 mmol/L) and include: tetany, circumoral tingling, muscle spasms, hypoactive reflexes, anxiety, hallucinations, hypotension, myocardial infarction, seizures, lethargy, stupor, and **Trousseau's sign or Chvostek's sign.**[32,37] Trousseau's sign is elicited by inflating a blood pressure cuff on the patient's upper arm, whereby hypocalcemic patients will experience tetany of the wrist and hand as evidenced by thumb adduction, wrist flexion, and metacarpophalangeal joint flexion. Chvostek's sign is elicited by tapping on the proximal distribution of the facial nerve (adjacent to the ear). This will produce a brief spasm of the upper lip, eye, nose, or face in hypocalcemic patients.

Causes of hypocalcemia include hypoparathyroidism, hypomagnesemia, alcoholism, hyperphosphatemia, blood product infusion (due to chelation by the citrate buffers), chronic renal failure, vitamin D deficiency, acute pancreatitis, alkalosis, and hypoalbuminemia. Medications that cause hypocalcemia include phosphate replacement products, loop diuretics, phenytoin (Dilantin, available as generic), phenobarbital (available as generic), corticosteroids, aminoglycoside antibiotics, and acetazolamide (available as generic).[34,39,42]

Oral calcium replacement products include calcium carbonate (OsCal®, GlaxoSmithKline and various generics; Tums®, GlaxoSmithKline and various generics) and calcium citrate (Citrical®, Mission Pharmacal, and various generics). IV calcium replacement products include calcium gluconate and calcium chloride (both products available as generic). ❻ *Calcium gluconate is preferred for peripheral use because it is less irritating to the veins; it may also be given intramuscularly.* Each 10 mL of a 10% calcium gluconate solution provides 90 mg (4.5 mEq or 2.25 mmol) of elemental calcium. Calcium chloride is associated with more venous irritation and is generally reserved for administration via central line. Each 10 mL of a 10% calcium chloride solution contains 270 mg (13.5 mEq or 6.75 mmol) of elemental calcium. IV calcium products are given as a slow push or added to 500 to 1000 mL of 0.9% normal saline for slow infusion.[37,42]

For acute symptomatic hypocalcemia, 200 to 300 mg of elemental calcium is administered IV and repeated until symptoms are fully controlled. This is achieved by infusing 1 g of calcium chloride or 2 to 3 grams of calcium at a rate no faster than 30 to 60 mg of elemental calcium per minute. More rapid administration is associated with hypotension, bradycardia, or cardiac asystole. Total calcium concentration is commonly monitored in critically ill patients. Under normal circumstances, about half of calcium is loosely bound to serum proteins while the other half is free. Total calcium concentration measures bound and free calcium. Ionized calcium measures free calcium only. Under usual circumstances, a normal calcium level implies a normal free ionized calcium level. Ionized calcium should be obtained in patients with comorbid conditions that would lead to inconsistency between total calcium and free serum calcium (abnormal albumin, protein, or immunoglobulin concentrations). For chronic asymptomatic hypocalcemia, oral calcium supplements are given at doses of 2 to 4 g/day of elemental calcium. Many patients with calcium deficiency have concurrent vitamin D deficiency that must also be corrected in order to restore calcium homeostasis.[2,37,38]

Hypercalcemia is defined as a calcium concentration greater than 10.2 mg/dL (2.55 mmol/L). It may be categorized as mild if total serum calcium is 10.3 to 12 mg/dL (2.575 to 3 mmol/L), moderate if total serum calcium is 12.1 to 13 mg/dL

(3.025 to 3.25 mmol/L), or severe when serum concentration is greater than 13 mg/dL (3.25 mmol/L). Causes of hypercalcemia include hyperparathyroidism, malignancy, Paget's disease, granulomatous diseases (e.g., tuberculosis, sarcoidosis, or histoplasmosis), hyperthyroidism, immobilization, multiple bony fractures, acidosis, and milk-alkali syndrome. Multiple medications cause hypercalcemia and include thiazide diuretics, estrogens, lithium (available as generic), tamoxifen (Nolvadex®, available as generic), vitamin A, vitamin D, and calcium supplements.[2,33,37,42]

Because the severity of symptoms and the absolute serum concentration are poorly correlated in some patients, institution of therapy should be dictated by the clinical scenario. All patients with hypercalcemia should be treated with aggressive rehydration: normal saline at 200 to 300 mL/hour is a routine initial fluid prescription. For patients with mild hypocalcemia, hydration alone may provide adequate therapy. The moderate and severe forms of hypercalcemia are more likely to have significant manifestations and require prompt initiation of additional therapy. These patients may present with anorexia, confusion, and/or cardiac manifestations (bradycardia and arrhythmias with ECG changes). Total calcium concentrations greater than 13 mg/dL (3.25 mmol/L) are particularly worrisome, as these levels can unexpectedly precipitate acute renal failure, ventricular arrhythmias, and sudden death.

Once fluid administration has repleted the ECF, forced diuresis (with associated calcium loss) can be initiated with a loop diuretic. For this approach to be successful, normal kidney function is required. In renal failure patients, the alternative therapy is emergent hemodialysis. Other treatment options include bisphosphonates (zoledronic acid [Zometa®, Novartis], pamidronate [Aredia®, available as generic]), hydrocortisone (available as generic), mithramycin (Mithracin®), calcitonin, and gallium. Given their efficacy and favorable side-effect profile, bisphosphonates are typically the agents of choice. Table 24–9 outlines the treatment options for hypercalcemia including time to onset of effect, duration of effect, and efficacy.[2,34,37,38]

Phosphorus

Phosphorus is primarily found in the bone (80% to 85%) and ICF (15% to 20%): the remaining less than 1% is found in the ECF. Note that phosphorus is the major anion within the cells. Given this distribution, serum phosphate concentration does not accurately reflect total body phosphorus stores. Phosphorus is expressed in milligrams (mg) or millimoles (mmol), not as milliequivalents (mEq). Because phosphorus is the source of phosphate for adenosine triphosphate (ATP) and phospholipid synthesis, manifestations of phosphorus imbalance are variable.

Dietary intake, parathyroid hormone levels, and renal function are the major determinants of the serum phosphorus concentration, which is normally 2.7 to 4.5 mg/dL (0.87 to 1.45 mmol/L).[2,35–37] Hypophosphatemia is defined by a serum phosphorus concentration less than 2.5 mg/dL (0.81 mmol/L); severe hypophosphatemia occurs when the phosphorus concentration is less than 1 mg/dL (0.323 mmol/L). Hypophosphatemia can be caused by increased distribution to the ICF (hyperglycemia, insulin therapy, or malnourishment), decreased absorption (starvation, excessive use of phosphorus-binding antacids, vitamin D deficiency, diarrhea, or laxative abuse) or increased renal loss (diuretic use, diabetic ketoacidosis, alcohol abuse, hyperparathyroidism, or burns).[38,39] ❼ *In the critical care setting, hypophosphatemia can result in impaired diaphragmatic contractility and acute respiratory failure.* Medications that cause hypophosphatemia include diuretics (acetazolamide [Diamox, available as generic], furosemide [Lasix, available as generic], hydrochlorothiazide [Hydrodiuril, available as generic]), sucralfate (Carafate, available as generic), corticosteroids, cisplatin (available as generic), antacids (aluminum carbonate, calcium carbonate, and magnesium oxide [antacids all available as generic]), foscarnet (Foscavir, Astra Zeneca), phenytoin (Dilantin, available as generic), phenobarbital (available as generic), and phosphate binders (sevelamer [Renagel, Genzyme Corp.], and calcium acetate [PhosLo, Nabi]).

Signs and symptoms of hypophosphatemia include paresthesias, muscle weakness, myalgias, bone pain, anorexia, nausea, vomiting, RBC hemolysis, acute respiratory failure, seizures, and coma.[38,40] For mild hypophosphatemia, patients should be encouraged to eat a high-phosphorus diet including eggs, nuts, whole grains, meat, fish, poultry, and milk products. For moderate hypophosphatemia (1 to 2.5 mg/dL) (0.323 to 0.808 mmol/L), oral supplementation of 1.5 to 2 g/day

TABLE 24–9. Selected Treatment Options for the Management of Hypercalcemia

Therapy	Dose	Onset	Duration	Efficacy[a]
Normal saline	3–6 L/day	Hours	Hours	1–2 mg/dL
Furosemide (Lasix®, available as generic)	80–160 mg/day	Hours	Hours	1–2 mg/dL
Hydrocortisone (available as generic)	200 mg/day	Hours	Days	Mild
Calcitonin (Miacalcin®, Novartis)	4–8 units/kg	Hours	Hours	1–2 mg/dL
Mithramycin (Mithracin®)	25 mcg/kg	12 hours	Days	1–5 mg/dL
Pamidronate[b] (Aredia®, available as generic)	30–90 mg/week	Days	1–4 weeks	1–5 mg/dL
Zoledronic acid (Zometa®, available as generic)	4–8 mg	Days	Weeks	1–5 mg/dL
Gallium (Ganite®, Genta Inc.)	200 mg/m^2	Days	Days–Weeks	1–5 mg/dL

[a]Expected decrease in serum Ca.
[b]Preferred bisphosphonate.

(30 to 60 mmol/day) is usually adequate. Diarrhea may be a dose-limiting side effect with oral phosphate replacement products. Injectable phosphate products are reserved for patients with severe hypophosphatemia or those in the intensive care unit.[41] The available agents are provided as sodium or potassium salts; however, unless concurrent hypokalemia is present, sodium phosphate is usually used. Empirically, if the serum phosphorus is 2.3 to 2.7 mg/dL (0.74 to 0.87 mmol/L), the corresponding IV phosphorus dose is 0.08 to 0.16 mmol/kg; for a serum phosphorus of 1.5 to 2.2 mg/dL (0.48 to 0.71 mmol/L), the replacement dose is 0.16 to 0.32 mmol/kg; and the dose is 0.32 to 0.64 mmol/kg when the serum phosphorus is less than 1.5 mg/dL (0.48 mmol/L).[2] IV phosphorus preparations are usually infused over 4 to 12 hours. Table 24–10 compares the available phosphate replacement products.

Hyperphosphatemia is defined by a serum phosphorus concentration greater than 4.5 mg/dL (1.45 mmol/L). The manifestations of hyperphosphatemia include findings of hypocalcemia (see above), paresthesias, ECG changes (prolonged QT interval and prolonged ST segment), and metastatic calcifications. Causes of hyperphosphatemia include impaired phosphorus secretion (hypoparathyroidism or renal failure), redistribution of phosphorus to the ECF (acid-base imbalance, rhabdomyolysis, muscle necrosis, or tumor lysis during chemotherapy), and increased phosphorus intake (various medications).[38] Medications that can cause hyperphosphatemia include enemas containing phosphorus (e.g., Fleet®, Fleet), laxatives containing phosphate or phosphorus, oral or parenteral phosphorus supplements (e.g., Neutra-Phos®, Ortho McNeil), vitamin D supplements, and the bisphosphonates (e.g., pamidronate, various manufacturers).[42]

Hyperphosphatemia is generally benign and rarely needs aggressive therapy. Dietary restriction of phosphate and protein is effective for most minor elevations. Phosphate binders such as aluminum-based antacids, calcium carbonate, calcium acetate (PhosLo®, Nabi), sevelamer (Renagel®, Genzyme), and lanthanum carbonate (Fosrenol®, Shire) may be necessary for some patients.[43] If patients exhibit findings of hypocalcemia (tetany), IV calcium should be administered empirically.

Magnesium

The body's normal daily magnesium requirement is 300 to 350 mg/day to maintain a serum magnesium concentration of 1.5 to 2.4 mg/dL (0.75 to 1.2 mmol/L). Because magnesium is the second most abundant ICF cation, serum concentrations are a relatively poor measure of total body stores. Magnesium catalyzes and/or activates more than 300 enzymes, provides neuromuscular stability, and is involved in myocardial contraction. Magnesium is generally not part of standard chemistry panels, and therefore must be ordered separately.[2,37,42,44,45]

Hypomagnesemia is defined as a serum magnesium less than 1.5 mg/dL (0.75 mmol/L), and is most frequently seen in the intensive care and postoperative settings. Hypomagnesemia results from inadequate intake (alcoholism, dietary restriction, or inadequate magnesium in total parenteral nutrition [TPN]), inadequate absorption (steatorrhea, cancer, malabsorption syndromes, or excess calcium or phosphorus in the GI tract), excessive GI loss of magnesium (diarrhea, laxative abuse, NG tube suctioning, or acute pancreatitis), or excessive urinary loss of magnesium (primary hyperaldosteronism, certain medications, diabetic ketoacidosis, and renal disorders). Medications that potentially can cause hypomagnesemia include aminoglycoside antibiotics, amphotericin B (available as generic), cisplatin (available as generic), insulin, cyclosporine (available as generic), loop diuretics, and thiazide diuretics. There is also a strong correlation between hypokalemia and hypomagnesemia.[38,42,46]

The findings of hypomagnesemia include muscle weakness, cramps, agitation, confusion, tremor, seizures, ECG changes (increased PR interval, prolonged QRS complex, and increased QT interval), findings of hypocalcemia (see above), refractory hypokalemia (see above), metabolic alkalosis, and digoxin toxicity.[42,47,48]

Asymptomatic mild magnesium deficiencies (1 to 1.5 mg/dL) (0.5 to 0.75 mmol/L) can be managed with increased oral intake of magnesium-containing foods or with oral supplementation. Magnesium oxide (MagOx®, Blaine Pharmaceuticals and various manufacturers) 400 mg tablets contain 241 mg (20 mEq or 10 mmol) of magnesium. Diarrhea is often a dose-limiting side effect of oral supplementation. Severely deficient patients (less than 1.0 mg/dL) (0.5 mmol/L) and all deficient

TABLE 24–10. Phosphate Replacement Products

Product	Route	mg $PO4^-$	mmol $PO4^-$	mEq (mmol) Na^+	mEq (mmol) K^+
Potassium phosphate (KPO_4/mL), available as generic	IV	94	3	0	4.4
Sodium phosphate ($NaPO_4$/mL), available as generic	IV	94	3	4	0
Neutra-Phos Powder®, Ortho McNeil	PO	250	8	7.1	7.1
Neutra-Phos-K Powder®, Ortho McNeil	PO	250	8	0	14.3
K-Phos®, Beach	PO	125	4	2.9	1.4
K-Phos Neutral Tablets®, Beach	PO	250	8	13.1	1.4

IV = intravenous; PO = oral.

critically ill patients should be managed with IV magnesium sulfate. Ten milliliters of a 10% magnesium sulfate solution contains 1 g of magnesium, which is equivalent to 98 mg (8.12 mEq or 4.06 mmol) of elemental magnesium. ❾ *Because magnesium concentration does not correlate well with total body magnesium stores, magnesium is often administered empirically to critically ill patients.*[2,37] Intravenous magnesium has been utilized for the treatment of acute asthma in the emergency department in patients not responding to standard therapy. High doses of IV magnesium sulfate are effective in reducing the risk of eclampsia in women with pre-eclampsia and is routinely administered in this setting.

The most common causes of hypermagnesemia are renal failure, often in conjunction with magnesium-containing medications (cathartics, antacids, or magnesium supplements), and lithium therapy (available as generic). Hypermagnesemia is defined as a serum magnesium concentration greater than 2.4 mg/dL (1.2 mmol/L). Mild hypermagnesemia is present if the serum magnesium concentration is between 2.5 and 4 mg/dL (1.25 to 2 mmol/L) and manifests as nausea, vomiting, cutaneous vasodilation, and bradycardia. Moderate hypermagnesemia is present if the serum magnesium concentration is between 4 and 12 mg/dL (2 to 6 mmol/L) and may manifest with hyporeflexia, weakness, somnolence, hypotension, and ECG changes (increased QRS interval). Severe hypermagnesemia is present if the serum magnesium concentration is greater than 13 mg/dL (6.5 mmol/L) and can manifest as muscle paralysis, complete heart block, asystole, respiratory failure, refractory hypotension, and death.[2,49]

All patients with hypermagnesemia should have all magnesium supplements or magnesium-containing medications discontinued.[2,37] Mild hypermagnesemia and moderate hypermagnesemia without cardiac findings can be treated with normal saline infusion and furosemide therapy (assuming the patient has normal renal function). Moderate hypermagnesemia with cardiac irritability and severe hypermagnesemia require IV calcium gluconate to reverse the neuromuscular and cardiovascular effects. Calcium gluconate given at typical doses of 1 to 2 g IV will have transient effects and can be repeated as clinically indicated. Hemodialysis may be necessary for those with severely compromised renal function.

CONCLUSION

Because disturbances in fluid balance are routinely encountered in clinical medicine, it is essential to have a thorough understanding of body fluid compartments and the therapeutic use of fluids. Similarly, disturbances in serum sodium, potassium, calcium, phosphorus, and magnesium are ubiquitous and must be mastered by all clinicians. Dysregulation of fluid and/or electrolyte status has serious implications regarding the concepts of drug absorption, volumes of distribution, and toxicity. Similarly, many medications can disrupt fluid and/or electrolyte balance as an unintended consequence.



Patient Encounter 8

TO, a 77-year-old male nursing home resident is admitted to the hospital with a 3-day history of altered mental status. The patient was unable to give a history or review of systems. On physical examination the vital signs revealed a blood pressure of 100/60 mm Hg, pulse 110 beats per minute, respirations 14/minutes, and a temperature of 101°F (38.3°C). Rales and dullness to percussion were noted at the posterior right base. The cardiac exam was significant for tachycardia. No edema was present. Laboratory studies included: sodium 160 mEq/L (160 mmol/L), potassium 4.6 mEq/L (4.6 mmol/L), chloride 120 mEq/L (120 mmol/L), bicarbonate 30 mEq/L (30 mmol/L), glucose 104 mg/dL (5.77 mmol/L), BUN 34 mg/dL (12.14 mmol/L), and creatinine 2.2 mg/dL (194.5 µmol/L). The CBC was within normal limits. Chest x-ray indicated a right lower lobe pneumonia.

The patient is 5′10″ (152.4 cm) and currently weighs 160 lb (72.6 kg). His normal weight is 170 pounds (77.1 kg).

- What is the likely cause for the increased sodium concentration in this patient?
- Increased insensible losses (from his fever caused by bacterial pneumonia) and lack of access to water (from his altered level of consciousness)

Calculate the TBW, ICF and ECF for this patient.
IBW = 73 kg. Normal weight = 77 kg (170 lb)
TBW = 77 kg × 0.6 = 46 L
ICF = 46 L × 0.33 = 15 L
ECF = 46 L × 0.67 = 31 L
Calculate TO's fluid deficit if one is present.
170 – 160 = 10/2.2 = 4.5 L, or using the sodium equation
0.6 (77) × [160/140 – 1] = 6.6 L
The fluid deficit is between 4.5 and 6.6 L. We will base our calculations upon a 5 L deficit

In the next 24 hours, the medical team wants to give 50% of the fluid deficit plus an extra 240 mL to account for insensible losses in addition to the patient's maintenance needs. Using the equation (1500 mL + 20 mL for each kg greater than 20 kg), calculate the rate of fluid administration for the total fluids needed in this 24-hour period and over the next 48 hours.

Calculate TO's daily maintenance fluids.

1500 mL + (20 mL/kg × 57 kg) = 2640 mL

Calculate TO's fluids for the first 24 hours.

0.5(5000) + 2640 + 240 = 5380 mL

5380/24 = 225 mL per hour × 24 hours

Calculate TO's fluids for the next 48 hours.

0.5(5000) + 2(2640) + 2(240) = 82,600 mL

8260/48 = 175 mL per hour × 48 hours

- What type of fluid should be used to treat TO's fluid disorder?
- Hypotonic solution such as dextrose 5% and $^1/_2$ normal saline or similar fluid

ABBREVIATIONS

ATP:	adenosine triphosphate
BUN:	blood urea nitrogen
CHF:	congestive heart failure
Cl:	chloride
CNS:	central nervous system
D5W:	dextrose 5% water
ECF:	extracellular fluid
ECG:	electrocardiogram
FFP:	fresh frozen plasma
GI:	gastrointestinal
ICF:	intracellular fluid
I&Os:	ins and outs
IV:	intravenous
JCAHO:	Joint Commission on Accreditation of Healthcare Organizations
K^+:	potassium
kg:	kilogram
KVO:	keep the vein open
L:	liter
LR:	lactated Ringer's (solution)
mEq:	milliequivalent
mg:	milligram
mL:	milliliter
mmol:	millimole
Na:	sodium
NG:	nasogastric
NS:	normal saline
PO:	per mouth
SIADH:	syndrome of inappropriate ADH secretion
TBW:	total body water
TPN:	total parenteral nutrition

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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25 Acid-Base Disturbances

Lee E. Morrow and Mark A. Malesker



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Define primary acid-base disturbances within the human body.
2. Apply simple formulas in order to determine the etiology of simple acid-base disturbances and the adequacy of compensation.
3. Integrate the supplemental concepts of the anion gap and the excess gap to help assess complex acid-base disturbances.
4. Discuss the most common causes of each primary acid-base irregularity.
5. Determine the appropriate management for patients with acid-base disorders.

Key Concepts

❶ Acid-base homeostasis is tightly regulated by the complex, but predictable, interactions of the kidneys, the lungs, and various buffer systems. The kidneys control serum bicarbonate (HCO_3^-) concentration through the excretion or reabsorption of filtered HCO_3^-, the excretion of metabolic acids, and synthesis of new HCO_3^-. The lungs control arterial carbon dioxide levels through changes in the depth and/or rate of respiration.

❷ Respiratory acidosis and alkalosis result from primary disturbances in the arterial carbon dioxide (CO_2) levels. Metabolic compensation of respiratory disturbances is a slow process, often requiring days for the serum HCO_3^- to reach the steady state.

❸ Respiratory acidosis is caused by respiratory insufficiency resulting in an increased arterial CO_2 concentration. The compensation for respiratory acidosis (if present for prolonged periods) is an increase in serum HCO_3^-.

❹ Respiratory alkalosis is caused by hyperventilation resulting in a decreased arterial CO_2 concentration. The compensation for respiratory alkalosis (if present for prolonged periods) is a decrease in serum HCO_3^-.

❺ Metabolic acidosis and alkalosis result from primary disturbances in the serum HCO_3^- concentration. Respiratory compensation of metabolic disturbances begins within minutes and is complete within 12 hours.

❻ Metabolic acidosis is characterized by a decrease in serum HCO_3^-. The anion gap is used to narrow the differential diagnosis, as this acidosis may be caused by addition of acids (increased anion gap) or loss of HCO_3^- (normal anion gap). The compensation for metabolic acidosis is an increase in ventilation with a decrease in arterial CO_2.

❼ Metabolic alkalosis is characterized by an increase in serum HCO_3^-. This disorder requires loss of fluid that is low in HCO_3^- from the body or addition of HCO_3^- to the body. The compensation for metabolic alkalosis is a decrease in ventilation with an increase in arterial CO_2.

❽ Arterial blood gases, serum electrolytes, physical examination findings, the medical history, and the patient's recent medications must be reviewed in order to establish the etiology of a given acid-base disturbance.

❾ It is critical to treat the underlying causative process to effectively resolve most observed acid-base disorders. However, supportive treatment of the pH and electrolytes is often needed until the underlying disease state is improved.

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Given its reputation for complexity and the need to memorize innumerable formulas, acid-base analysis intimidates many health care providers. In reality, acid-base disorders always obey well-defined biochemical and physiologic rules. The pH determines a patient's acid-base status and an assessment of the bicarbonate (HCO_3^-) and arterial carbon dioxide ($PaCO_2$) values identifies the underlying process. This makes them easy to recognize and interpret if a practical strategy is rigorously applied. This chapter will outline a clinically useful approach to acid-base abnormalities and then apply this approach in a series of increasingly complex clinical scenarios.

Disturbances of acid-base equilibrium occur in a wide variety of illnesses and are among the most commonly encountered disorders in critical care medicine. The importance of a thorough command of this content cannot be overstated given that acid-base disorders are remarkably common and may result in significant morbidity and mortality. Although severe derangements may affect virtually any organ system, the most serious clinical effects are cardiovascular (arrhythmias and impaired contractility), neurologic (coma and seizures), pulmonary (dyspnea, impaired oxygen delivery, and respiratory fatigue), and/or renal (hypokalemia). Changes in acid-base status also affect multiple aspects of pharmacokinetics (clearance and protein binding) and pharmacodynamics.

ACID-BASE HOMEOSTASIS

Acid-base homeostasis is responsible for maintaining blood hydrogen ion concentration [H^+] near normal despite the daily acidic and/or alkaline loads derived from the intake and metabolism of foods. Acid-base status is traditionally represented in terms of pH, the negative logarithm of [H^+]. Because [H^+] is equal to 24 times the ratio of $PaCO_2$ to HCO_3^-, the pH can be altered by a change in either the bicarbonate concentration or the dissolved carbon dioxide. A critically important concept is that [H^+] is dependent only on the *ratio* of $PaCO_2$ to HCO_3^- and not the absolute amount of either. As such, a normal $PaCO_2$ or HCO_3^- alone does not guarantee that the pH will be normal. Conversely, a normal pH does not imply that either the $PaCO_2$ or HCO_3^- will be normal.

❶ *Blood pH is normally tightly regulated by three distinct mechanisms:*

1. *Extracellular bicarbonate and intracellular protein buffering systems*
2. *Pulmonary regulation of $PaCO_2$, effectively allowing carbonic acid to be eliminated by the lungs as CO_2*
3. *Renal reclamation or excretion of HCO_3^- and excretion of acids such as ammonium.*

Because the kidneys excrete less than 1% of the estimated 13,000 mEq of H^+ ions generated in an average day, renal failure can be present for prolonged periods before life-threatening imbalances occur. Conversely, cessation of breathing for minutes results in profound acid-base disturbances.[1]

The best way to assess a patient's acid-base status is to review the results of an arterial blood gas (ABG) specimen. Blood gas analyzers directly measure the pH and $PaCO_2$ while the HCO_3^- value is calculated using the Henderson-Hasselbalch equation. A more direct measure of serum HCO_3^- is obtained by measuring the total venous carbon dioxide (tCO_2). Because dissolved carbon dioxide is almost exclusively in the form of HCO_3^-, tCO_2 is essentially equivalent to the measured serum HCO_3^- concentration. This value is routinely reported on basic chemistry panels. In the remainder of this chapter the pH and $PaCO_2$ values should be assumed to come from an arterial blood gas while HCO_3^- values should be considered to be measured serum concentrations.

BASIC PATHOPHYSIOLOGY

Under normal circumstances the arterial pH is tightly regulated between 7.35 and 7.45. **Acidemia** is an abnormally low arterial blood pH (less than 7.35) while **acidosis** is a pathologic process that acidifies body fluids. Similarly, **alkalemia** is an abnormally high arterial blood pH (less than 7.45) while **alkalosis** is a pathologic process that alkalinizes body fluids. As such, although a patient can simultaneously have acidosis *and* alkalosis, the end result will be acidemia *or* alkalemia.

Changes in the arterial pH are driven by changes in the $PaCO_2$ and/or the serum HCO_3^-. Carbon dioxide is a volatile acid that is regulated by the depth and rate of respiration. Because CO_2 can be either "blown off" or "retained" by the respiratory system, it is referred to as being under respiratory control. ❷ *A respiratory acid-base disorder is a pH disturbance caused by pathologic alterations of the respiratory system or its central nervous system control.* ❸❹ *Such an alteration may result in the accumulation of $PaCO_2$ beyond normal limits (greater than 45 mm Hg or 6 kPa), a situation termed respiratory acidosis, or it may result in the loss of $PaCO_2$ beyond normal limits (less than 35 mm Hg or 4.7 kPa), a condition termed respiratory alkalosis. Variations in respiratory rate and/or depth allow the lungs to achieve changes in the $PaCO_2$ very quickly (within minutes).*

Bicarbonate is a base that is regulated by renal metabolism via the enzyme carbonic anhydrase. As such, bicarbonate is often referred to as being under metabolic control. ❺ *A metabolic acid-base disorder is a pH disturbance caused by derangement of the pathways responsible for maintaining a normal HCO_3^- level.* ❻❼ *This may result in a pathologic accumulation of HCO_3^- (greater than 26 mEq/L or mmol/L), a condition termed metabolic alkalosis, or it may result in the loss of HCO_3^- beyond normal (less than 22 mEq/L or mmol/L), a condition termed metabolic acidosis. In contrast to the lungs' rapid effects on CO_2, the kidneys change the HCO_3^- very slowly (hours to days).*

TABLE 25–1. The Six Simple Acid-Base Disorders

Type of Disorder	pH	$PaCO_2$[d]	HCO_3^-
1. Metabolic acidosis	↓	Decreased[b] $PaCO_2 = (1.5 \times HCO_3^-) + 8$	Decreased[a]
2. Metabolic alkalosis	↑	Increased[b] $PaCO_2 = (0.9 \times HCO^{3-}) + 15$	Increased[a]
3. Acute respiratory acidosis	↓	Increased[a]	~Normal $\Delta HCO_3^- = 0.1 \times \Delta PaCO_2$[d]
4. Chronic respiratory acidosis	↓	Increased[a]	Increased[c] $\Delta HCO_3^- = 0.35 \times \Delta PaCO_2$[d]
5. Acute respiratory alkalosis	↑	Decreased[a]	~Normal $\Delta HCO_3^- = 0.2 \times \Delta PaCO_2$[d]
6. Chronic respiratory alkalosis	↑	Decreased[a]	Decreased[c] $\Delta HCO_3^- = 0.4 \times \Delta PaCO_2$[d]

[a]Primary disorder.
[b]Respiratory compensation: If inappropriate, see Table 25–2.
[c]Metabolic compensation: If inappropriate, see Table 25–2.
[d]$PaCO_2$ in millimeters of mercury.

Respiratory and metabolic derangements can occur in isolation or in combination. If a patient has an isolated primary acid-base disorder that is not accompanied by another primary acid-base disorder, a **simple (uncomplicated) disorder** is present. The most common clinical disturbances are simple acid-base disorders. If two or three simple acid-base disorders are simultaneously present the patient has a **mixed (complicated) disorder**. More complex clinical situations lead to mixed acid-base disturbances.

Because CO_2 is a volatile acid, it can rapidly be changed by the respiratory system. If a respiratory acid-base disturbance is present for minutes to hours it is considered an **acute disorder** while if it is present for days or longer it is considered a **chronic disorder**. By definition, the metabolic machinery that regulates HCO_3^- results in slow changes in serum bicarbonate and all metabolic disorders are chronic. This means that there are six simple acid-base disorders as outlined in Table 25–1.[2]

Changes that follow the primary disorder and attempt to restore the blood pH to normal are referred to as compensatory changes. It should be stressed that compensation never normalizes the pH. ❺ *Because all metabolic acid-base disorders are chronic and the normal respiratory system can quickly alter the $PaCO_2$, essentially all metabolic disorders are accompanied by some degree of respiratory compensation.*[3] ❷ *Similarly, chronic respiratory acid-base disorders are typically accompanied by attempts at metabolic compensation.*[4,5] *However, with acute respiratory acid-base disorders there is insufficient time for the metabolic pathways to compensate significantly.*[6] *As such, acute respiratory derangements are essentially uncompensated.*

The amount of compensation (metabolic or respiratory) can be reliably predicted based on the degree of derangement in the primary disorder. Table 25–1 outlines the simple acid-base disorders and provides formulas for calculating the expected compensatory responses. Although it isn't mandatory to memorize these formulas in order to interpret acid-base problems, they can be helpful tools. If the measured values differ markedly from the calculated values (the measured serum HCO_3^- is greater than 2 mEq/L from the calculated value or the measured $PaCO_2$ is more than 4 mm Hg from the calculated value), a second acid-base disorder is present as outlined in Table 25–2.

APPLICATION OF BASIC PATHOPHYSIOLOGY

When given an ABG for interpretation, it is essential to use an approach that is focused yet comprehensive. An algorithm illustrating this concept is shown in Fig. 25–1. The first step is to identify all abnormalities in the pH, $PaCO_2$, and/or HCO_3^- and then decide which abnormal values are primary and which are compensatory. This is best done by first looking at the pH. Whichever side of 7.40 the pH is on, the process that

TABLE 25–2. Diagnosis of Concurrent Acid-Base Disturbances when Compensation Is Inappropriate

Primary Acid-Base Disturbance	Assessment of Compensation	Concurrent Acid-Base Disturbance
Metabolic acidosis	$PaCO_2$ too low	Respiratory alkalosis
	$PaCO_2$ too high	Respiratory acidosis
Metabolic alkalosis	$PaCO_2$ too low	Respiratory alkalosis
	$PaCO_2$ too high	Respiratory acidosis
Respiratory acidosis	HCO_3^- too low	Metabolic acidosis
	HCO_3^- too high	Metabolic alkalosis
Respiratory alkalosis	HCO_3^- too low	Metabolic acidosis
	HCO_3^- too high	Metabolic alkalosis

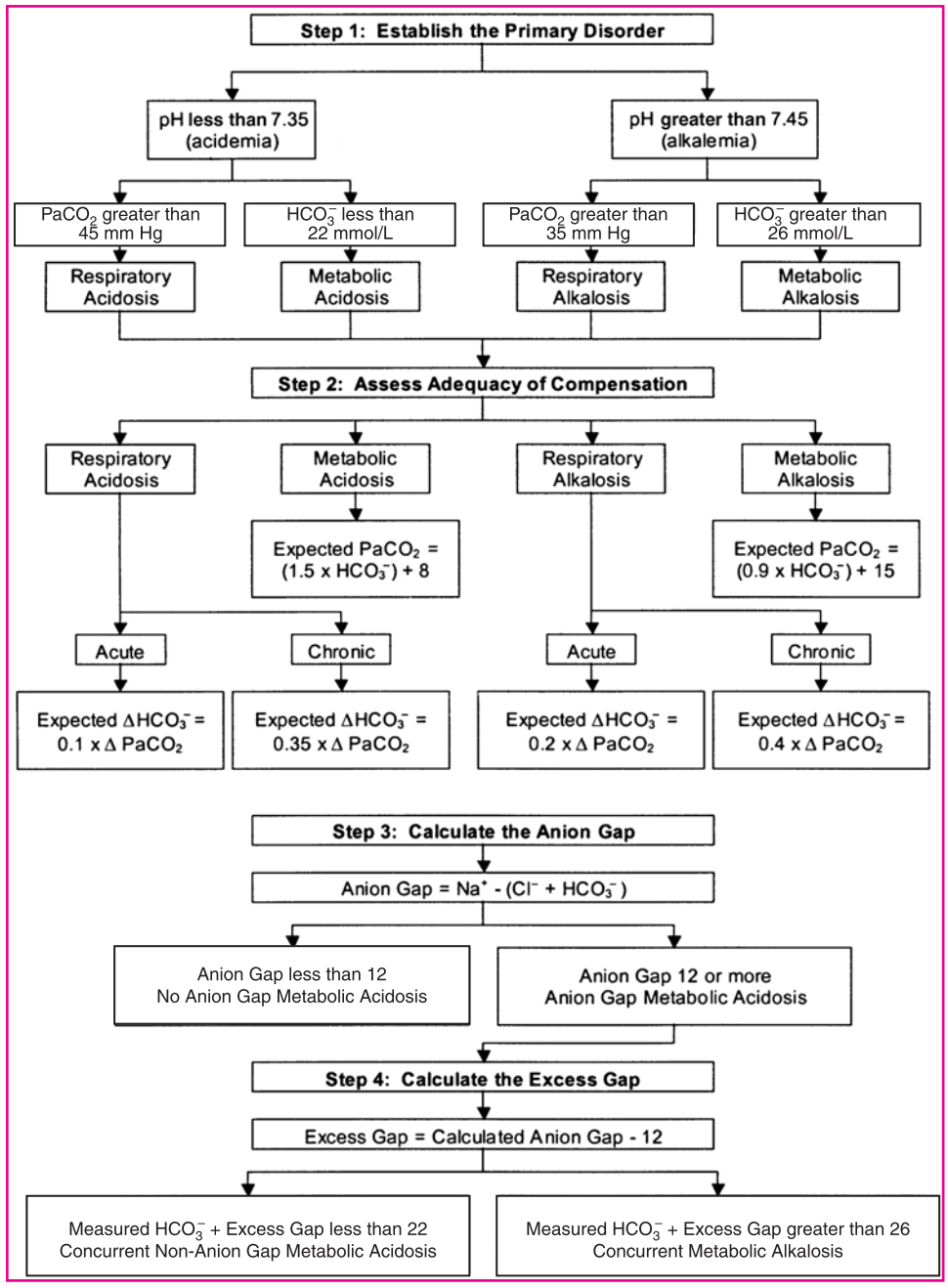


FIGURE 25–1. An algorithmic approach to acid-base disorders. Normal values: pH 7.35 to 7.45, $PaCO_2$ 35 to 45 mm Hg (4.7 to 6 kPa), HCO_3^- 22 to 26 mEq/L (mmol/L), anion gap less than 12 mEq/L (mmol/L). Note that $PaCO_2$ should be in millimeters of mercury to use the equations in the figure. Cl^-, chloride ion; HCO_3^-, bicarbonate; Na^+, sodium ion; $PaCO_2$, partial pressure of arterial carbon dioxide.

caused it to shift to that side is the primary abnormality. If the arterial pH is lower than 7.40 (acidemia), an elevated $PaCO_2$ (greater than 45 mm Hg or 6 kPa, **respiratory acidosis**) or a lowered HCO_3^- (less than 22 mEq/L or mmol/L, **metabolic acidosis**) would be the primary abnormality. If the arterial pH is higher than 7.40 (alkalemia), a decreased $PaCO_2$ (less than 35 or 4.7 kPa, **respiratory alkalosis**) or an increased HCO_3^- (greater than 25 mEq/L or mmol/L, **metabolic alkalosis**) would be the primary abnormality. Once the primary disorder is established, the second step is to apply the formulas from Table 25–1 to assess whether compensation is appropriate and to look for concurrent processes.[2]

An alternative to a diagnostic algorithm is use of a graphic nomogram. Nomograms are plots of the pH, $PaCO_2$, and

HCO_3^- that allow the user to rapidly determine whether arterial blood gas values are consistent with one of the six simple primary acid-base disturbances. Although nomograms are commonly used to identify acid-base disturbances in clinical practice, only individuals who fully comprehend the concepts of acid-base assessment should use these tools. Furthermore, nomograms have limited utility when dealing with complex acid-base derangements.

Acid-base disturbances are always manifestations of underlying clinical disorders. It is useful to specifically define the primary acid-base abnormality, as each disorder is caused by a limited number of disease processes. Establishing the specific disease process responsible for the observed acid-base disorder is clinically important because treatment of a given acid-base disorder will only be accomplished by correcting the underlying disease process.



Patient Encounters 1 through 5: Application of Basic Pathophysiology

Case Study 1

First, consider a patient with a pH of 7.16, a $PaCO_2$ of 70 mm Hg (9.3 kPa), and an HCO_3^- of 27 mEq/L (mmol/L). This person is acidemic (the pH is less than 7.35) with an increased $PaCO_2$ (greater than 45 mm Hg or 6 kPa) and an HCO_3^- that is minimally elevated (normal range 22 to 26 mEq/L or mmol/L). This appears to represent an acute respiratory acidosis with metabolic compensation. To ensure that the value of the serum HCO_3^- represents appropriate compensation, the formulas shown in Table 25–1 are applied. Because the $PaCO_2$ has increased by 30 mm Hg (4 kPa) and the expected change (Δ) in the HCO_3^- is 0.1 x $\Delta PaCO_2$ (in millimeters of mercury), our expected ΔHCO_3^- is 3 mEq/L or mmol/L (0.1 x 30 mEq/L or mmol/L). By adding this expected compensation (3 mEq/L or mmol/L) back to a normal HCO_3^- (24 mEq/L or mmol/L), it becomes evident that this patient's measured HCO_3^- of 27 mEq/L (or mmol/L) is consistent with metabolic compensation. These blood gases were obtained from a patient who had overdosed on heroin, a potent respiratory depressant.

Case Study 2

The next patient has a pH of 7.34, a $PaCO_2$ of 70 mm Hg (9.3 kPa), and an HCO_3^- of 35 mEq/L (mmol/L). Now both the $PaCO_2$ and the HCO_3^- are significantly elevated, two abnormalities with opposite effects on the pH. Because the pH is lower than 7.40, the primary disorder is the elevated $PaCO_2$—again a respiratory acidosis. The markedly elevated bicarbonate and the near-normal pH suggest that metabolic compensation has occurred and that the respiratory acidosis is chronic. Again, this degree of compensation (11 mEq/L or mmol/L) is appropriate. Because the $PaCO_2$ has increased by 30 mm Hg (4 kPa) and the expected ΔHCO_3^- is 0.35 x $\Delta PaCO_2$ (in millimeters of mercury) (see Table 25–1), the expected ΔHCO_3^- is 0.35 x 30 or ~11 mEq/L (mmol/L).

The changes in this patient's pH and HCO_3^- should be compared with the values from the patient in Case Study 1. It is critical to differentiate acute and chronic respiratory acidosis, as the acute form is often a medical emergency that requires intubation and mechanical ventilation, whereas the chronic form is typically a stable condition. The blood gases in Case Study 2 came from a patient with advanced emphysema who is a "CO_2 retainer" due to ineffective ventilation. Because this patient's disease is chronic, the elevated $PaCO_2$ developed very slowly and allowed for metabolic compensation.

Case Study 3

Now consider a patient whose ABG shows a pH of 7.50, a $PaCO_2$ of 29 mm Hg (3.86 kPa), and an HCO_3^- of 22 mEq/L (mmol/L). Because this person is alkalemic, the low $PaCO_2$ is the primary disturbance. Again, this degree of metabolic compensation (2 mEq/L or mmol/L) is appropriate. Because the $PaCO_2$ has decreased by 11 mm Hg (1.46 kPa) and the expected ΔHCO_3^- is 0.2 x $\Delta PaCO_2$ (in millimeters of mercury) (see Table 25–1) the HCO_3^- is expected to change by 0.2 x 11 or ~2 mEq/L (mmol/L). This ABG represents acute respiratory alkalosis with minimal metabolic compensation. These blood gases were obtained from a normal, healthy individual who was having an ABG collected as part of a research protocol. Anxiety caused by the anticipation of an arterial puncture for blood gas collection often causes hyperventilation with acute respiratory alkalosis.

Case Study 4

This patient has an ABG with the following values: pH of 7.50, a $PaCO_2$ of 47 mm Hg (6.3 kPa), and an HCO_3^- of 36 mEq/L (mmol/L). Again, both the $PaCO_2$ and the HCO_3^- are elevated, two abnormalities with opposite effects on the pH. Because the pH is higher than 7.40 the primary disorder is the elevated HCO_3^- (a metabolic alkalosis). In this instance the elevated $PaCO_2$ is consistent with respiratory compensation. From Table 25–1, the formula for the expected compensatory level of the $PaCO_2$ is (0.9 x HCO_3^-) + 15. In this case the predicted $PaCO_2$ would be (0.9 x 36) + 15, or 47 mm Hg (6.3 kPa). These blood gases are from a patient with congestive heart failure who is on chronic diuretic therapy that has caused her metabolic alkalosis. Although respiratory compensation has occurred, this compensation did not (and should not) return the pH entirely to normal.

Case Study 5

The final patient in this section has an ABG with a pH of 7.20, a $PaCO_2$ of 20 mm Hg (2.7 kPa), and an HCO_3^- of 8 mEq/L (mmol/L). Because the patient is acidemic the low bicarbonate is the primary abnormality and a metabolic acidosis is present. The $PaCO_2$ is consistent with respiratory compensation, as the expected value is $PaCO_2$ = (1.5 x HCO_3^-) + 8 which equals (1.5 x 8) + 8, or 20 mm Hg (2.7 kPa) (see Table 25–1). These blood gases came from a patient with chronic renal insufficiency who was hospitalized for gastroenteritis with profound diarrhea. In this instance, the patient had lost extensive amounts of HCO_3^- in her stool and was unable to adequately regenerate HCO_3^- given her underlying renal disease.

ADVANCED PATHOPHYSIOLOGY

The concepts in this section will be used to further expand the diagnostic algorithm shown in Fig. 25–1. Under normal circumstances the serum is in the isoelectric state. This means that the positively charged entities reported in a standard chemistry panel (cations: sodium and potassium) should be exactly balanced by the negatively charged entities (anions: chloride and bicarbonate). However, this relationship is consistently incorrect, as the measured cations are higher than the measured anions by 10 to 12 mEq/L (mmol/L). This discrepancy results from the presence of unmeasured anions (e.g., circulating proteins, phosphates, and sulfates). This apparent difference in charges, the serum **anion gap**, is calculated as follows:

$$\text{Anion gap} = \text{sodium} - (\text{chloride} + \text{bicarbonate})$$

Because the serum potassium content is relatively small and is tightly regulated, it is generally omitted from the calculation.

It is important to realize that the serum HCO_3^- concentration may be affected by the presence of unmeasured endogenous acids (lactic acidosis or ketoacidosis). Bicarbonate will attempt to buffer these acids, resulting in a 1 mEq loss of serum HCO_3^- for each 1 mEq of acid titrated. Because the cation side of the equation is not affected by this transaction, the loss of serum HCO_3^- results in an increase in the calculated anion gap. Identification of an increased anion gap is very important for identifying the etiology of the acid-base disorder. The concept of the increased anion gap will be applied later in the case studies section.

Any time an ABG is analyzed it is wise to concurrently inspect the serum chemistry values to calculate the anion gap. The body does not generate an anion gap to compensate for a primary disorder. As such, if the calculated anion gap exceeds 12 mEq/L (mmol/L) there is a primary metabolic acidosis regardless of the pH or the serum HCO_3^- concentration. The anion gap may be artificially lowered by decreased serum albumin, multiple myeloma, lithium intoxication, or a profound increase in the serum potassium, calcium, or magnesium.

Calculation of the anion gap also facilitates determination of the **excess gap** or the degree to which the calculated anion gap exceeds the normal anion gap. The excess gap is calculated as follows:

$$\text{Excess gap} = [\text{sodium} - (\text{chloride} + \text{bicarbonate})] - 12$$

The excess gap represents the amount of HCO_3^- that has been lost due to buffering unmeasured cations. The excess gap can be added back to the measured HCO_3^- to determine what the patient's bicarbonate would be if these endogenous acids were not present. This is a very valuable tool that can be used in narrowing the differential diagnosis of certain acid-base disorders as well as in uncovering occult or mixed acid-base disorders.

In summary, the approach to assessment of acid-base status involves four key steps: (1) initial inspection of the pH, $PaCO_2$, and HCO_3^-; (2) assessment of the adequacy of compensation; (3) calculation of the anion gap; and (4) calculation of the excess gap.

ETIOLOGY AND TREATMENT

❽ *After an acid-base disorder has been completely characterized, the patient's medical history, physical exam, and medications should be reviewed in order to establish the etiology of the given disorder.* Tables 25–3 through 25–7 outline the most commonly encountered causes of the primary acid-base disorders. The therapeutic approach to each of these acid-base derangements should emphasize a search for the cause, as opposed to immediate attempts to normalize the pH. ❾ *Although supportive measures to prevent the sequelae of marked acid-base abnormalities is often required, these therapies will be required indefinitely if the causative process is not also identified and corrected.*[7,8]

All patients with significant disturbances in their acid-base status require continuous cardiovascular and hemodynamic monitoring. Because frequent assessment of the patient's response to treatment is critical, an arterial line is often placed to minimize patient discomfort with serial ABG collections. If

TABLE 25–3. Common Causes of Metabolic Acidosis

Elevated Anion Gap[a]	Normal Anion Gap[a]
Intoxications	Bowel fistula
Methanol	Diarrhea
Ethylene glycol	Dilutional acidosis
Salicylates	Drugs
Paraldehyde	Acetazolamide[b]
Isoniazid	Ammonium chloride[b]
Ketoacidosis	Amphotericin B[b]
Diabetic	Arginine hydrochloride[c]
Ethanol	Cholestyramine[b]
Starvation	Hydrochloric acid[b]
Lactic acidosis	Lithium[b]
Carbon monoxide poisoning	Parenteral nutrition[b]
Drugs	Topiramate[b]
IV lorazepam (due to vehicle)[c]	Zonisamide[b]
Metformin[b]	Lead poisoning
Nitroprusside (due to cyanide accumulation)[b]	Renal tubular acidosis
Nucleoside reverse transcriptase inhibitors[b]	Surgical drains
Propofol[c]	Ureteral diversion
Seizures	Villous adenomas (some)
Severe hypoxemia	
Shock	
Renal failure	

[a]Anion gap = serum sodium concentration – (serum chloride concentration + serum bicarbonate concentration). Under normal circumstances the anion gap should be 10 mEq/L (mmol/L) or less.
[b]May be observed with therapeutic doses or overdoses.
[c]Typically observed only with overdoses.



Patient Encounters 6 through 10: Application of Advanced Pathophysiology

Case Study 6

Now consider a psychiatric patient who presents with a pH of 7.50, a $PaCO_2$ of 20 mm Hg (2.7 kPa), an HCO_3^- of 16 mEq/L (mmol/L), a sodium concentration of 140 mEq/L (mmol/L), and a chloride level of 103 mEq/L (mmol/L). Because this person is alkalemic, the low $PaCO_2$ is the primary disturbance and represents respiratory alkalosis. If this disturbance is a chronic respiratory alkalosis with metabolic compensation, the expected ΔHCO_3^- is 0.4 x $\Delta PaCO_2$ (in millimeters of mercury) or 0.4 x 20, which is 8 mEq/L (mmol/L). As such, the predicted HCO_3^- concentration should be 24 mEq/L (mmol/L) [normal] – 8 mEq/L (mmol/L) [expected compensation] or 16 mEq/L (16 mmol/L).

Given the ABG values shown, most clinicians would stop at this point and erroneously conclude that the patient has a chronic respiratory alkalosis with metabolic compensation. However, calculation of the anion gap reveals a "hidden" disorder. The anion gap for this patient is 140 – (103 + 16) = 21 mEq/L (mmol/L). The presence of this abnormally large anion gap indicates that a second primary disorder (an anion gap metabolic acidosis) is also present. The excess anion gap (21 – 12 = 9 mEq/L [mmol/L]) should be added back to the measured serum HCO_3^- (16 mEq/L [mmol/L]) to tell us the patient's baseline HCO_3^- level (before buffering the acid that has widened the anion gap). Doing so provides a normal starting HCO_3^- of 25 mEq/L (mmol/L), indicating that no further primary abnormalities are present.

This patient had ingested a large quantity of aspirin resulting in the classic findings of a salicylate overdose: a centrally mediated respiratory alkalosis with a concurrent anion gap metabolic acidosis.

Case Study 7

These values come from an unconscious man in the intensive care unit: pH of 7.40, $PaCO_2$ of 40 mm Hg (5.3 kPa), HCO_3^- of 24 mEq/L (mmol/L), sodium concentration of 145 mEq/L (mmol/L), and chloride level of 100 mEq/L (mmol/L). In this case, all of the ABG and electrolyte values are surprisingly normal. However, the anion gap is elevated [145 – (100 + 24) = 21 mEq/L or mmol/L]. The increased anion gap identifies a metabolic acidosis even though the pH is normal. The excess anion gap is 21 – 12 = 9 mEq/L (mmol/L). Adding the excess gap back to the measured HCO_3^- (24 mEq/L or mmol/L) gives a baseline HCO_3^- value of 33 mEq/L (mmol/L). This abnormally high value tells us that the patient has a concurrent metabolic alkalosis. This patient had end-stage kidney disease and after missing several dialysis sessions developed increasing uremia (causing the anion gap metabolic acidosis) with intense vomiting (causing the metabolic alkalosis). The acute alkalosis from his vomiting offset his chronic acidosis of renal failure, resulting in a normal pH. This is another example of a "hidden" acid-base derangement that would routinely be missed by clinicians who do not utilize a systematic approach to ABG interpretation.

Case Study 8

This intoxicated patient has a pH of 7.50, a $PaCO_2$ of 20 mm Hg (2.7 kPa), an HCO_3^- of 15 mEq/L (mmol/L), a sodium concentration of 145 mEq/L (mmol/L), and a chloride level of 100 mEq/L (mmol/L). Here the pH is high, the $PaCO_2$ and HCO_3^- are low, and there is an anion gap of 30 mEq/L (mmol/L). Because the patient is alkalemic, the low $PaCO_2$ is the primary disturbance and the patient has a respiratory alkalosis. By definition, the increased anion gap is consistent with a metabolic acidosis. The excess gap is 18 mEq/L (mmol/L), indicating that the patient's original HCO_3^- was 33 mEq/L (mmol/L), indicating a concurrent metabolic alkalosis. Despite this "triple disorder," the pH is only mildly abnormal. This man had alcoholic ketoacidosis (causing the anion gap metabolic acidosis), with persistent vomiting (causing metabolic alkalosis), and an aspiration pneumonia (causing respiratory alkalosis). Triple disorders represent the most complex acid-base derangements. A patient *cannot* have four primary acid-base disorders, as it is impossible to simultaneously hyperventilate (respiratory alkalosis) and hypoventilate (respiratory acidosis).

Case Study 9

The next labs are from a patient who was brought to the hospital unconscious and was quickly intubated. The blood work drawn prior to intubation shows a pH of 7.10, a $PaCO_2$ of 50 mm Hg (6.7 kPa), an HCO_3^- of 15 mEq/L (mmol/L), a sodium concentration of 145 mEq/L (mmol/L), and a chloride level of 100 mEq/L (mmol/L). This person is acidemic and has an elevated $PaCO_2$ with a low bicarbonate. Furthermore, the anion gap is markedly abnormal at 30 mEq/L. As such, the patient has a respiratory acidosis and an anion gap metabolic acidosis as primary disorders. Adding the excess gap (18 mEq/L or mmol/L) to the measured HCO_3^- (15 mEq/L or mmol/L) gives a starting bicarbonate of 33 mEq/L. This represents a concurrent primary metabolic alkalosis and the presence of a triple disorder. This patient had diabetic ketoacidosis (anion gap metabolic acidosis) with prominent vomiting (metabolic alkalosis) who became obtunded and was hypoventilating (respiratory acidosis).

Case Study 10

The final patient is a young woman with a pH of 7.15, a $PaCO_2$ of 15 mm Hg (2 kPa), an HCO_3^- of 5 mEq/L (mmol/L), a sodium concentration of 140 mEq/L (mmol/L) , and a chloride level of 110 mEq/L (mmol/L). She is acidemic with a low $PaCO_2$, a low bicarbonate, and an increased calculated anion gap (25 mEq/L or mmol/L). The expected $PaCO_2$ with respiratory compensation is (1.5 x HCO_3^-) + 8 or 15.5 mm Hg (2.1 kPa). As such, these values look like a simple anion gap metabolic acidosis with respiratory compensation. However, after adding the excess gap (13 mEq/L or mmol/L) back to the measured serum bicarbonate (5 mEq/L or mmol/L) it is apparent that this patient had a baseline HCO_3^- of 18 mEq/L (mmol/L). This patient has a concurrent anion gap metabolic acidosis and a non-anion gap metabolic acidosis. This woman was in the recovery phase of diabetic ketoacidosis. During this period, a non-anion gap acidosis can be present due to the kidneys' inability to regenerate bicarbonate from the ketoacids lost in the urine.

the anion gap was initially abnormal, serial chemistries should be followed to ensure that the anion gap resolves with treatment. Specific treatment decisions depend on the underlying pathophysiologic state (e.g., dialysis for renal failure, insulin for diabetic ketoacidosis, or improving tissue perfusion and oxygenation for lactic acidosis).

Metabolic Acidosis

❻ *Metabolic acidosis is characterized by a reduced arterial pH, a primary decrease in the HCO_3^- concentration, and a compensatory reduction in the $PaCO_2$. The etiologies of metabolic acidosis are divided into those that lead to an increase in the anion gap and those associated with a normal anion gap and are listed in Table 25–3.* Although there are numerous mnemonics to recall the differential diagnosis of metabolic acidosis, two simple ones are shown in Table 25–4. High anion gap metabolic acidosis is most frequently caused by lactic acidosis, ketoacidosis, and/or renal failure. Although there is considerable variation, the largest anion gaps are caused by ketoacidosis, lactic acidosis, and methanol or ethylene glycol ingestion.[9]

Symptoms of metabolic acidosis are attributable to changes in the cardiovascular, musculoskeletal, neurologic, or pulmonary function. Respiratory compensation requires marked increases in minute ventilation and may lead to dyspnea. Acidemia predisposes to ventricular arrhythmias and reduces cardiac contractility, each of which can result in pulmonary edema and/or systemic hypotension. Neurologic symptoms range from lethargy to coma and are usually proportional to the severity of the pH derangement. Chronic metabolic acidosis leads to a variety of musculoskeletal problems including impaired growth, rickets, osteomalacia, or osteopenia. These changes are believed to be caused by the release of calcium and phosphate during bone buffering of excess H^+ ions.

As previously discussed, in anion gap metabolic acidosis, the isoelectric state is maintained because unmeasured anions are present. With a *normal* anion gap metabolic acidosis, the isoelectric state is maintained by an increase in the measured chloride. Because of this, normal anion gap metabolic acidosis is often referred to as hyperchloremic acidosis.

In patients with a normal anion gap metabolic acidosis it is often helpful to calculate the urine anion gap (UAG). The UAG is calculated as follows:

$$UAG = (Urine\ Na^+ + Urine\ K^+) - Urine\ Cl^-$$

TABLE 25–4. Mnemonics for the Differential Diagnoses of Metabolic Acidosis

Elevated Anion Gap[a]	Normal Anion Gap[a]
M – Methanol	**U** – Ureteral diversion
U – Uremia	**S** – Saline infusion
D – Diabetic ketoacidosis	**E** – Exogenous acid
P – Paraldehyde	**D** – Diarrhea
I – Isoniazid	
L – Lactic acidosis	**C** – Carbonic anhydrase inhibitors
E – Ethylene glycol	**A** – Adrenal insufficiency
S – Salicylates	**R** – Renal tubular acidosis

[a]Anion gap = serum sodium concentration – (serum chloride concentration + serum bicarbonate concentration). Under normal circumstances the anion gap should be 10 mEq/L (mmol/L) or less.

TABLE 25–5. Common Causes of Metabolic Alkalosis

Urine Cl^- less than 10 mEq/L (less than10 mmol/L)	Urine Cl^- greater than 10 mEq/L (greater than10 mmol/L)
Alkali administration	Drugs[a]
IV bicarbonate therapy	Corticosteroid therapy
Oral alkali therapy	Diuretics
Parenteral nutrition with acetate	Hypokalemia
"Contraction alkalosis" post-diuretic use	Mineralocorticoid excess
Decreased chloride intake	Hyperaldosteronism
Loss of gastric acid	Bartter's syndrome
Vomiting	Cushing's syndrome
Nasogastric suction	
Post-hypercapnia	
Villous adenomas (some)	

[a]May be observed with therapeutic doses or overdoses.

TABLE 25–6. Common Causes of Respiratory Acidosis

Central nervous system disease	Pneumonia
Brain stem lesions	Pneumonitis
Central sleep apnea	Pulmonary edema
Infection	Restrictive lung disease
Intracranial hypertension	Ascites
Trauma	Chest wall disorder
Tumor	Fibrothorax
Vascular	Kyphoscoliosis
Drugs[a]	Obesity
Aminoglycosides	Pleural effusion
Anesthetics	Pneumoconiosis
β-Blockers	Pneumothorax
Botulism toxin	Progressive systemic sclerosis
Hypnotics	Pulmonary fibrosis
Narcotics	Spinal arthritis
Neuromuscular blocking agents	Smoke inhalation
Organophosphates	Upper airway obstruction
Sedatives	Foreign body
Neuromuscular disease	Laryngospasm
Guillain-Barré syndrome	Obstructive sleep apnea
Muscular dystrophy	Others
Myasthenia gravis	Abdominal distention
Polymyositis	Altered metabolic rate
Pulmonary disease	Congestive heart failure
Lower airway obstruction	Hypokalemia
Chronic obstructive pulmonary disease	Hypothyroidism
Foreign body	Inadequate mechanical ventilation
Status asthmaticus	

[a]May be observed with therapeutic doses or overdoses.

TABLE 25–7. Common Causes of Respiratory Alkalosis

Central nervous system disease	Pulmonary disease
Infection	Early restrictive lung disease
Trauma	Infection
Tumor	Pneumothorax
Vascular	Pulmonary edema
Drug- or toxin-induced[a]	Pulmonary embolism
Catecholamines	Tissue hypoxia
Doxapram	Burn injury
Methylphenidate	Excessive mechanical ventilation
Methylxanthines	Fever
Nicotine	Hepatic failure
Progesterone	Hypoxemia
Salicylates	Pain
Psychiatric disease	Post-metabolic acidosis
Anxiety	Pregnancy
Hyperventilation	Severe anemia
Hysteria	Thyrotoxicosis
Panic disorder	

[a]May be observed with therapeutic doses or overdoses.

The normal UAG ranges from 0 to 5 mEq/L (mmol/L) and represents the presence of unmeasured urinary anions. In metabolic acidosis, the excretion of NH_4^+ and concurrent Cl^- should increase markedly if renal acidification is intact. This results in UAG values from –20 to –50 mEq/L (mmol/L). This occurs because the urinary Cl^- concentration now markedly exceeds the urinary Na^+ and K^+ concentrations. Diagnoses consistent with an excessively negative UAG include proximal (type 2) renal tubular acidosis, diarrhea, or administration of acetazolamide or hydrochloric acid (HCl). Excessively positive values of the UAG suggest a distal (type 1) renal tubular acidosis.

In order to effectively treat metabolic acidosis, the *causative process* must be identified and treated.[17] The role of adjunctive therapy with sodium bicarbonate ($NaHCO_3$) is not universally agreed upon. However, most individuals would agree that $NaHCO_3$ is indicated when renal dysfunction precludes adequate regeneration of HCO_3^- or when severe acidemia (pH less than 7.10) is present. The metabolic acidosis seen with lactic acidosis and ketoacidosis generally resolves with therapy targeted at the underlying cause and $NaHCO_3$ may be unnecessary regardless of the pH. The metabolic acidosis of renal failure, renal tubular acidosis, or intoxication with ethylene glycol, methanol, or salicylates is much more likely to require $NaHCO_3$ therapy.

If $NaHCO_3$ is used, the plasma HCO_3^- should not be corrected entirely. Instead, aim at increasing HCO_3^- above an absolute value of 10 mEq/L. The total HCO_3^- deficit can be calculated from the current bicarbonate level ($HCO_{3\,curr}^-$), the desired bicarbonate level ($HCO_{3\,post}^-$), and the body weight (in kilograms) as follows:

$$HCO_3^- \text{ deficit} = [(2.4/HCO_{3\,curr}^-) + 0.4] \times \text{weight} \times (HCO_{3\,curr}^- - HCO_{3\,post}^-)$$

No more than half of the calculated HCO_3^- deficit should be given initially to avoid volume overload, hypernatremia, hyperosmolarity, overshoot alkalemia, and/or hypokalemia. The calculated HCO_3^- deficit reflects only the present situation and does not account for ongoing H^+ production and HCO_3^- loss. When giving HCO_3^- therapy, serial blood gases are needed to monitor therapy.

Another option for patients with severe acidemia is tromethamine (THAM). This inert amino alcohol buffers acids and CO_2 through its amine ($-NH_2$) moiety:

$$THAM\text{-}NH_2 + H^+ = THAM\text{-}NH_3^+$$

$$THAM\text{-}NH_2 + H_2O + CO_2 = THAM\text{-}NH_3^+ + HCO_3^-$$

Protonated THAM (with Cl^- or HCO_3^-) is excreted in the urine at a rate that is slightly higher than creatinine clearance. As such, THAM augments the buffering capacity of the blood without generating excess CO_2. THAM is less effective in patients with renal failure and toxicities may include hyperkalemia, hypoglycemia, and possible respiratory depression.

Metabolic Alkalosis

❼ *Metabolic alkalosis is characterized by an increased arterial pH, a primary increase in the HCO_3^- concentration, and a compensatory increase in the $PaCO_2$.* Patients will always hypoventilate to compensate for metabolic alkalosis—even if it results in profound hypoxemia. For a metabolic alkalosis to persist there must concurrently be a process that elevates serum HCO_3^- concentration (gastric or renal loss of acids) and another that impairs renal HCO_3^- excretion (hypovolemia, hypokalemia, or mineralocorticoid excess). The etiologies of metabolic alkalosis are listed in Table 25–5.

Patients with metabolic alkalosis rarely have symptoms attributable to alkalemia. Rather, complaints are usually related to volume depletion (muscle cramps, positional dizziness, and weakness) or to hypokalemia (muscle weakness, polyuria, and polydipsia).

In order to effectively treat metabolic alkalosis, the *causative process* must be identified and treated. The major causes of metabolic alkalosis are often readily apparent after carefully reviewing the patient's history and medication list. Always look for administration of compounds such as citrate in blood products and acetate in parenteral nutrition that can raise the HCO_3^- level. If the etiology of the metabolic alkalosis is still unclear, measurement of the urinary chloride may be useful. Some processes leading to metabolic alkalosis (vomiting, nasogastric suction losses, and factitious diarrhea) will have low urinary Cl^- levels (less than 25 mEq/L or mmol/L), while others (diuretics, hypokalemia, and mineralocorticoid excess) will have higher urinary Cl^- levels (greater than 40 mEq/L or mmol/L).

In general, contributing factors such as diuretics, nasogastric suction, and corticosteroids should be discontinued if possible. Any fluid deficits should be treated with IV normal saline. Recognize that patients with varieties of metabolic

alkalosis with high urine Cl^- (though rather uncommon) will be resistant to saline loading. Potassium supplementation should always be given if it is also deficient.

In patients with mild or moderate alkalosis who require ongoing diuresis but have rising HCO_3^- levels, the carbonic anhydrase inhibitor acetazolamide can be used to reduce the HCO_3^- concentration. Acetazolamide is typically dosed at 250 mg every 6 to 12 hours as needed to maintain the pH in a clinically acceptable range. If alkalosis is profound and potentially life-threatening (due to seizures or ventricular tachyarrhythmias) consideration can be given to hemodialysis or transient HCl infusion. The hydrogen ion deficit (in milliequivalents or millimoles) can be estimated from the current bicarbonate level ($HCO_3^-{}_{curr}$), the desired bicarbonate level ($HCO_3^-{}_{post}$), and the body weight (in kilograms) as follows:

$$H^+ \text{ deficit} = 0.4 \times \text{weight} \times (HCO_3^-{}_{curr} - HCO_3^-{}_{post})$$

After estimating the H^+ deficit, 0.1 to 0.2 N HCl is infused at 20 to 50 mEq/hour (mmol/hour) into a central vein. Arterial pH must be monitored at least hourly and the infusion stopped as soon as clinically feasible. Ammonium chloride and arginine hydrochloride, agents that result in the formation of HCl, should not be given, as they may lead to significant toxicity. Ammonium chloride causes accumulation of ammonia and is associated with encephalopathy. Arginine hydrochloride can induce life-threatening hyperkalemia through unclear mechanisms.

Respiratory Acidosis

❸ *Respiratory acidosis is characterized by a reduced arterial pH, a primary increase in the arterial $PaCO_2$ and, when present for sufficient time, a compensatory rise in the HCO_3^- concentration.* Because increased CO_2 is a potent respiratory stimulus, respiratory acidosis represents ventilatory failure or impaired central control of ventilation as opposed to an increase in CO_2 production. As such, most patients will have hypoxemia in addition to hypercapnia. The most common etiologies of respiratory acidosis are listed in Table 25–6.

Severe, acute respiratory acidosis produces a variety of neurologic abnormalities. Initially these include headache, blurred vision, restlessness, and anxiety. These may progress to tremors, asterixis, somnolence, and/or delirium. If untreated, terminal manifestations include peripheral vasodilation leading to hypotension and cardiac arrhythmias. Chronic respiratory acidosis is typically associated with cor pulmonale and peripheral edema.

In order to effectively treat respiratory acidosis, the *causative process* must be identified and treated. If a cause is identified, specific therapy should be started. This may include naloxone for opiate-induced hypoventilation or bronchodilator therapy for acute bronchospasm. Because respiratory acidosis represents ventilatory failure, an increase in alveolar ventilation is required. This can often be achieved by controlling the underlying disease (e.g., bronchodilators and corticosteroids in asthma) and/or physically augmenting ventilation.

Although their precise role and mechanisms of action are unclear, agents such as medroxyprogesterone, theophylline, and doxapram stimulate respiration and have been used to treat mild to moderate respiratory acidosis. Moderate or severe respiratory acidosis requires assisted ventilation. This can be provided to spontaneously breathing patients via bilevel positive airway pressure (BiPAP) delivered via a tight-fitting mask, or by intubation followed by mechanical ventilation. In mechanically ventilated patients, respiratory acidosis is treated by increasing the minute ventilation. This is achieved by increasing the respiratory rate and/or tidal volume.

As with the treatment of metabolic acidosis, the role of $NaHCO_3$ therapy is not well defined for respiratory acidosis. Realize that administration of $NaHCO_3$ can paradoxically result in increased CO_2 generation ($HCO_3^- + H^+ \rightarrow H_2CO_3 \rightarrow H_2O + CO_2$) and worsened acidemia. Careful monitoring of the pH is required if $NaHCO_3$ therapy is started for this indication. The use of THAM in respiratory acidosis (see metabolic acidosis, above) has unproven safety and benefit.

The goals of therapy in patients with chronic respiratory acidosis are to maintain oxygenation and to improve alveolar ventilation if possible. Because of the presence of renal compensation it is usually not necessary to treat the pH, even in patients with severe hypercapnia. Although the specific treatment varies with the underlying disease, excessive oxygen and sedatives should be avoided, as they can worsen CO_2 retention.

Respiratory Alkalosis

❹ *Respiratory alkalosis is characterized by an increased arterial pH, a primary decrease in the arterial $PaCO_2$ and, when present for sufficient time, a compensatory fall in the HCO_3^- concentration.* Respiratory alkalosis represents hyperventilation and is remarkably common. The most common etiologies of respiratory acidosis are listed in Table 25–7 and range from benign (anxiety) to life-threatening (pulmonary embolism). Some causes of hyperventilation and respiratory acidosis are remarkably common (hypoxemia or anemia).

The symptoms produced by respiratory alkalosis result from increased irritability of the central and peripheral nervous systems. These include light-headedness, altered consciousness, distal extremity paresthesias, circumoral paresthesia, cramps, carpopedal spasms, and syncope. Various supraventricular and ventricular cardiac arrhythmias may occur in extreme cases, particularly in critically ill patients. An additional finding in many patients with severe respiratory alkalosis is hypophosphatemia, reflecting a shift of phosphate from the extracellular space into the cells. Chronic respiratory alkalosis is generally asymptomatic.

It is imperative to identify serious causes of respiratory alkalosis and institute effective treatment. In spontaneously breathing patients, respiratory alkalosis is typically only mild or moderate in severity and no specific therapy is indicated. Severe alkalosis generally represents respiratory acidosis imposed on metabolic alkalosis and may improve with sedation. Patients receiving mechanical ventilation are treated with reduced minute ventilation achieved by decreasing the respiratory rate and/or tidal volume. If the alkalosis persists in the ventilated patient, high-level sedation or paralysis is effective.

SUMMARY

Acid-base disturbances are common clinical problems that are not difficult to analyze if approached in a consistent manner. The pH, $PaCO_2$, and HCO_3^- should be inspected to identify all abnormal values. This should lead to an assessment of which deviations represent the primary abnormality and which represent compensatory changes. The serum electrolytes should always be used to calculate the anion gap. In cases in which the anion gap is increased, the excess anion gap should be added back to the measured HCO_3^-. The anion gap and the excess gap are useful tools that can identify hidden disorders. This rigorous assessment of the patient's acid-base status, incorporated with the available clinical data, increases the likelihood that the clinician will successfully determine the cause of each identified disorder. Although supportive therapy is often required for profound acid-base disturbances, definitive therapy must target the underlying process that has led to the observed derangements.



Patient Care and Monitoring

1. Every patient with a suspected acid-base disturbance should have an arterial blood gas and a serum chemistry panel drawn concurrently. The results of these tests should be reviewed using a systematic approach to ensure proper interpretation.
2. What is the primary disorder? Has compensation occurred?
3. Is the anion gap excessively large? If so, does calculation of the excess gap identify another acid-base disorder?
4. Continuous cardiovascular and hemodynamic monitoring should be used for significant pH disturbances, as the most serious sequelae of acid-base disorders include electrolyte abnormalities, cardiac dysrhythmias, and systemic hypotension.
5. All acid-base abnormalities result from underlying disease processes. Definitive therapy for these disturbances requires treatment of the illness that has disrupted the pH equilibrium.
6. Review each patient's history, physical exam, and current medication list for potential causes of the observed acid-base disorder.
7. Serial arterial blood gases and serum chemistries should be compared, as every patient's acid-base status is continuously changing based on the underlying disease state and any therapy initiated.

ABBREVIATIONS

ABG:	arterial blood gas
BiPAP:	bilevel positive airway pressure
Cl^-:	chloride ion
CO_2:	carbon dioxide
Δ(delta):	change
H^+:	hydrogen ion
HCl:	hydrochloric acid
HCO_3^-:	bicarbonate
$HCO_{3\,curr}^-$:	current bicarbonate
$HCO_{3\,post}^-$:	post-therapy bicarbonate
Hg:	mercury
K^+:	potassium ion
kg:	kilogram
kPa:	kilopascal
L:	liter
mEq:	milliequivalent
mm:	millimeter
mmol:	millimole
Na^+:	sodium ion
$NaHCO_3$:	sodium bicarbonate
NH_2:	terminal amine group
NH_4^+:	ammonium
pH:	logarithm of the hydrogen ion concentration
$PaCO_2$:	partial pressure of arterial carbon dioxide
tCO_2:	total venous carbon dioxide
THAM:	tromethamine
UAG:	urine anion gap

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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26 Multiple Sclerosis

Melody Ryan



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Identify risk factors for multiple sclerosis.
2. Describe pathophysiologic findings of multiple sclerosis.
3. Recognize common presenting symptoms of multiple sclerosis.
4. Distinguish between the forms of multiple sclerosis based on the patient presentation and course of disease.
5. Compare and contrast multiple sclerosis disease-modifying treatment choices for a specific patient.
6. Determine appropriate symptomatic treatment choices and a detailed therapeutic plan for a specific patient.
7. Develop a monitoring plan for a patient placed on specific medications.

Key Concepts

❶ Multiple sclerosis symptoms are a function of the position of lesions within the central nervous system (CNS).
❷ The McDonald criteria allow the clinician to use the clinical exam in combination with magnetic resonance imaging (MRI) and cerebrospinal fluid data to make a diagnosis sooner, and thus begin treatment earlier.
❸ The clinical course of multiple sclerosis has been described in four basic patterns: relapsing remitting, secondary progressive, primary progressive, and progressive relapsing.
❹ Acute relapses are treated with corticosteroids to speed recovery of the patient.
❺ Disease-modifying therapies are used to decrease the number of relapses, prevent permanent neurologic damage, and prevent disability.
❻ Symptomatic treatment minimizes the impact of multiple sclerosis on quality of life.
❼ Dose-response curves have been observed with the beta interferons.
❽ There is no consensus on the best medication for initial therapy.
❾ Mitoxantrone should be reserved for patients with rapidly advancing disease who have failed other therapies.
❿ Multiple sclerosis patients must be treated with agents specific for upper motor neuron spasticity.

Multiple sclerosis (MS) is a complex inflammatory disease of the central nervous system (CNS) that is variable in terms of symptoms and presentation. The name refers to two features of the disease: multiple describes the number of CNS lesions; and sclerosis refers to the demyelinated lesions. Today, these lesions are usually called plaques, rather than scleroses. Although scientific understanding of MS has progressed at a rapid pace, there are still many areas of evolving knowledge.



Patient Encounter, Part 1

CN is a 28-year-old woman who complains of a 2-day history of weakness and tingling in her right arm and leg. These symptoms began over a 4-hour period. She also reports an episode 2 years ago of right eye pain and blurred vision that resolved over 1 month. She was diagnosed with optic neuritis at that time. Following an MRI, she is diagnosed with relapsing remitting MS today.

- What is optic neuritis?
- Why was her MS classified as relapsing remitting?
- How would you treat the episode today?

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EPIDEMIOLOGY AND ETIOLOGY

Epidemiology

Approximately 400,000 Americans have MS. Most are diagnosed with MS between the ages of 20 and 50 years. Twice as many women as men develop MS.[1] Risk factors associated with developing MS include: family history of MS, autoimmune diseases, or migraine; and personal history of autoimmune diseases or migraine.[2]

MS prevalence decreases with decreases in latitude.[3] The geographic risk of developing MS is not fixed. When people move from a higher- to a lower-risk area, the migrants' MS risk is intermediate between the risk of the original and the new areas. However, when individuals move from a lower- to higher-risk area, there is not much change in the migrants' MS risk.[3] Furthermore, future risk of developing MS may depend on the age at the time of the move; adolescence is the critical time period.[3]

Etiology

Inheritance Theory

MS probably has a genetic component; there is a 5% risk for family members of MS patients. Monozygotic twins, who share the same genetic material, are at highest risk, with a 25% to 30% concordance rate.[4] However, a straightforward inheritance pattern cannot fully explain the etiology of MS, because only a small proportion of patients have a known family member with MS.[4]

Environment Theory

Over 20 infectious agents have been incriminated as etiologic agents; for many the causal relationship has been disproved, and for others there is conflicting evidence. Human herpesvirus 6 (HHV-6) is currently the most likely causative virus. HHV-6 may initiate the autoimmune processes of MS in one of two ways. First, HHV-6 is structurally similar to myelin basic protein. When T cells become sensitive to HHV-6, the cells may attack myelin basic protein. Second, HHV-6 may directly stimulate the complement cascade, activating autoimmune processes.[5] Infection with HHV-6 alone cannot fully explain MS, because HHV-6 is found in 75% of all people, but MS is much more rare.

PATHOPHYSIOLOGY

While the actual causative agent of MS is not clear, the final result is the development of an autoimmune disorder with areas of CNS demyelination and axonal transection.

Demyelination

An unknown antigen presented by the major histocompatibility complex (MHC) class II molecules causes T cells to become autoreactive (Fig. 26–1). Once activated, T cells penetrate the blood–brain barrier by attachment to upregulated adhesion molecules and production of matrix metalloproteinases that cause blood–brain barrier breakdown. In the CNS, the T cells come into contact with antigen-presenting cells and proliferate. The T-helper cells differentiate into proinflammatory T helper-1 (Th1) cells and anti-inflammatory T helper-2 (Th2) cells.[7] T helper-1 cells secrete cytokines that enhance macrophage and microglial cells that may attack **myelin**.[7]

B cells likely cross previously damaged sections of the blood–brain barrier to arrive in the CNS, an area normally free of B cells. Autoreactive T cells cause B cells to form autoantibodies to myelin. B-cell antibodies also initiate the complement cascade which causes myelin degradation.[7]

Axonal Transection

Transection or severing of the axon disrupts nerve signals completely and irreversibly.[8] There is growing evidence that cytotoxic (CD8+) T cells cause axonal injury.[5] Axonal transection begins as early as 2 weeks after diagnosis and continues throughout the course of the disease.[9]

CLINICAL PRESENTATION, DIAGNOSIS, AND CLINICAL COURSE

Diagnosis

MS diagnostic criteria were revised in 2001 and are known as the McDonald criteria (Fig. 26–2).[18–20] MS diagnosis requires that plaques be disseminated in time and space. Previously, diagnosis relied heavily on clinical examination. ❷ *The McDonald criteria allow the clinician to use the clinical exam in combination with magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) data to make a diagnosis sooner, and thus begin treatment earlier (Table 26–1).*

Clinical Course

❸ *The clinical course of MS has been described in four basic patterns: relapsing remitting, secondary progressive, primary progressive, and progressive relapsing* (Fig. 26–3). Relapsing remitting MS develops into secondary progressive MS in 50% of patients within 10 years and 75% of patients within 25 years of initial diagnosis.[22] Rating scales used to assess the clinical effects of MS are shown in Table 26–2. MS reduces overall life expectancy 6 to 7 years.[24] Suicide is disproportionately high in MS patients, accounting for about 15% of MS-related deaths.[25]

TREATMENT

Desired Outcomes and General Approach to Treatment

The overall goal of MS treatment is to prevent permanent neurologic damage. There are three general approaches to

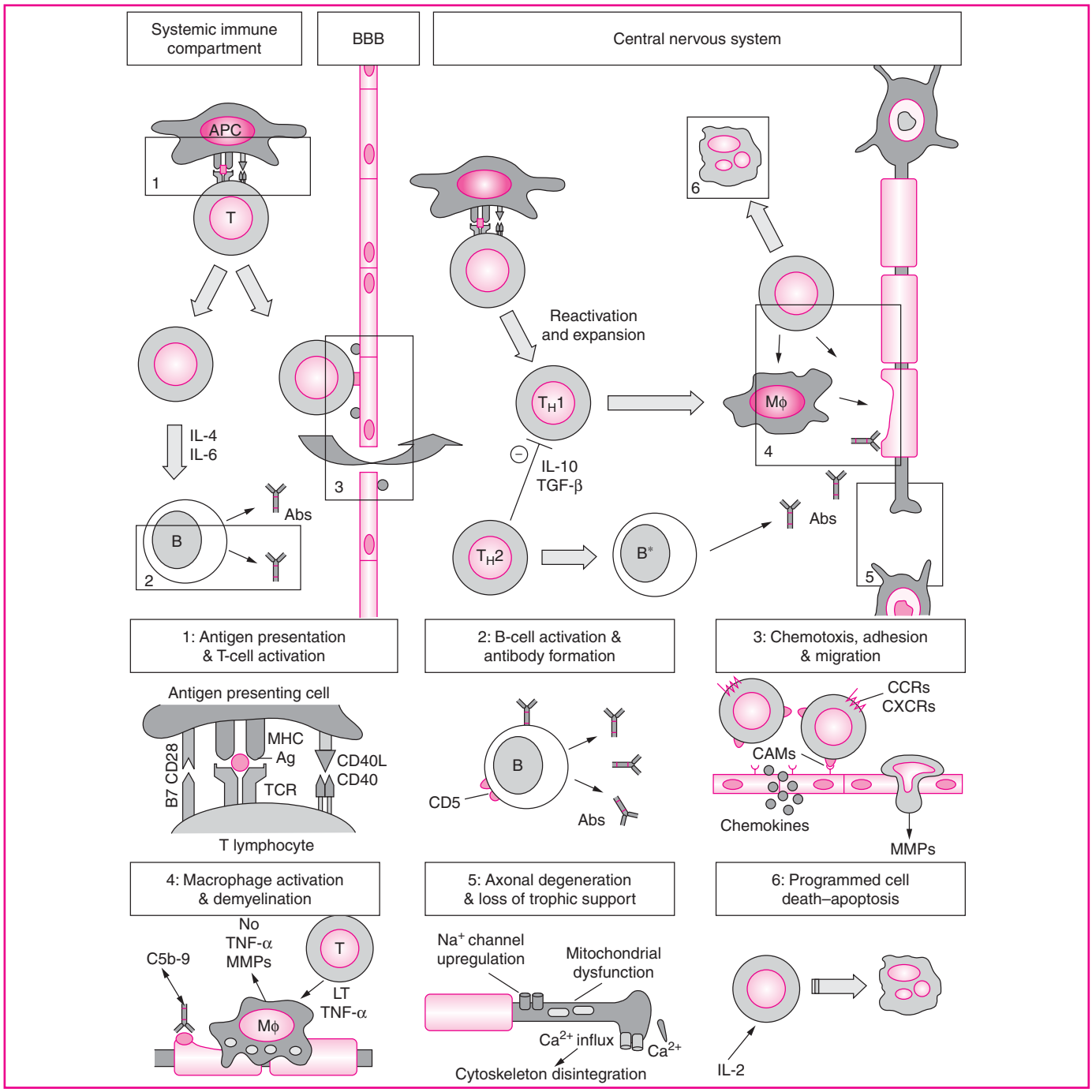


FIGURE 26–1. Synoptic view of the immune response in the pathogenesis of multiple sclerosis. Autoreactive T cells recognize with their TCR a specific autoantigen presented by MHC class II molecules and the simultaneous delivery of co-stimulatory signals (CD 28, B7, CD40, CD 40L) on the cell surface of APCs, such as macrophages, in the systemic immune compartment (*panel 1*). Activated T lymphocytes can cross the BBB in order to enter the CNS. The mechanisms of transendothelial migration is mediated by the complex interplay of CAMs, chemokines, and their receptors (CCRs, CXCRs) and MMPs (*panel 3*). Within the CNS, T cells activate microglia cells/macrophages (Mϕ) to enhanced phagocytic activity; production of cytokines, such as TNF-α and LT; and the release of toxic mediators, such as NO, propagating demyelination and axonal loss. Abs crossing the BBB or locally produced by B cells or mast cells (B*) contribute to this process. Autoantibodies activate the complement cascade resulting in the formation of the membrane-attack complex (C5b-9) and its subsequent lysis of the target structure (*panels 2 and 4*). The upregulation of Na^+ and Ca^{2+} channels on the axon as well as mitochondrial dysfunction and loss of trophic support contribute to axonal disintegration and degeneration (*panel 5*). The inflammatory response is regulated by anti-inflammatory cytokines, such as IL-10 or TGF-β, as well as IL-2, inducing programmed cell death (apoptosis) in immunoreactive T lymphocytes (*panel 6*). Abs, autoantibodies; Ag, antigen; APC, antigen-presenting cells; BBB, blood–brain barrier; CAM, cellular adhesion molecule; CNS, central nervous system; IL, interleukin; LT, lymphotoxin; MHC, major histocompatibility complex; MMP, matrix metalloproteinases; NO, nitric oxide; T, T cell; TCR, T-cell receptor; TGF, transforming growth factor; TNF, tumor necrosis factor. (From Wiendl H, Kieseier BC, Disease-modifying therapies in multiple sclerosis: An update on recent and ongoing trials and future strategies. Expert Opin Investig Drugs 2003;12:689–712, with permission.)

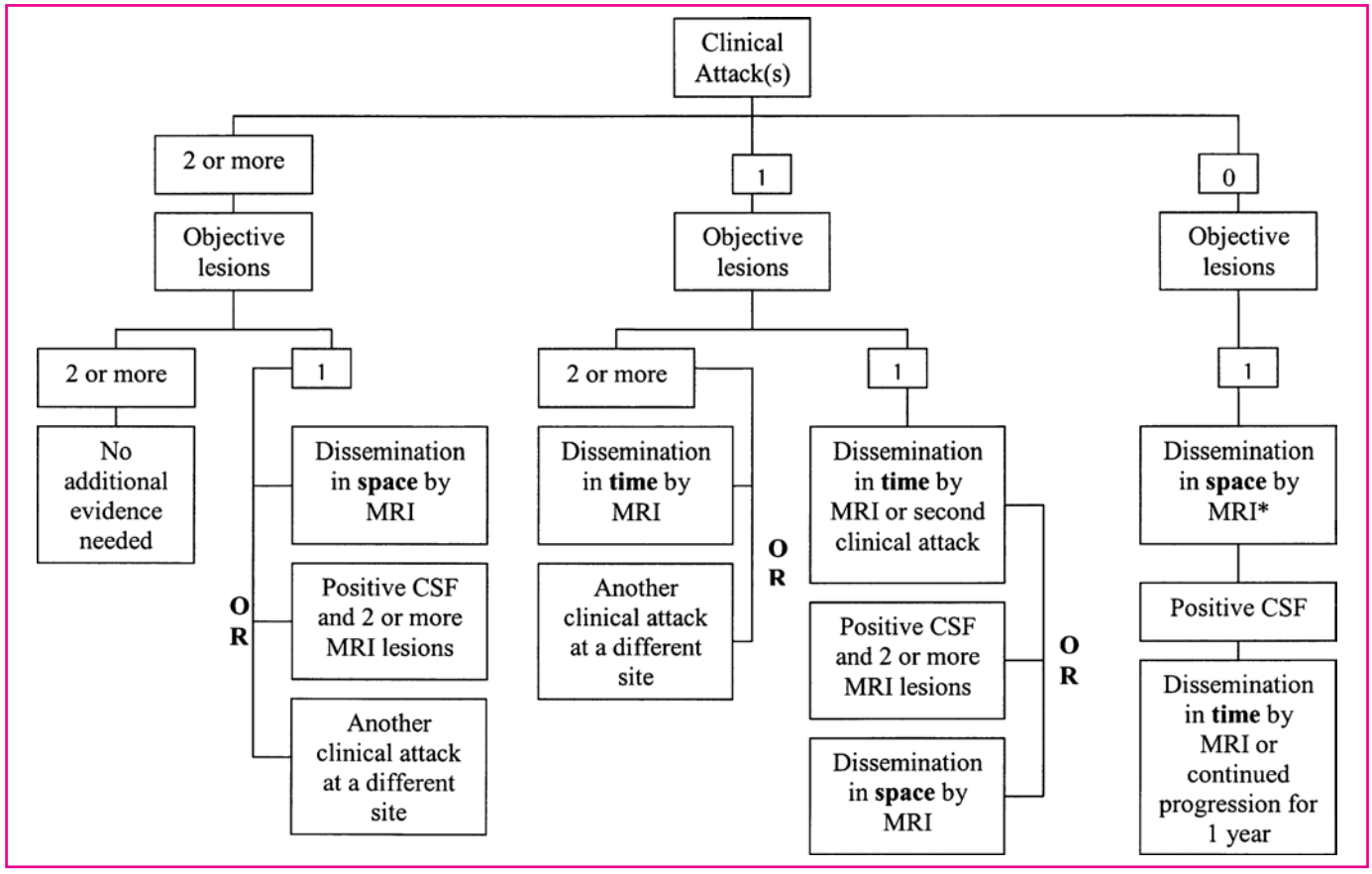


FIGURE 26–2. McDonald diagnostic criteria for MS. MRI evidence of dissemination over time is a gadolinium-enhancing lesion on a MRI done at least 3 months following onset of clinical attack at a site different from the initial attack, or a gadolinium-enhancing lesion or new T2-weighted lesion 6 months following onset of clinical attack. Positive CSF is oligoclonal immunoglobulin G bands in CSF but not serum or elevated immunoglobulin G index. Positive evoked potentials are delayed, but maintain a well-preserved wave form.
*Dissemination in space by MRI evidence of nine or more T2-weighted brain lesions, or two or more cord lesions, or four to eight brain and one cord lesion, or positive visual evoked potentials with four to eight MRI lesions, or positive visual evoked potentials with less than four brain lesions plus one cord lesion.
MRI, magnetic resonance imaging; CSF, cerebrospinal fluid.

treatment. ❹ First, *acute relapses are treated with corticosteroids to speed recovery.* ❺ Second, *disease-modifying therapies are used to decrease the number of relapses, prevent permanent neurologic damage, and prevent disability.* ❻ Third, *symptomatic treatment minimizes the impact of MS on quality of life.*

TABLE 26–1. Diagnostic Tests for MS[21]

Test	Findings in Multiple Sclerosis
Magnetic resonance imaging	
T2 weighted	Demyelinated plaques, both active and inactive
Gadolinium enhanced	Active demyelinating plaques
Cerebrospinal fluid analysis	Oligoclonal bands of immunoglobulin G
	Elevated immunoglobulin G index
Evoked potentials	Slowed nerve impulse conduction

Pharmacologic Treatment

Treatment of Acute Relapses

The mechanism of action of corticosteroids used for acute relapses is not completely clear, but may involve the following actions:

- Prevention of inflammatory cytokine activation;
- Inhibition of T-cell activation;
- Prevention of immune cells from entering the CNS; and
- Increased death of activated immune cells.[26]

Corticosteroids hasten functional recovery after relapses.[27] Intravenous adrenocorticotropic hormone, intravenous methylprednisolone, or oral prednisone are used for treatment of relapses. Generally, intravenous methylprednisolone is considered the drug of choice for acute relapses.[28]

Recent studies show equal efficacy of equivalent doses of intravenous and oral dosage forms.[30,31] Some clinicians are now using oral prednisone for patients experiencing relapses to avoid the discomfort, inconvenience, and expense of intravenous therapy.

Adverse Effects

Short-term use of corticosteroids is not associated with most of the adverse effects of chronic steroid use. The most common adverse effects encountered are gastrointestinal upset, insomnia, and mood swings.[28]

Dosing and Administration

Methylprednisolone is usually given 1 g/day intravenously as one or divided doses for 3 to 5 days. Oral prednisone 1250 mg/day provides an equivalent dose.

Clinical improvement usually begins during corticosteroid treatment. No standard exists for the administration of an oral prednisone taper after the intravenous methylprednisolone treatment. If a taper is given, it is usually completed over 1 to 2 weeks.

Outcome Evaluation

- Monitor the patient for improvement of relapse symptoms.
- Educate the patient regarding possible adverse effects of acute use of corticosteroids and have her or him report any unexpected occurrences.

Disease-Modifying Therapies

A number of agents have been used to modify the disease course of MS. This chapter will focus on the five agents that have an indication for use in MS: subcutaneous interferon beta 1a (Rebif); intramuscular interferon beta 1a (Avonex); interferon



Clinical Presentation[10–17]

❶ *MS symptoms are a function of the position of lesions within the CNS.* Because myelin increases the speed of nerve impulse transmission, demyelination slows the speed of transmission. No impulses can be transmitted if the axon is transected. The primary symptoms of MS are caused by this delay or cessation of impulses. Secondary symptoms of MS result from the primary symptoms.

Primary Symptoms	Frequency of Occurrence	Related Secondary Symptoms
Urinary symptoms	90%	
Incontinence		Decubitus ulcers
Urinary retention		Urinary tract infections
Spasticity	60%	Falls, care difficulties, pain, gait problems
Visual symptoms		
Optic neuritis	55%	Falls, care difficulties
Diplopia		
Bowel symptoms		
Incontinence	29–51%	Decubitus ulcers
Constipation	35–54%	Pain
Depression	50%	Suicide
Cognitive deficits	50%	Care difficulties
Weakness		Falls, care difficulties, gait problems
Fatigue	76–92%	
Uhthoff's phenomenon	80%	
Sexual dysfunction		
Erectile dysfunction	70%	
Female sexual dysfunction	72%	
Tremor	25%	
Pain		
Trigeminal neuralgia	2%	
Lhermitte's sign	9%	
Dysesthetic pain	18%	

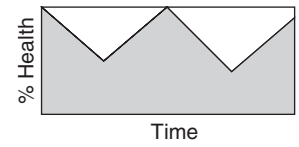
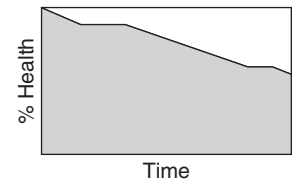
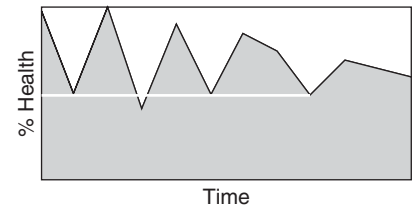
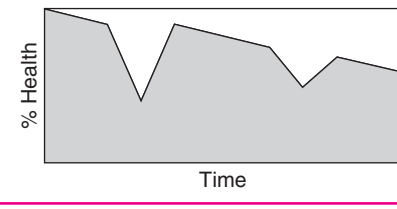
MS Type	Definition	Patients Affected	Example
Relapsing Remitting	Episodes of acute worsening of neurologic function (relapses) followed by a varying degree of recovery, with a stable course between attacks (remissions)	85%	
Primary Progressive	Gradual, nearly continuous, worsening with minor fluctuations but no distinct relapses	10%	
Secondary Progressive	Initial relapsing-remitting disease course followed by progression with or without occasional relapses, minor remissions, and plateaus	50% of relapsing remitting patients within 10 years of diagnosis	
Progressive Relapsing	Progressive disease from onset, with clear acute relapses, with or without recovery, with periods between relapses characterized by continuing progression	5%	

FIGURE 26–3. Comparison of clinical course of multiple sclerosis by type.

beta 1b (Betaseron); glatiramer acetate (Copaxone); and mitoxantrone (Novantrone). A broad look across all studies of these immunomodulators shows about 30% reduction in relapses.[32]

Beta Interferons

Pharmacology and Mechanism of Action The mechanism of action of beta interferons is complex and not completely understood. The following properties are thought to be important to the mechanism of action:

- Decrease in T-cell activation, decreasing cytokine secretion and preserving myelin;
- Prevention of upregulation of adhesion molecules on activated T cells, limiting the number of T cells that can get into the brain;
- Suppression of matrix metalloproteinases, maintaining the integrity of the blood–brain barrier;
- Decrease in microglial proliferation, preserving myelin;
- Promotion of formation of Th-2 cells rather than Th-1 cells, decreasing inflammation; and
- Inhibition of viruses, important if MS has a viral etiology.[7,33]

Efficacy ***Patients with relapsing remitting MS:*** A meta-analysis of all beta interferons determined that treated patients were 27% and 19% less likely to have a relapse during the first and second years of treatment, respectively, than those who had



Patient Encounter, Part 2

CN begins to improve after 2 days of methylprednisolone 1 g intravenously daily. The treatment team wants to begin a disease-modifying treatment.

- Do you agree that she should be on a disease-modifying treatment? Why?
- If so, which treatment would you choose? Recommend a dosing regimen.
- How should the patient be counseled on the chosen treatment?
- Develop a care plan for the patient.

TABLE 26–2. Clinical Rating Scales Used in MS[23]

Expanded Disability Status Scale (EDSS)
Rates functional systems from 0 (normal) to 10 (death due to MS)
Emphasis is on ambulation over other symptoms
Multiple Sclerosis Functional Composite (MSFC)
Three-part tool rating ambulation, limb function, and cognitive function
Composite score is compared to standardized population
Correlates better with magnetic resonance imaging data than EDSS

TABLE 26–3. Comparison of Disease-Modifying Therapies[27,38–40,43,46]

Drug	Dose	Route	Frequency	Adverse Effects
Interferon beta 1a (Avonex)	30 mcg	IM	Weekly	Flu-like symptoms 61% Anemia 8%
Interferon beta 1a (Rebif)	44 mcg	SQ	Three times per week	Flu-like symptoms 28% Injection site reactions 66% Leukopenia 22% Increased aspartate aminotransferase/ alanine transaminase 17–27%
Interferon beta 1b (Betaseron)	0.25 mg	SQ	Every other day	Flu-like symptoms 60–76% Injection site reactions 50–85% Asthenia 49% Menstrual disorder 17% Leukopenia 10–16% Increased aspartate aminotransferase/ alanine transaminase 4–19%
Glatiramer acetate (Copaxone)	20 mg	SQ	Daily	Injection site reaction 90% Systemic reaction 15%
Mitoxantrone (Novantrone)	12 mg/m^2 up to 140 mg/m^2	IV	Every 3 months	Nausea 76% Alopecia 61% Menstrual disorders 61% Urinary tract infection 32% Amenorrhea 25% Leukopenia 19% γ-Glutamyl transpeptidase increase 15%

received placebo.[34] Early treatment after a first clinical attack delayed time to a second attack by 9 to 13 months compared to placebo.[35,36] ***Patients with secondary progressive MS who experience relapses:*** Beta interferons have mixed results for slowing disease progression in secondary progressive MS. The MS Therapy Consensus Group states that treatment is most likely to be effective if clinical relapses or MRI signs of inflammatory activity are present.[37]

Adverse Effects Adverse effects are common with the beta interferons (Table 26–3). Commonly, flulike symptoms consist of fever, fatigue, muscle aches, malaise, and chills. Symptoms begin a few hours after the injection and dissipate 8 to 24 hours later.[38] Preventive measures can be employed (Table 26–4). In temperature-sensitive patients, beta interferon–induced fever can transiently worsen MS symptoms.[39] Injection site reactions can range from redness to necrosis. There are preventative and treatment measures for injection site reactions (see Table 26–4). At the threshold laboratory values shown in Table 26–4, interferon should be temporarily discontinued. When values return to normal, interferon can be resumed with gradual dose increases and careful monitoring.[39] Alpha and gamma interferons have been associated with depression. MS patients also commonly are depressed, even without beta interferon treatment. Because of conflicting data, it is difficult to determine whether beta interferons cause or worsen MS-related depression.[15]

Neutralizing Antibodies Antibodies to beta interferons can form over time and reduce the clinical effect of beta interferons.[40] The clinical effect of neutralizing antibodies is seen 18 to

TABLE 26–4. Prevention or Treatment Strategies for Beta Interferon Adverse Effects[38,39]

Flu-like Symptoms	Injection Site Reaction	Laboratory Abnormalities[a]
• Inject dose in the evening • Begin at $^1/_4$ – $^1/_2$ dose for 2 weeks of treatment, then increase to a full dose • Use ibuprofen 200 mg before and 6 and 12 hours after injection • Alternatives to ibuprofen include acetaminophen, prednisone taper, and pentoxifylline	• Bring medication to room temperature • Ice injection site prior to the injection • Rotate injection sites • If severe, use hydrocortisone 1% cream on the site • If necrotic: temporarily discontinue; consult dermatologist; do not use topical corticosteroids	• Hemoglobin less than 9.4 g/dL (94 g/L or 5.8 mmol/L) • White blood cells less than 3×10^3/mm^3 (less than 3×10^3/μL or less than 3×10^9/L) • Absolute neutrophil count less than 1.5×10^3/mm^3 (less than 1.5×10^3/μL or less than 1.5×10^9/L) • Platelets less than 75×10^3/mm^3 (less than 75×10^3/μL or less than 75×10^9/L) • Bilirubin greater than 2.5 times baseline • AST/ALT greater than 5 times baseline • Alkaline phosphatase greater than 5 times baseline

[a]At these threshold values, beta interferon should be temporarily discontinued and laboratory values monitored.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

24 months after treatment begins.[40] **Neutralizing antibodies** can form against all of the beta interferons, but frequency and route of administration affect neutralizing antibody development: 28% to 47% for subcutaneous interferon beta-1b; 12% to 28% for subcutaneous interferon beta-1a; and 2% to 6% for intramuscular interferon beta-1a.[40]

Many issues surrounding neutralizing antibodies remain such as standardization of the neutralizing antibody assay, testing recommendations, and treatment recommendations for positive tests.[41] Neutralizing antibodies may disappear even with continued treatment. Neutralizing antibodies exhibit cross-reactivity with the other beta interferons.[41]

Dosing and Administration Dose, frequency, and route of administration differ between the beta interferon products (see Table 26–3). ❼ *Dose-response curves have been observed with the beta interferons.* However, it is not known if the total weekly dose or the frequency of administration is most important.[37]

Glatiramer Acetate

Pharmacology and Mechanism of Action The mechanism of action of glatiramer acetate is not fully known; however, the following properties have been observed:

- Binds to MHC class II, blocking the activation of T cells;
- Activates Th-2 cells, preventing inflammation; and
- Activated Th-2 cells secrete brain-derived neurotrophic factor, which may be neuroprotective.[7,33]

Efficacy Glatiramer acetate reduces relapses by 28% each year compared to placebo. Additionally, relapses occurred later compared to placebo (322 days versus 219 days).[42]

Adverse Effects Patients commonly report pain, redness, itching, swelling, and bruising at injection sites (see Table 26–3). Icing the injection site before and after the injection improves these reactions. If the patient experiences significant pain at the injection site, topical anesthetics can be used. The systemic reaction may involve flushing, chest tightness, palpitations, anxiety, and shortness of breath. This reaction usually occurs within 30 minutes of the injection and lasts no longer than 30 minutes. Many patients may experience this reaction only once. If desired, doses can be reduced by 75% for the week following the reaction, then increased by 25% per week until the patient returns to the full dose.[43]

Issues with Self-Injected Disease-Modifying Therapies

Adherence Adherence and continuation of these injectable medications can be a significant problem. Overall, there is no significant difference between the rates of discontinuation for the products (17% to 41%). The main reasons for discontinuation are adverse effects and lack of efficacy. Realistic expectations regarding therapy improve adherence rates.[44]

Choosing Therapy ❽ *There is no consensus on the best medication for initial therapy.* Comparative beta interferon trials indicate better efficacy with more frequent and/or higher dosing.[37] This consideration must be balanced with neutralizing antibody development and patient acceptance and tolerance.

Patient Education Refer to Table 26–5 for key components of patient education for self-injection.

Mitoxantrone

Pharmacology and Mechanism of Action Mitoxantrone is an anthracenedione antineoplastic that is indicated for multiple sclerosis. The mechanisms of action thought to be important for MS are as follows:

- Causes **apoptosis** in T and antigen-presenting cells, preventing initial T cell activation;
- Inhibits DNA and RNA synthesis, decreasing the proliferation of T cells, B cells, and macrophages;
- Decreases cytokine release, preventing inflammation; and
- Inhibits macrophages, preventing myelin degradation.[45]

Efficacy Mitoxantrone is indicated for secondary progressive MS, progressive relapsing MS, and for patients with worsening relapsing remitting MS. It reduces the clinical attack rate and attack-related MRI outcome measures in patients with relapsing disease. ❾ Because of significant potential for toxicities, *mitoxantrone should be reserved for patients with rapidly advancing disease who have failed other therapies.*[27]

Adverse Effects Adverse effects are seen regularly in patients given mitoxantrone (see Table 26–3). Patients often experience bluish discoloration of the sclera and the urine for 24 hours after infusion.[46] Transient leukopenia and neutropenia are common with a nadir 10 to 14 days after the infusion. Patients should avoid exposure to infectious individuals during this time.[46] Patients taking mitoxantrone should not receive live virus vaccines; other vaccines should be held for 4 to 6 weeks after a mitoxantrone dose.[46] Amenorrhea, caused by a direct toxic effect on the ovary, may be permanent, an important consideration because the MS population includes women of childbearing potential.[27]

TABLE 26–5. Patient Education for Self-Injection

Keep all non-refrigerated supplies together and out of the reach of children and pets
Allow medications to warm to room temperature
Wash hands thoroughly
Choose injection site, rotating between sites
Ice area to be injected for no more than 15 minutes, if desired
Clean injection site thoroughly with alcohol or soap and water
Administer injection
Ice injection site for no more than 15 minutes after injection, if desired

Cardiotoxicity is a serious, rare adverse effect of mitoxantrone. The incidence of congestive heart failure was 0.15% in patients with normal left ventricular ejection fraction and 2.18% in those who had asymptomatic left ventricular ejection fraction of less than 50% at baseline.[46] Therefore, mitoxantrone should not be used in patients with baseline cardiomyopathy, even if asymptomatic. The risk of cardiotoxicity is dose-related. The maximum lifetime dose of mitoxantrone is 140 mg/m^2, or about 3 years of MS therapy. The use of cyclooxygenase-2 inhibitors should be avoided in patients receiving mitoxantrone because of a potential for worsening cardiac toxicity.[46]

Acute myelogenous leukemia has been observed in 0.07% of MS patients treated with mitoxantrone.[46] This form of acute leukemia appears within 2 to 4 years of initiating mitoxantrone and is generally responsive to standard antileukemic therapy.

Dosing and Administration Mitoxantrone is infused intravenously over 30 minutes to reduce the chance of cardiotoxicity.[46] Mitoxantrone is administered every 3 months, if cardiac function and laboratory values are normal (Table 26–6).

Monitoring Disease-Modifying Therapies

- Assess the patient periodically for changes in primary or secondary symptoms.
- Monitor the patient for adverse effects according to the specific medication (see Tables 26–3 and 26–6).
- Assess regularly for adherence with appointments and all components of therapy.

Symptomatic Therapies

MS patients develop many symptoms that require treatment. The symptoms most unique to MS are fatigue and **spasticity**; these will be discussed in more depth. Other important symptoms such as urinary incontinence, pain, and depression, are discussed only briefly because there are other chapters in this text devoted to the management of these symptoms.



Patient Encounter, Part 3

After 3 years of treatment, CN has had one additional relapse, but otherwise is doing fairly well. At her routine clinic appointment, she describes some difficulty walking due to leg spasticity and urinary incontinence episodes that occur about twice a week.

- What treatment options are available for spasticity, and which would you choose?
- Should this patient's incontinence be treated?
- If so, what medication would you recommend?
- Recommend a dosing regimen and monitoring plan.

Fatigue

There are nonpharmacologic and pharmacologic strategies for decreasing the impact of fatigue on the lifestyle of MS patients (Table 26–7). Pharmacologic management of fatigue may include amantadine or stimulants; however, evidence of efficacy from randomized controlled trials is limited.

Spasticity

The goals of treating spasticity can be patient-specific. For ambulatory patients, reducing spasticity may improve mobility. For bed-bound patients, treating spasticity may relieve pain and

TABLE 26–6. Monitoring Disease-Modifying Therapies

Therapy	Tests	Frequency
Beta interferons (Avonex, Betaseron, Rebif)	Complete blood count, bilirubin, electrolytes, AST, ALT, γ-glutamyl transferase, alkaline phosphatase	Baseline, 4–6 weeks, 12 weeks, then every 3 months
	EDSS, MSFC, neurologic history and examination	Every 3 months during the first year of therapy then every 6 months
Mitoxantrone (Novantrone)	Complete blood count, bilirubin, AST, ALT, alkaline phosphatase, pregnancy test	Before each infusion
	Electrocardiogram	Baseline
	Echocardiogram or multiple gated acquisition (MUGA) scan	Baseline and every 6–12 months; prior to each infusion after 100 mg/m^2
	EDSS, MSFC, neurologic history and examination	Every 3 months during the first year of therapy then every 6 months
Glatiramer acetate (Copaxone)	EDSS, MSFC, neurologic history and examination	Every 3 months during the first year of therapy then every 6 months

ALT, alanine aminotransferase; AST, aspartate aminotransferase; EDSS, Expanded Disability Status Scale; MSFC, Multiple Sclerosis Functional Composite.

TABLE 26–7. Pharmacologic and Nonpharmacolgic Treatments for Fatigue[47]

Nonpharmacologic	Pharmacologic
• Appropriate rest:activity ratio • Use of assistive devices to conserve energy • Environmental modifications to make activities more energy-efficient • Cooling strategies to avoid the fatigue caused by elevations in core body temperature due to heat, exercise-related exertion, and fever • Regular aerobic exercise, geared to the person's ability, to promote cardiovascular health, strength, improved mood, and reduce fatigue • Stress management techniques	*First-line therapies:* Amantadine 100 mg orally every morning and early afternoon Modafinil 200 mg orally daily *Second-line therapies:* Pemoline 75–140 mg/day divided into 2–3 doses Methylphenidate 10–20 mg every morning and noon

ease transfers and care. Physical therapy is a nonpharmacologic treatment for spasticity.[11]

MS patients usually have upper motor neuron spasticity. This type of spasticity cannot be treated with muscle relaxants such as carisoprodol. ⑩ *MS patients must be treated with agents specific for upper motor neuron spasticity* (Table 26–8).[48] MS spasticity is classified as focal or generalized. If the spasticity primarily involves only one muscle group, it is focal and may benefit from botulinum toxin administration.[11] Systemic medications are used for generalized spasticity. No clear conclusion can be reached regarding the superiority in efficacy of one antispasticity agent over another; medication selection is usually based on adverse effects (see Table 26–8).[11,48]

Other Symptoms

Two types of urinary tract symptoms are commonly seen in MS: incomplete bladder emptying and incontinence. Incomplete bladder emptying is due to dyscoordination of the external urethral sphincter and detrusor activity.[14] Most patients who develop this condition require intermittent or permanent urinary catheterization.[14] Incontinence in most MS patients is caused by neurogenic detrusor overactivity. First-line treatment is anticholinergics such as oxybutynin, tolterodine, flavoxate, or tricyclic antidepressants with antimuscarinic properties.

Bowel symptoms in MS patients can include both fecal incontinence and constipation. Fecal incontinence is difficult to treat. Some patients may have improvement if they use a regular schedule for emptying the bowel with laxative suppositories or enemas. Alternatively, antidiarrheal medications such as loperamide can be used.[14]

Desipramine and sertraline are efficacious for MS-related depression.[15] If beta interferon treatment appears to be causing depression, discontinuation could be considered.

Phosphodiesterase 5 inhibitors such as sildenafil are effective for MS-induced erectile dysfunction.[14] In women, vaginal dryness or dyspareunia may respond to lubricating jellies.

Outcome Evaluation

- Assess patient for improvement of primary and secondary symptoms.
- Monitor for adverse effects of prescribed medications.
- Monitor for adherence with regimen.
- Monitor for emergence of symptoms of depression

TABLE 26–8. Comparison of Antispasticity Agents[11]

Place in Therapy	Medication	Mechanism of Action	Dose
First-line	Baclofen	Pre- and postsynaptic γ-aminobutyric acid β receptor blocker	5 mg orally three times daily, increase by 5 mg/dose every 3 days to a maximum of 80 mg/day
	Tizanidine	Centrally-acting α_2-receptor agonist	4 mg orally daily, increase by 2–4 mg 3–4 times daily to a maximum of 36 mg/day
Second-line	Dantrolene	Direct inhibitor of muscle contraction by decreasing the release of calcium from skeletal muscle sarcoplasmic reticulum	25 mg orally daily, increase to 25 mg 3–4 times daily, then increase by 25 mg every 4–7 days to a maximum of 400 mg/day
	Diazepam	γ-Aminobutyric acid agonist	2–10 mg orally 3–4 times/day
Third-line	**Intrathecal** baclofen	Pre- and postsynaptic γ-aminobutyric acid β receptor blocker	Titrated individually, usual range 62–749 mcg/day
Focal spasticity	Botulinum toxin	Prevents release of acetylcholine in the neuromuscular junction	Individualized



Patient Care and Monitoring

1. Once diagnosed, work with the patient to select either a beta interferon or glatiramer acetate, considering:

- Route of administration
- Frequency of administration
- Adverse-effect profile and other concerns (e.g., neutralizing antibodies and concomitant depression)

2. Obtain the required baseline laboratory studies (Table 26–6).
3. Educate the patient regarding self-injection (Table 26–5).
4. Assess the patient for symptomatic treatment needs.
5. Initiate needed symptomatic treatments.
6. Refer the patient to the National MS Society for information, newsletters, and local support groups (www.nmss.org).
7. Instruct the patient to contact the clinician for any sudden changes in symptoms that may suggest a relapse.
8. Monitor the patient for efficacy and adverse effects of disease-modifying and symptomatic therapies every 3 months for the first year and every 6 months thereafter and as required for selected therapy (Table 26–6).
9. Treat any relapses with methylprednisolone intravenously or prednisone orally.

ABBREVIATIONS

Abs: autoantibodies
ALT: alanine aminotransferase
APC: antigen-presenting cell
AST: aspartate aminotransferase
BBB: blood–brain barrier
CAM: cellular adhesion molecule
CNS: central nervous system
CSF: cerebrospinal fluid
EDSS: Expanded Disability Status Scale
HHV-6: human herpesvirus 6
IL: interleukin
LT: lymphotoxin
MHC: major histocompatibility complex
MMP: matrix metalloproteinase
MRI: magnetic resonance imaging
MS: multiple sclerosis
MSFC: Multiple Sclerosis Functional Composite
MUGA: multiple gated acquisition
NO: nitric oxide
TCR: T-cell receptor
TGF: transforming growth factor
Th-1: T helper-1 cells
Th-2: T helper-2 cells
TNF: tumor necrosis factor

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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27 EPILEPSY

Timothy E. Welty and Edward Faught



LEARNING OBJECTIVES

UPON COMPLETION OF THE CHAPTER, THE READER WILL BE ABLE TO:

1. Describe the epidemiology and social impact of epilepsy.
2. Define terminology related to epilepsy, including seizure, convulsion, and epilepsy.
3. Describe the basic pathophysiology of seizures.
4. Describe the basic pathophysiology of epilepsy.
5. Differentiate and classify seizure types when provided a description of the clinical presentation of the seizure and electroencephalogram.
6. Identify key therapeutic decision points in the treatment of epilepsy.
7. Establish therapeutic goals for pharmacotherapy in a patient with epilepsy.
8. Discuss nonpharmacologic treatments for epilepsy.
9. Recommend an appropriate pharmacotherapeutic regimen for the treatment of epilepsy.
10. Select appropriate monitoring parameters for a pharmacotherapeutic regimen of epilepsy.
11. Devise a plan for switching a patient from one antiepileptic regimen to a different regimen.
12. Recognize complications of pharmacotherapy for epilepsy.
13. Analyze potential drug interactions with antiepileptic drugs.
14. Determine when and how to discontinue antiepileptic drug therapy.
15. Educate a patient or caregiver on epilepsy and pharmacotherapy for this disorder.

KEY CONCEPTS

❶ A distinction between convulsions, a single seizure, pseudoseizure, and epilepsy should be made in patients presenting with possible seizures.

❷ Selection of appropriate pharmacotherapy is dependent upon distinguishing, identifying, and understanding different seizure types.

❸ Prior to starting pharmacologic therapy, it is essential to determine the risk of the patient having a subsequent seizure.

❹ Mechanisms of action, effectiveness for specific seizure types, common adverse effects, and potential for drug interactions are key elements in selecting medications for individual patients.

❺ Patients receiving antiepileptic drugs for seizures should have regular monitoring for seizure frequency, seizure patterns, acute adverse effects, chronic adverse effects, and possible drug interactions.

❻ Antiepileptic drug therapy should usually be initiated carefully using a titration schedule to minimize adverse events.

❼ Changes in antiepileptic drug regimens should be done in a stepwise fashion, keeping in mind drug interactions that may be present and necessitate dosage changes in concomitant drugs.

❽ Discontinuation of antiepileptic drugs should be done gradually, only after the patient has been seizure-free for 2 to 5 years and with careful consideration of factors predictive of seizure recurrence.

❾ Children and women with epilepsy have unique problems related to the use of antiepileptic drugs.

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EPIDEMIOLOGY, SOCIAL IMPACT, AND ETIOLOGY

Epidemiology

Epilepsy is a disorder that afflicts approximately 2 million individuals in the United States, with an age-adjusted prevalence of approximately 4 to 7 cases per 1000 persons.[1] The incidence of epilepsy in the United States is estimated at 35 to 75 cases per 100,000 persons per year, which is similar to that of other developed countries.[2,3] In developing countries, the incidence is higher at 100 to 190 cases per 100,000 persons per year, possibly related to poor health care and prenatal care, increased risk of neurologic trauma, and increased rates of infections. About 8% of the United States' population will experience a seizure during their lifetime. New-onset seizures occur most frequently in infants below 1 year of age and in adults after age 55.[4] However, the largest number of patients suffering from epilepsy is between the ages of 15 and 64 years.

Social Impact

Epilepsy is a disorder with profound impact on a patient's lifestyle. All states limit driving for individuals who have recently had a seizure with impaired consciousness and restrictions vary from state to state.[5] Patients who live in communities without adequate public transportation face major impediments to simple activities of daily life, such as purchasing groceries or getting to a job. Education is also problematic for patients with epilepsy.[6,7] Individuals with persistent seizures have poor school attendance. Fifty percent of patients with epilepsy complain of cognitive difficulties and believe their seizures interfere with learning. Additionally, patients with epilepsy score 50% lower on standardized examinations and have lower graduation rates from high school and college. Transportation and educational difficulties combine with persistent seizures to cause patients with epilepsy to be unemployed or underemployed. Thus, this group of patients faces multiple financial difficulties and often does not have health insurance.

Finally, patients with epilepsy are often dependent upon caregivers to assist with medications, transportation, and ensuring their safety. Caregivers should be informed of the patients' medical needs and how to assist should a seizure occur.

Etiology

For nearly 80% of patients with epilepsy, the underlying etiology is unknown.[8] The most common recognized causes of epilepsy are head trauma and stroke. Developmental and genetic defects are the cause of about 5% of cases of epilepsy. Central nervous system (CNS) tumors, central nervous system infections, and neurodegenerative diseases are other common causes. Other important causes of epilepsy are human immunodeficiency virus infection or neurocysticercosis infection, primarily occurring in Latin America.

Isolated seizures that are not epilepsy can be caused by stroke, central nervous system trauma, central nervous system infections, metabolic disturbances (e.g., hyponatremia and hypoglycemia), and hypoxia. If these underlying causes of seizures are not corrected, they may lead to the development of recurrent seizures or epilepsy. Medications can also cause seizures. Some drugs that are commonly associated with seizures include tramadol, bupropion, theophylline, some antidepressants, some antipsychotics, amphetamines, cocaine, imipenem, lithium, excessive doses of penicillins or cephalosporins, and sympathomimetics or stimulants.

PATHOPHYSIOLOGY

Seizures

Regardless of the underlying etiology, all seizures involve a sudden electrical disturbance of the cerebral cortex. A population of neurons fires rapidly and repetitively for seconds to minutes. Cortical electrical discharges become excessively rapid, rhythmic, and synchronous. This phenomenon is presumably related to an excess of excitatory neurotransmitter action, a failure of inhibitory neurotransmitter action, or a combination of the two. In the individual patient, however, it is usually impossible to identify which neurochemical factors are responsible.

Neurotransmitters

The major excitatory neurotransmitter in the cerebral cortex is glutamate.[9] When glutamate is released from a presynaptic neuron, it attaches to one of several receptor types on the postsynaptic neuron. The result is opening of membrane channels to allow sodium or calcium to flow into the postsynaptic neuron, thus depolarizing it and transmitting the excitatory signal.[10] Many antiepileptic drugs (e.g., phenytoin, carbamazepine, and lamotrigine) work by interfering with this mechanism, either by blocking the release of glutamate or by blocking the sodium or calcium channels, thus preventing excessive excitation.[11] These drugs typically do not block normal neuronal signaling, only the excessively rapid firing characteristic of a seizure. For this reason they do not usually affect normal brain function.

The major inhibitory neurotransmitter in the cerebral cortex is γ-aminobutyric acid (GABA). It attaches to neuronal membranes and opens chloride channels. When chloride flows into the neuron, it becomes hyperpolarized and less excitable. This mechanism is probably critical for shutting off seizure activity by controlling the excessive neuronal firing. Some antiepileptic drugs, primarily barbiturates and benzodiazepines, work by enhancing the action of GABA.

Cortical function is modulated by many other neurotransmitters. However, their role in the pathophysiology of epilepsy and in the action of antiepileptic drugs is not yet well known.

Neuronal Mechanisms

Seizures originate in a group of neurons which do not have normal electrical behavior.[12] Individual neuronal firing is prolonged and repetitive. This long, abnormal depolarization is called a paroxysmal depolarizing shift (PDS).

The excessive electrical discharges can spread to other neurons, either adjacent ones or distant ones connected by fiber tracts. The seizure thus spreads to other areas of the brain, recruiting them into the uncontrolled firing pattern. The neurons involved may not be abnormal themselves, but are diverted from their normal functioning to participate in the wildly excessive discharges. The degree of spread and the location of brain areas involved determine the clinical manifestations of the seizure.

Nearly all seizures stop spontaneously, because after seconds to minutes brain inhibitory mechanisms become strong enough to shut off the abnormal excitation.

Epilepsy

Epilepsy is the tendency to have seizures on a chronic, recurrent basis. This implies that there is a permanent change in cortical function which renders neurons more likely to participate in a seizure discharge. This process is referred to as epileptogenesis, and the exact way in which it occurs is not known. A process thought to be similar to epileptogenesis in humans occurs after prolonged, intermittent electrical stimulation of animal brains and is known as kindling. Epilepsy may develop days, months, or many years after an insult to the cortex. It may be that an originally small group of abnormal neurons causes adjacent or connected neurons to gradually become abnormal as well, by bombarding them over time with frequent, repeated electrical impulses. When the network of abnormal neurons becomes sufficiently large, it becomes capable of sustaining an excessive firing pattern for at least several seconds: a seizure. This hyperexcitable network of neurons is then the seizure focus.

If the change in cortical electrical characteristics is permanent, why don't seizures occur all the time? This is probably because the occurrence of an individual seizure depends upon an interplay of environmental and internal brain factors which from time to time result in loss of the normal mechanisms that contain and control abnormal neuronal firing. Some common factors are sleep loss and fatigue, but it is impossible to determine what sets off a particular seizure in most patients.

In some patients, epilepsy worsens over time, with the seizures becoming more frequent as patients grow older. This does not occur in most patients with epilepsy. In those so affected, it is possible that the seizures themselves may cause some damage to the cortex; loss of neurons, especially inhibitory neurons, has been demonstrated in tissue from seizure foci. Other changes occur in brain areas affected by seizures: reorganization of connections between groups of neurons may strengthen excitatory connections and weaken inhibitory connections, making the occurrence of future seizures more likely. Additionally, epilepsy is associated with an increased mortality rate.[13] For these reasons, an argument can be made for controlling epileptic seizures with medications as early as possible. This may reduce the possibility of permanent changes in brain function, although this hypothesis is unproven.

Genetic Factors

Patients with seizures may be concerned that their children or other family members will inherit epilepsy. This fear is usually unfounded. Patients with acquired causes of seizures, such as head trauma or stroke, will not transmit the problem. There is a group of patients, however, who apparently have epilepsy on a genetic basis. Most of these individuals have primary generalized epilepsy.[14,15] Usually these patients develop seizures during childhood. However, the hereditary tendency is not strong. Complex inheritance patterns are usually seen, indicating the likely involvement of several abnormal genes or other factors for seizures to be clinically expressed in offspring. Thus, most patients can be reassured that their children and siblings are unlikely to develop epilepsy. Increasing numbers of epilepsy syndromes are being identified as being of genetic origin, and once the specific genes are identified it may be possible to target drug therapies more specifically toward individual biochemical defects.

SEIZURE CLASSIFICATION AND PRESENTATION

General Principles

Careful diagnosis and identification of seizure types is essential to proper treatment of epilepsy. Numerous schemes and descriptions of seizures exist, but the International League Against Epilepsy (ILAE) has established the currently accepted standard for classifying epileptic seizures (Fig. 27–1) and epilepsies or epilepsy syndromes (Table 27–1).[16,17] Classification of epileptic seizures is based upon electroencephalographic (EEG) findings combined with the clinical findings or semiology of the seizure events. Clinical presentations of seizures vary widely, depending on the region and amount of brain involved in the seizure.

Primary Generalized Seizures

If the entire cerebral cortex is involved in the seizure from the onset of the seizure, the seizure is classified as primary generalized. The following are types of primary generalized seizures.

- *Tonic-clonic:* Characterized by a sudden loss of consciousness accompanied by tonic extension and rhythmic clonic contractions of all major muscle groups. The duration of the seizure is usually 1 to 3 minutes. These seizures are often described as "grand mal."

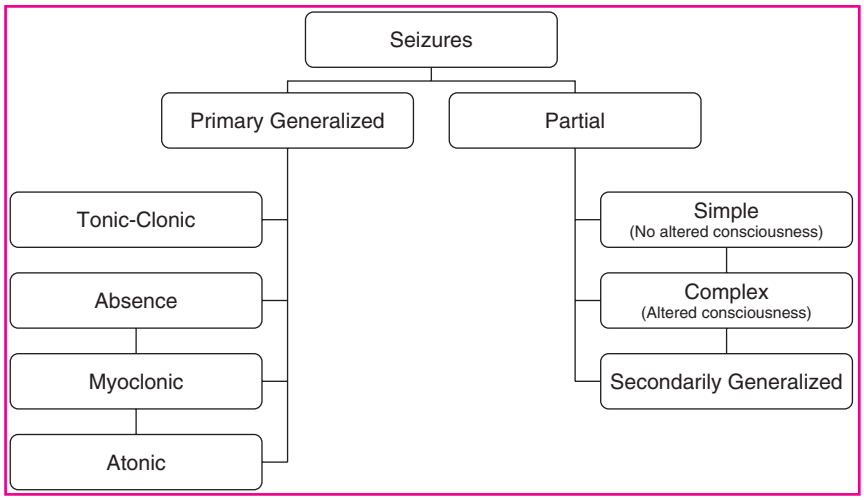


FIGURE 27–1. International League Against Epilepsy classification of epileptic seizures. Data from reference 16.

- *Absence:* Sudden and brief (i.e., several seconds in duration) losses of consciousness without muscle movements. These seizures are often described as daydreaming or blanking out episodes. A common term for these seizures is "petit mal."
- *Myoclonic:* Single and very brief jerks of all major muscle groups. Patients with these may not lose consciousness, due to the seizure lasting less than 3 to 4 seconds. Patients may describe these seizures as shoulder shrugs or spinal chills. Myoclonic seizures may cluster and build into a generalized tonic-clonic seizure.
- *Atonic:* The patient loses consciousness and muscle tone. No muscle movements are typically noted, and the patient will fall when they are not lying down or sitting in a chair. These seizures may be described as "falling out."

TABLE 27–1. International League Against Epilepsy Classification Scheme for Epilepsies and Epilepsy Syndromes

I. Localization-related (focal, local, or partial) epilepsies and epileptic syndromes
  A. Idiopathic with age-related onset
    1. Benign childhood epilepsy with centrotemporal spikes
    2. Childhood epilepsy with occipital paroxysms
  B. Symptomatic
II. Generalized epilepsies and epileptic syndromes
  A. Idiopathic and age-related onset
    1. Benign neonatal epilepsy
    2. Childhood absence epilepsy (pyknolepsy)
    3. Juvenile myoclonic epilepsy (impulsive petit mal)
    4. Juvenile absence epilepsy with generalized tonic-clonic seizure on awakening
  B. Secondary (idiopathic or symptomatic)
    1. West syndrome (infantile spasms)
    2. Lennox-Gastaut syndrome
  C. Symptomatic
    1. Nonspecific etiology (early myoclonic encephalopathy)
    2. Specific syndromes (epileptic seizures that may complicate many diseases, e.g., Ramsay-Hunt syndrome, Unverricht's disease)

Data from reference 17.

Partial Seizures

When the seizure begins in a localized area of the brain, it is defined as partial. There are three types of partial seizures in the current classification system.

- *Simple:* The patient will have a sensation or uncontrolled muscle movement of a portion of their body without an alteration in consciousness. The type of sensation or movement is dependent on the location of seizure in the brain.
- *Complex:* Although the seizure is localized in a specific area of the brain, like a simple partial seizure, this seizure causes an alteration in the patient's level of consciousness.
- *Secondarily generalized:* Seizures that start as a simple or complex partial seizure and spread to involve the entire brain. Patients may report a warning or aura, and these are actually the start of the seizure.

Epilepsy Syndromes

Classification of epilepsies and epilepsy syndromes is helpful in determining appropriate pharmacotherapy. This classification scheme is based on the type of seizures a patient has and an attempt to identify the etiology of the epilepsy or epilepsy syndrome.

- *Idiopathic epilepsies:* These syndromes are thought to be due to genetic alterations, but the underlying etiology is not identified. Neurologic functions are completely normal apart from the occurrence of seizures.
- *Symptomatic epilepsies:* There is an identifiable cause for the seizures, such as trauma or hypoxia.



Clinical Presentation and Diagnosis

General

Typically, health care providers are not able to observe a patient's seizures, and for most types of seizures the patient has no memory of the event. It is important to obtain a careful history from the patient and any individuals who witnessed the seizures.

Common Descriptions of Seizures

The clinical presentation of seizures will vary from patient to patient depending on the portion of brain involved in the seizure. Events will tend to be stereotypical for an individual patient.

Patients who experience seizures may complain of paroxysmal spells of:

- Blanking out spells, lapses in memory, periods of altered consciousness
- Warnings or auras consisting of various sensations or automatic, uncontrolled movements
- Daydreaming
- Jerks, shoulder shrugs, and sudden chills of the spine
- Falling out

Associated Symptoms

- Incontinence, usually of urine
- Tongue biting
- Traumatic injuries, usually associated with falling during a seizure

Diagnosis

Description of events: The patient and any witnesses to the seizures should be carefully interviewed to obtain a full and complete description of typical seizures.

Neurologic examination: Usually, the neurologic physical examination is completely normal. Any neurologic deficits that are identified should be fully investigated, because seizures do not usually cause permanent, detectable neurologic deficits.

Electroencephalogram

A routine EEG can be helpful if epileptiform discharges are seen. However, the EEG may be normal between seizures, and most routine EEGs are not performed during a seizure. Maneuvers such as sleep deprivation, photic stimulation, hyperventilation, or prolonged monitoring can help reveal EEG changes consistent with epilepsy.

Neuroimaging (preferably a magnetic resonance imaging [MRI] scan of the brain): Imaging of the brain is important to rule out obvious causes of seizures such as stroke or tumors. An MRI is also helpful in detecting mesial temporal sclerosis, a finding often associated with mesial temporal lobe epilepsy and predictive of positive surgical outcomes.

Video-EEG monitoring: A procedure consisting of continuous video monitoring of the patient with a simultaneous EEG. Usually a patient is monitored in the hospital for 4 to 5 days. This procedure is used to determine if the patient is truly having seizures, to determine the specific type of seizures the patient is having, and to localize the area of the brain that is the origin for the seizures.

- *Cryptogenic epilepsies:* In these epilepsies the seizures are the result of an underlying neurologic disorder that is often ill-defined or undocumented. Neurologic functions are often abnormal or developmentally delayed in patients with cryptogenic epilepsies.

A complete description of a patient's epilepsy should include the seizure type with the epilepsy or syndrome type (i.e., idiopathic, symptomatic, or cryptogenic).

Commonly encountered epilepsy syndromes are:

- *Juvenile myoclonic epilepsy (JME):* A primary generalized epilepsy syndrome that usually starts in the early to middle teenage years and has a strong familial component. Patients have myoclonic jerks and tonic-clonic seizures and may also have absence seizures.
- *Lennox-Gastaut syndrome (LGS):* Patients with this syndrome have cognitive dysfunction and mental retardation. Their seizures usually consist of a combination of tonic-clonic, absence, atonic, and myoclonic seizures.
- *Mesial temporal lobe epilepsy (MTLE):* A type of epilepsy that consists of partial seizures arising from the mesial temporal lobe of the brain. Often this type of epilepsy is associated with an anatomic change described as hippocampal sclerosis. Patients with this type of epilepsy often have excellent outcomes with surgery for epilepsy.
- *Infantile spasms:* A seizure syndrome that occurs in infants less than 1 year of age. It is characterized by a specific EEG pattern and spasms or jitters and is also known as West's syndrome. Infants with infantile spasms often develop other seizure types and epilepsies later in life.

Other Classifications

The ILAE is proposing a new classification system that improves the description of the seizure type and epilepsy.[18,19] The proposed scheme revolves around five axes:

- Axis 1: description of the seizure event
- Axis 2: epileptic seizure type or types
- Axis 3: any syndrome type
- Axis 4: etiology when known
- Axis 5: degree of impairment by the epilepsy.

This classification system is undergoing final review and should become the standard in the near future.

Diagnosis

❶ Determining a correct and accurate diagnosis is essential prior to any consideration of pharmacotherapy. When a patient complains of paroxysmal, stereotypical spells that may be seizures, it must be determined if the spells are really seizures. Numerous other disorders, including syncope, psychogenic nonepileptic events (i.e., pseudoseizures), anxiety attacks, cardiac arrhythmias, hypoglycemia, transient ischemic

attacks, tics, and complicated migraine headaches, are often mistaken for seizures by patients and caregivers.

A proper diagnostic workup of a patient presenting with seizures should include the following elements:

- Thorough neurologic examination
- Electroencephalogram
- Laboratory tests (CBC, LFT, and serum chemistry)
- Neuroimaging (preferably magnetic resonance imaging)

Patients with epilepsy may have completely normal findings in these assessments. Many of the tests are done to rule out other causes of seizures (e.g., infection or electrolyte imbalance). Often the EEG appears normal between seizures.[20] Several manipulations can be done in an attempt to capture seizure or seizure-like activity on the EEG. These include sleep deprivation, photic stimulation, prolonged (greater than 20 minutes) EEG recording, and 24-hour EEG monitoring with video correlation.

TREATMENT

Desired Outcomes

The ultimate outcome goal for any patient with epilepsy is elimination of all seizures without any adverse effects of the treatment. An effective treatment plan would allow the patient to pursue a normal lifestyle with complete control of seizures. Specifically, the treatment should enable the patient to drive, perform well in school, hold a reasonable job, and function effectively in the family and community. However, due to the intractability of the seizures or sensitivity to antiepileptic drugs (AEDs), many patients are not able to achieve these outcomes. In these cases, the goal of therapy is to provide a tolerable balance between reduced seizure severity and/or frequency and medication adverse effects that optimizes the individual's ability to have a lifestyle as nearly normal as possible.

General Approach to Treatment

❷ Once it is concluded that the patient has seizures, the type of seizure and epilepsy syndrome, if any, must be determined. Proper identification and classification of the seizure type is most helpful in selecting appropriate pharmacotherapy. Without an accurate classification of the seizure type, it is possible to select a medication that is ineffective or even harmful to the patient.

❸ Additionally, the risk of a subsequent seizure must be determined. If there is an underlying treatable cause, such as hyponatremia or a CNS infection, the risks of another seizure and the development of epilepsy are very small. In these cases, the only pharmacotherapy that is necessary is to correct the underlying problem and possibly short-term use of an AED. Risk factors for repeated seizures in patients without an underlying disorder include:

- Structural CNS lesion
- Abnormal EEG
- Partial seizure type
- Positive family history
- Postictal motor paralysis[21]

If no risk factors are present, the risk of another seizure is 10% to 15%. However, if two or more risk factors are present, the risk of another seizure is 100%.

When sufficient evidence is available to determine that the patient has real seizures and is at risk for another seizure, pharmacotherapy is usually started (Fig. 27–2). The patient should be in agreement with the plan, be willing to take the medication, and be able to monitor seizure frequency and adverse drug effects in some way. Design of an appropriate pharmacotherapeutic plan is based on the patient's seizure type, the common adverse-effect profile of possible AEDs, and economic factors (e.g., cost of the drug, insurance formulary, and ability to pay). Other patient factors such as gender, concomitant drugs, age, and lifestyle also need to be considered.

Nonpharmacologic Treatment

Several nonpharmacologic treatments for epilepsy are available. For some patients, surgery is the treatment approach with the greatest probability of achieving a seizure-free state.[22] The most common surgical approach for epilepsy is temporal lobectomy. When the seizure focus can be localized and it is in a region of the brain that is not too close to critical areas, such as those responsible for speech or muscle control, surgical removal of the focus can result in 80% to 90% of patients becoming seizure-free. According to a National Institutes of Health Consensus Conference, three criteria should be met for patients to be candidates for surgery.[23] These criteria are a definite diagnosis of epilepsy, failure of adequate drug therapies, and definition of the electroclinical syndrome (i.e., localization of the seizure focus in the brain). Other surgical procedures, that are less likely to make a patient seizure-free, include corpus callosotomy and extra-temporal lesion removal.

Vagal nerve stimulation is another nonpharmacologic approach to treating seizures.[24] In this treatment, a unit that generates an intermittent electrical current is placed under the skin in the chest. A wire is tunneled under the skin to the left vagus nerve in the neck. The unit generates a small electrical current that stimulates the vagus nerve every 5 minutes. Additional stimulations can be initiated by the patient swiping a magnet over the device located in the chest. This treatment approach is essentially equivalent in efficacy to starting a new medication, but the precise mechanism for its effect has not been elucidated. Approximately 25% to 50% of patients who have a vagal nerve stimulator placed will experience at least a 50% reduction in seizure frequency. However, fewer than 10% become seizure-free. Adverse effects include hoarseness, swallowing difficulties, tingling or vibration in the neck, infection

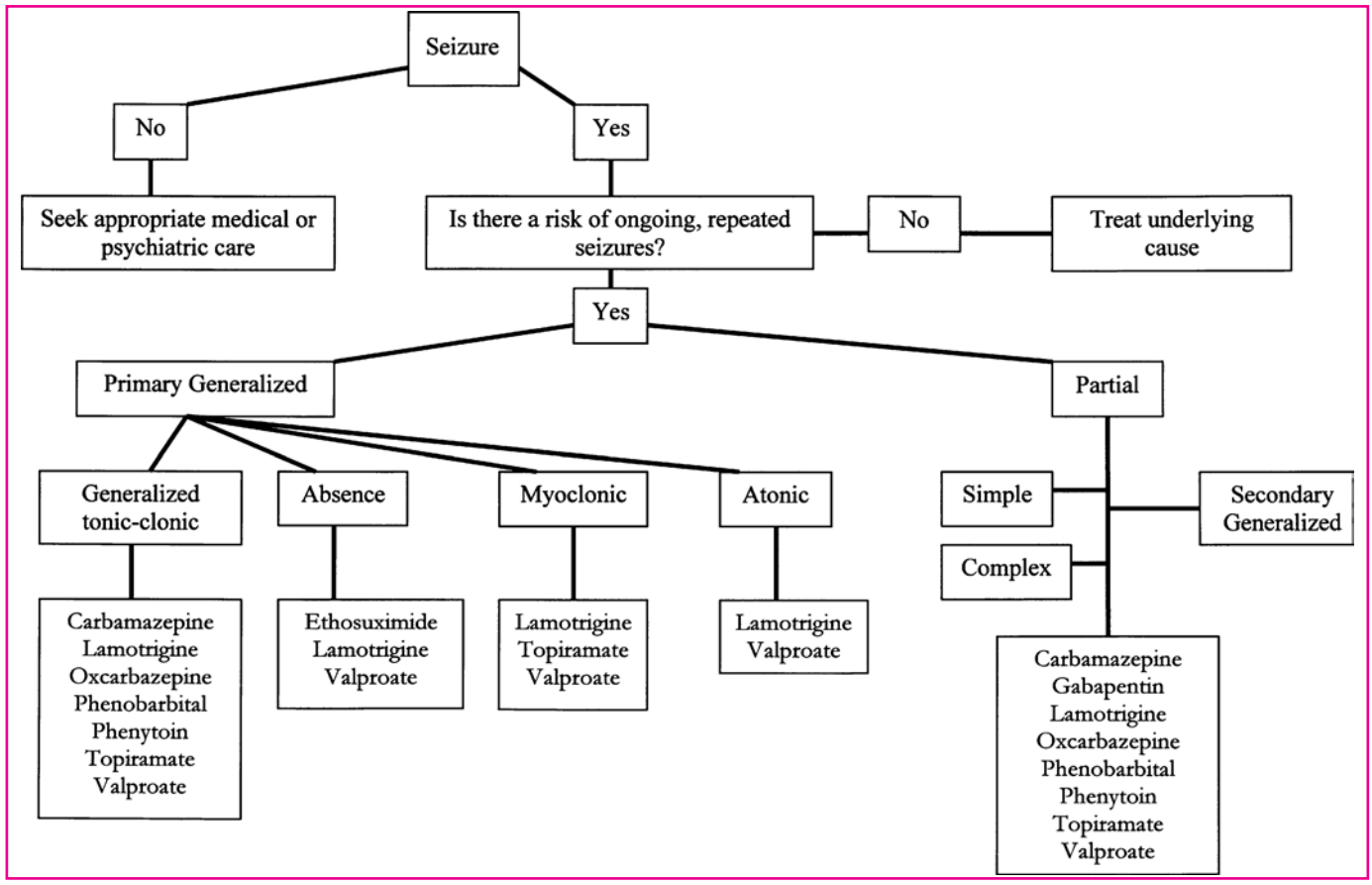


FIGURE 27–2. Treatment algorithm for management of seizure disorders.

or bleeding due to surgery, and rarely laryngeal spasms. Vagal nerve stimulation is usually reserved for patients who do not respond to several drugs and are not surgical candidates.

One of the oldest nonpharmacologic treatments is the ketogenic diet.[25] Modern use of the diet was started in the 1920s. This diet produces a ketoacidotic state through the elimination of nearly all carbohydrates. To initiate the diet, patients undergo 24 to 48 hours of fasting until ketones are detected in the urine. The diet consisting of dietary fats (e.g., butter, heavy cream, and fatty meats) and protein with no added sugar is started. Daily urinalysis for ketones is performed to ensure that the patient remains in ketosis. Any inadvertent consumption of sugar results in the need to reinitiate the diet. Pharmacists have an important role in maintaining the diet, by determining the sugar or carbohydrate content of medications the patient is taking. This diet is typically used only in children with difficult-to-control seizures. In certain patients the diet can be extremely effective, resulting in complete seizure control and reduction of AEDs. However, it is hard to maintain a ketotic state, and palatability of the diet is a concern. Additionally, there are concerns about growth retardation in children and hypercholesterolemia with prolonged use of the diet.

Pharmacologic Therapy

Special Considerations

❹ Use of the AEDs presents some unique challenges, some of which relate to their pharmacokinetic properties, which need to be clearly understood.[26]

Michaelis-Menten Metabolism

Phenytoin metabolism is capacity-limited, meaning the maximum capacity of hepatic enzymes to metabolize the drug is reached within the normal dosage range. This is defined as Michaelis-Menten metabolism or Michaelis-Menten pharmacokinetics. The clinical significance is that small changes in doses result in disproportionate and large changes in serum concentrations. The patient is at risk of sudden toxicity if too large a dose increase is made, or a breakthrough seizure may occur if too large a reduction in dose is made. Due to individual differences in metabolism, each patient follows a different curve in the relationship between dose and serum concentrations. These differences can be defined only by careful use of serum concentration and dosing data. There are numerous schemes for determining appropriate dosage adjustments of

phenytoin, and these are discussed in pharmacokinetics textbooks. For routine clinical practice, dosage adjustments for adults with normal protein binding of phenytoin and a steady-state serum concentration can be made using the following plan.

- For serum concentrations less than 7 mcg/mL (28 μmol/L) the total daily dose is increased by 100 mg.
- For serum concentrations of 7 to 12 mcg/mL (28–48 μmol/L) the total daily dose is increased by 50 mg.
- For serum concentrations greater than 12 mcg/mL (48 μmol/L) the total daily dose is increased by no more than 30 mg.[27]

Protein Binding

Some AEDs, especially phenytoin and valproate, are highly bound to plasma proteins. When interpreting a reported concentration for these drugs, it is important to remember that the value represents the total (i.e., bound and unbound) concentration in the blood. Because of differences in the metabolism of these drugs, the clinical effects of altered protein binding are different for different drugs.

Normally, 88% to 92% of phenytoin is bound to plasma protein, leaving 8% to 12% unbound. The unbound component is able to leave the blood to produce the clinical effect in the CNS, produce dose-related side effects in the CNS and at other sites, distribute to other peripheral sites, and be metabolized. Certain patient groups are known to have decreased protein binding, resulting in an increased percentage of drug that is unbound. These patient groups include:

- Those with renal failure
- Those with hypoalbuminemia
- Neonates
- Pregnant women
- Those taking multiple highly protein-bound drugs
- Patients in critical care

Due to the Michaelis-Menten metabolism of phenytoin, alterations in its protein binding will result in increased severity of dose-related adverse effects. In patients with suspected changes in protein binding, it is useful to measure unbound phenytoin concentrations.

When valproate protein binding is altered, the risk for severe dose-related adverse effects is much less compared to phenytoin. Michaelis-Menten metabolism is not a factor with valproate, so hepatic enzymes are able to efficiently metabolize the additional unbound portion.

Autoinduction

Carbamazepine is a potent inducer of hepatic microsomal enzymes. Not only does it increase the rate of metabolism for many other drugs, it increases the rate of its own metabolism. Hepatic enzymes become maximally induced over several weeks, necessitating a small initial dose of carbamazepine that is increased over time to compensate for the enzyme induction (Fig. 27–3). Most dosage regimens for carbamazepine call for a starting dose that is 25% to 30% of the typical maintenance dose of 15 mg/kg per day. The dosage is increased weekly until the target maintenance dose is achieved within 3 to 4 weeks. Titration of the carbamazepine dose lessens the risk for severe dose-related adverse effects when carbamazepine is first started.

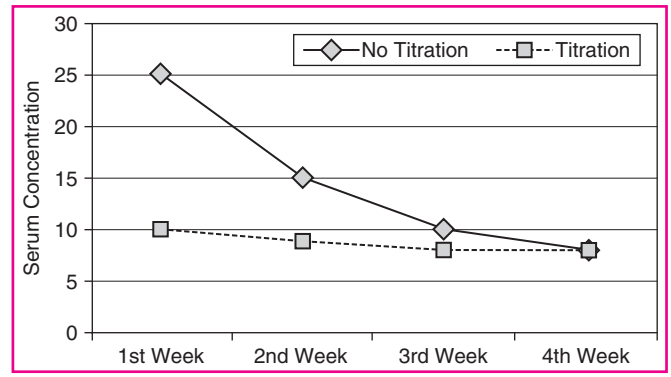


FIGURE 27–3. Serum concentrations of carbamazepine in the presence and absence of appropriate dose titration. Carbamazepine induces its own metabolism, so maintenance dose requirements are much greater than starting doses. To avoid excessive adverse effects, starting doses should be 25% to 30% of the target maintenance doses and increased gradually to the target maintenance dose, usually over 3 to 4 weeks.

Drug Selection and Seizure Type

The key to selecting effective pharmacotherapy is to base the decision on the seizure type. Several consensus treatment guidelines from the Scottish Intercollegiate Guidelines Network, the National Institute for Clinical Excellence in the United Kingdom, and the American Academy of Neurology all use determination of seizure type as the basis for selection of pharmacotherapy (Table 27–2).[28–30] While the guidelines make recommendations for specific drugs to be used in certain seizure types, the consensus recommendations utilize only data available from the medical literature. In many cases, a recommendation is not made, because there are no published data on which to make an evidence-based decision. Therefore, a drug may not currently be recommended for a seizure type simply because it has not been studied for that seizure type. Absence of a recommendation should not be taken to mean that the drug is ineffective for a specific seizure type.

Outside of the evidence-based guidelines, other pharmacologic treatments are commonly used or avoided. For initial treatment of absence seizures, ethosuximide and valproate are commonly used, not only in the United Kingdom, but also in the United States. Zonisamide may be also used for initial treatment of absence and myoclonic seizures. In absence and myoclonic seizures, carbamazepine, oxcarbazepine, gabapentin, tiagabine, and pregabalin should be avoided, as they have been associated with an exacerbation of these types of seizures.

TABLE 27–2. Evidence-Based Guidelines for Initial Monotherapy Treatment of Epilepsy

Seizure Type	American Academy of Neurology	Scottish Intercollegiate Guidelines Network	United Kingdom National Institute for Clinical Excellence
Primary generalized tonic-clonic	Carbamazepine[a] Lamotrigine[a] Oxcarbazepine[a] Phenobarbital[a] Phenytoin[a] Topiramate[a] Valproate[a]	Lamotrigine Valproate	Carbamazepine Lamotrigine Topiramate Valproate *Second-line:* Clobazam[b] Levetiracetam Oxcarbazepine
Absence	Lamotrigine (children)	Ethosuximide Lamotrigine Valproate	Ethosuximide Lamotrigine Valproate *Second-line:* Clobazam[b] Clonazepam Topiramate
Myoclonic	Not mentioned	Lamotrigine Valproate	Valproate Topiramate (children with severe myoclonic epilepsy of infancy) *Second-line:* Clobazam[b] Clonazepam Lamotrigine Levetiracetam Piracetam[b] Topiramate
Tonic	Not mentioned	Not mentioned	Lamotrigine Valproate *Second-line:* Clobazam[b] Clonazepam Levetiracetam Topiramate
Atonic	Not mentioned	Not mentioned	Lamotrigine Valproate *Second-line:* Clobazam[b] Clonazepam Levetiracetam Topiramate
Partial with or without secondary generalization	Carbamazepine Gabapentin Lamotrigine Oxcarbazepine Phenobarbital Phenytoin Topiramate Valproate	Phenytoin Carbamazepine Valproate Lamotrigine Oxcarbazepine	Carbamazepine Lamotrigine Oxcarbazepine Valproate Topiramate *Second-line:* Clobazam[b] Gabapentin Levetiracetam Phenytoin Tiagabine

[a]Based upon data from newly diagnosed epilepsy patients of multiple seizure types.
[b]Not currently available in the United States.
Data from references 27, 28, 29, 30.



Patient Encounter 1, New-Onset Seizures

AG, a 20-year-old male college student, is seen by his physician 4 days after an apparent seizure during finals week. According to his roommate, he suddenly fell to the floor and had a generalized tonic-clonic seizure. This seizure lasted for 1 to 2 minutes. The patient was incontinent for urine during the seizure. He was sleepy and confused when the paramedics arrived 10 minutes later. Due to final examinations he reports being sleep-deprived. His physical exam is completely normal and no focal neurologic deficits were observed.

- What diagnostic tests should be done at this time?
- Should these tests be performed prior to starting medications?
- His MRI is normal, and focal epileptiform activity originating from his left temporal lobe is observed on the EEG.
- Should an AED be started at this point?
- If you decide to treat, what drug and dose would you use?
- How should that drug be monitored?

Three months later he has another seizure, but this time it is characterized by a rising feeling in his stomach followed by confused speech, lip smacking, repetitive movements of his right hand, and unresponsiveness. This episode lasts for 2 to 3 minutes, and it takes 15 minutes for his speech to return to normal.

- If he is receiving an AED, should a second AED be started at this time?
- What tests and evaluations should you do before starting a second AED?
- If a second drug is started, what drug and dose would you use?

Refractory seizure (i.e., unresponsive to at least two first-line AEDs) treatment is somewhat different. According to the American Academy of Neurology (AAN) Practice Parameter, topiramate is useful as monotherapy for primary generalized tonic-clonic seizures, and there is insufficient evidence to make any recommendation regarding gabapentin, lamotrigine, oxcarbazepine, tiagabine, levetiracetam, or zonisamide.[31] Combinations of drugs are not addressed by the AAN, but may be useful in patients with difficult-to-control primary generalized seizures. This practice parameter also gives the highest recommendation to oxcarbazepine and topiramate as monotherapy in patients with refractory partial epilepsy. Additionally, lamotrigine is noted to be effective as monotherapy for refractory partial seizures, but was associated with a high dropout rate in the clinical trials. All AEDs, except ethosuximide, are effective in combination therapy for partial seizures.

Complications of Pharmacotherapy

❺ Adverse effects of AEDs are frequently dose-limiting or can cause a drug to be discontinued. Two types of adverse effects occur with AEDs: dose-related (Table 27–3) and idiosyncratic. Concentration-related adverse effects happen with increasing frequency and severity as the dose or concentration of a drug is increased. For many AEDs, common concentration-related adverse effects include sedation, ataxia, and diplopia. When selecting an AED, these adverse effects should be carefully considered and used as one of the selection criteria. ❻ For example, if a patient has a job that requires mental alertness, it is best to choose an AED that is less likely to cause sedation (e.g., lamotrigine).

Idiosyncratic adverse effects are not dose- or concentration-related and will almost always result in the AED being discontinued. Rash, hepatotoxicity, and hematologic toxicities are the most common idiosyncratic reactions seen with AEDs. Because many of these adverse effects are life-threatening or potentially life-threatening, the AED should be discontinued immediately when the reaction is observed. Carbamazepine, phenytoin, phenobarbital, valproate, lamotrigine, oxcarbazepine, and felbamate are most likely to cause these types of reactions. Many of these reactions are thought to occur primarily on an immunologic basis, which raises the possibility of cross-reactivity. This is especially true for carbamazepine, phenytoin, phenobarbital, and oxcarbazepine, for which 15% to 25% of patients who have an idiosyncratic reaction to one drug will have a similar reaction to the other drugs.

Chronic Adverse Reactions

Because AEDs are administered for long periods of time, adverse effects due to prolonged drug exposure are of concern. Some chronic adverse effects that have been associated with AEDs include peripheral neuropathy and cerebellar atrophy. Other chronic adverse effects are extensions of acute adverse effects, for example weight gain.

One chronic adverse effect that is of concern is osteoporosis.[32,33] Carbamazepine, phenytoin, phenobarbital, oxcarbazepine, and valproate have all been shown to decrease bone mineral density, even after only 6 months of treatment. Data on the relationship between other AEDs and osteoporosis are not currently available. Multiple studies have shown the risk of osteoporosis due to chronic AED use to be similar to the risk with chronic use of corticosteroids. Patients taking carbamazepine, phenytoin, phenobarbital, or valproate for longer than 6 months should take supplemental calcium and vitamin D. Additionally, routine monitoring for osteoporosis should be performed every 2 years, and patients should be instructed on ways to protect themselves from fractures.

Practical Issues

Comorbid Disease States

Patients with epilepsy often have comorbid disease states. Disorders such as chronic headaches and asthma are frequent problems. For patients who also have asthma, care must be taken to identify drug interactions between AEDs

TABLE 27–3. Characteristics of Common Antiepileptic Drugs

Drug	Mechanism of Action	Dose	Pharmacokinetic Parameters	Usual Serum Concentration Range	Dose-Related Adverse Effects	Idiosyncratic Adverse Effects
Carbamazepine	Modulate sodium channels	*Loading dose:* Not recommended due to excessive dose-related toxicity *Maintenance dose:* Titrate dosage to target over 3–4 weeks Adults: 10–20 mg/kg per day as a divided dose Children: 20–30 mg/kg per day as a divided dose	*Half-life:* 10–25 hours with chronic dosing *Apparent volume of distribution:* 0.8–1.9 L/kg *Protein binding:* 67–81% *Primary elimination route:* Hepatic	4–12 mcg/mL (17–51 µmol/L)	Diplopia, drowsiness, nausea, sedation	Aplastic anemia, hyponatremia, leukopenia, osteoporosis, rash
Clonazepam	Enhance GABA activity	*Loading dose:* Not recommended due to increased adverse effects *Maintenance dose:* Initiate at 0.5 mg one to three times daily, titrate dose to effectiveness usually 3–5 mg daily in 2 to 3 divided doses	*Half-life:* 30–40 hours *Apparent volume of distribution:* 3.2 L/kg *Protein binding:* 47–80% *Primary elimination route:* Hepatic	Not established	Ataxia, memory impairment, sedation, slowed thinking	
Ethosuximide	Modulate calcium channels	*Loading dose:* Not recommended due to increased adverse effects *Maintenance dose:* Initiate at 250 mg twice daily and titrate to 500–1000 mg twice daily	*Half-life:* 60 hours 60 hours *Apparent volume of distribution:* 0.6–0.7 L/kg *Protein binding:* None *Primary elimination route:* Hepatic	40–100 mcg/mL (283–708 µmol/L)	Ataxia, sedation	Hepatotoxicity, neutropenia, rash
Felbamate	Inhibit glutamate activity	*Loading dose:* Not recommended due to increased adverse effects *Maintenance dose:* 1200–3600 mg/day in 3–4 divided doses	*Half-life:* Monotherapy: 20 hours Concurrent enzyme inducers: 11–16 hours *Apparent volume of distribution:* 0.7–0.8 L/kg *Protein binding:* 25–35% *Primary elimination route:* Hepatic	Not established	Anxiety, insomnia, nausea	Anorexia, aplastic anemia, headache, hepatotoxicity, weight loss

(*Continued*)

TABLE 27–3. Characteristics of Common Antiepileptic Drugs *(Continued)*

Drug	Mechanism of Action	Dose	Pharmacokinetic Parameters	Usual Serum Concentration Range	Dose-Related Adverse Effects	Idiosyncratic Adverse Effects
Gabapentin	Modulate calcium channels and enhance GABA activity	*Loading dose:* Not recommended due to short half-life *Maintenance dose:* 900–3600 mg/day in 3–4 divided doses (doses up to 10,000 mg/day have been tolerated)	*Half-life:* 5–7 hours (proportional to creatinine clearance) *Apparent volume of distribution:* 0.6–0.8 L/kg *Protein binding:* less than 10% *Primary elimination route:* Renal	Not established	Drowsiness, sedation	Peripheral edema, weight gain
Lamotrigine	Modulate sodium channels	*Loading dose:* Not recommended due to increased risk of rash *Maintenance dose:* 150–800 mg/day in 2–3 divided doses. Doses should be initiated and titrated according to the manufacturer's recommendations to reduce the risk of rash	*Half-life:* Monotherapy: 24 hours Concurrent enzyme inducers: 12–15 hours Concurrent enzyme inhibitors: 55–60 hours *Apparent volume of distribution:* 1.1 L/kg *Protein binding:* 55% *Primary elimination route:* Hepatic	Not established	Ataxia, drowsiness, headache, insomnia, sedation	Rash
Levetiracetam	Unknown	*Loading dose:* Not recommended due to excessive adverse effects *Maintenance dose:* 1000–3000 mg/day. Start at 1000 mg/day and titrate upward as indicated by response	*Half-life:* 6–8 hours *Apparent volume of distribution:* 0.5–0.7 L/kg *Protein binding:* less than 10% *Primary elimination route:* 70% renal 30% hepatic	Not established	Somnolence, dizziness	Depression
Oxcarbazepine	Modulate sodium channels	*Loading dose:* Not recommended due to excessive adverse effects *Maintenance dose:* 600–1200 mg/day. Start at 300 mg twice daily and titrate upward as indicated by response	*Half-life:* Parent drug ~2 hours; 10-monohydroxy metabolite ~9 hours *Apparent volume of distribution:* 0.5–0.7 L/kg *Protein binding:* 40% *Primary elimination route:* Hepatic	Not established	Diplopia, dizziness, somnolence	Hyponatremia, 25–30% cross sensitivity in patients with hypersensitivity to carbamazepine

Phenobarbital	Modulate sodium channels	*Loading dose:* 10–20 mg/kg as single or divided intravenous infusions or orally in divided doses over 24–48 hours *Maintenance dose:* Adults: 1–4 mg/kg per day, as a single or divided dose Children: 3–6 mg/kg per day, as divided dose Neonates: 1–3 mg/kg per day, as divided dose	*Half–life:* Adults: 49–120 hours Children: 37–73 hours Neonates: ~115 hours *Volume of distribution:* 0.7–1 L/kg *Protein binding:* ~50% *Primary elimination route:* Hepatic	15–40 mcg/mL (65–172 µmol/L)	Ataxia, drowsiness, sedation	Attention deficit, cognitive impairment, hyperactivity, osteoporosis, passive-aggressive behavior
Phenytoin	Modulate sodium channels	*Loading dose:* Adults: 15–20 mg/kg single intravenous dose or divided oral dose Infants less than 3 months: 10–15 mg/kg single intravenous dose Neonates: 15–20 mg/kg single intravenous dose *Maintenance dose:* Adults: 5–7 mg/kg per day, as single or divided dose Children: 6–15 mg/kg per day, as divided dose Neonates: 3–8 mg/kg per day, as divided dose	*Half-life:* Follows capacity-limited or Michaelis-Menten pharmacokinetics Half-life increases as the dose and serum concentration increases *Volume of distribution:* Adults: 0.7 L/kg Children: 0.8 L/kg Neonates: 1.2 L/kg *Protein binding:* Adults, children: 88–92% Neonates: 65% *Primary elimination route:* Hepatic	10–20 mcg/mL (40–79 µmol/L) total concentration 1–2 mcg/mL (4–8 µmol/L) unbound concentration	Ataxia, diplopia, drowsiness, sedation	Anemia, gingival hyperplasia, hirsutism, lymphadenopathy, osteoporosis, rash
Pregabalin	Modulate calcium channels	*Loading dose:* Not recommended due to increased adverse effects *Maintenance dose:* Initiate at 150 mg/day in 2–3 divided doses and titrate to a maximum dose of 600 mg/day	*Half-life:* 6.3 hours, proportional to creatinine clearance *Apparent volume of distribution:* 0.5 L/kg *Protein binding:* Negligible *Primary elimination route:* *Renal*	Not established	Ataxia, blurred vision, dizziness, dry mouth, somnolence	Edema, weight gain
Tiagabine	Enhance GABA activity	*Loading dose:* Not recommended due to excessive adverse effects *Maintenance dose:* 32–56 mg/day in four divided doses Doses should be titrated upward over 6 weeks, starting at 4 mg/day	*Half-life:* Monotherapy: 7–9 hours Concurrent enzyme inducers: 2.5–4.5 hours *Apparent volume of distribution:* 0.6–0.8 L/kg *Protein binding:* 96% *Primary elimination route:* Hepatic	Not established	Dizziness, somnolence, irritability, slowed thinking	

(*Continued*)

TABLE 27–3. Characteristics of Common Antiepileptic Drugs (*Continued*)

Drug	Mechanism of Action	Dose	Pharmacokinetic Parameters	Usual Serum Concentration Range	Dose-Related Adverse Effects	Idiosyncratic Adverse Effects
Topiramate	Modulate sodium channels; inhibit glutamate activity; enhance GABA activity	*Loading dose:* Not recommended due to excessive adverse effects *Maintenance dose:* 100–400 mg/day in 2–3 divided doses Doses should be started at 25–50 mg/day and gradually titrated upward over 3–6 weeks to avoid excessive adverse effects	*Half-life:* Monotherapy: 21 hours Concurrent enzyme inducers: 11–16 hours *Apparent volume of distribution:* 0.55–0.8 L/kg *Protein binding:* 13–17% *Primary elimination route:* 60% renal 40% hepatic	Not established	Ataxia, dizziness, drowsiness, slowed thinking	Acute glaucoma, metabolic acidosis, oligohidrosis, paresthesias, renal calculi, weight loss
Valproic acid/ divalproex sodium	Modulate sodium channels	*Loading dose:* 20–40 mg/kg *Maintenance dose:* Adults: 15–45 mg/kg per day in 2–4 divided doses Children: 5–60 mg/kg per day in 2–4 divided doses	*Half-life:* Adults: 8–15 hours Children: 4–15 hours Infants less than 2 months: 65 hours *Volume of distribution:* 0.1–0.5 L/kg *Protein binding:* 90% (decreases with increasing serum concentrations) *Primary elimination route:* Hepatic	50–100 mcg/mL (346–693 µmol/L); children may require concentrations up to 150 mcg/mL (1040 µmol/L)	Drowsiness, nausea, sedation, tremor	Hepatotoxicity, osteoporosis, pancreatitis, weight gain
Zonisamide	Modulate sodium and calcium channels	*Loading dose:* Not recommended due to excessive adverse effects *Maintenance dose:* 100–600 mg/day; start at 100 mg/day and titrate upward as indicated by response	*Half-life:* ~63 hours *Apparent volume of distribution:* 1.45 L/kg *Protein binding:* 40% *Primary elimination route:* Hepatic	Not established	Dizziness, somnolence	Metabolic acidosis, oligohidrosis, paresthesias, renal calculi

GABA, γ-aminobutyric acid.
Data from references 25, 35, 36, 37, 38.

and medications used for asthma. These interactions may necessitate close monitoring for changes in efficacy or increased toxicity, and dosage changes of other drugs may be necessary when an AED is added or removed. Patients with chronic headaches need special attention in the selection of an AED. Agents known to prevent headache (e.g., valproate and topiramate) may be preferred among several choices, and agents associated with increased headaches (e.g., lamotrigine and felbamate) may be a secondary or tertiary alternative.

Depression is a common problem in patients with epilepsy, with approximately 30% having symptoms of major depression at some point.[34] Patients with epilepsy should be routinely assessed for signs of depression, and treatment should be initiated if necessary. Certain AEDs may exacerbate depression, for example levetiracetam and phenytoin. Other AEDs (e.g., lamotrigine, carbamazepine, and oxcarbazepine) may be useful in treating depression. Changes in mood can be precipitated by addition or discontinuation of an AED. If treatment for depression is necessary, caution should be exercised in choosing an agent that does not increase seizure frequency and does not interact with AEDs.

Switching Drugs

❼ Changing from one AED to another can be a complex process. If the first drug is stopped too abruptly breakthrough seizures may occur. Stopping or adding a drug can introduce various problems with drug interactions which should be considered in any regimen change. Typically the new drug is started at a low initial dose and gradually increased over several weeks. Once the new drug is at a minimally effective dose, the drug to be discontinued is gradually tapered while the dose of the new drug continues to be increased to the target dose. During a transition between drugs, patients should be cautioned about the possibility of increased seizures or adverse reactions.



Patient Encounter 2, Switching a Patient to a Different Antiepileptic Drug

BC, a 22-year-old woman, was diagnosed 2 years ago with juvenile myoclonic epilepsy. She has been treated with valproate 1500 mg/day. Since starting valproate she has gained 45 pounds (20.5 kg), continues to have occasional myoclonic jerks, had a generalized tonic-clonic seizure 3 months ago, and is sexually active. Additionally, she complains of easily falling asleep during the day. Due to adverse effects, poor seizure control, and the risk of birth defects with valproate, the decision is made to switch to a different antiepileptic drug.

- What drug would be the optimal alternative drug for this patient?
- How should the new drug be started and the valproate discontinued?
- What instructions should be given to the patient regarding the switch to another drug?

Stopping Therapy

❽ Epilepsy is generally considered to be a lifelong disorder that requires ongoing treatment. However, many patients who are seizure-free may desire to discontinue their medications.[35] Patients who become seizure-free following surgery for their epilepsy may have medications slowly tapered starting 1 to 2 years after their surgery. Many patients will choose to stay on at least one medication following successful surgery to ensure that they remain seizure-free. Five criteria must be met before considering the discontinuation of AEDs.[36] They are:

- No seizures for 2 to 5 years
- Normal neurologic examination
- Normal intelligence quotient
- Single type of partial or generalized seizure
- Normal EEG with treatment

Individuals who fulfill all of these criteria have a 61% chance of remaining seizure-free after AEDs are discontinued. Additionally, there is a direct relationship between the duration of seizure freedom while taking medications and the chance of being seizure-free after medications are withdrawn. Withdrawal of AEDs is done slowly, usually with a tapering dose over at least 3 months.

Dosing

Dosing of AEDs is determined by general guidelines and response of the patient. Serum concentrations may be helpful in benchmarking a specific response. Therapeutic ranges that are often quoted are broad guidelines for dosing, but should never replace careful evaluation of the patient's response. It is not unusual for a patient to be well managed with serum concentrations or doses outside the typical ranges.



Patient Encounter 3, Discontinuing Antiepileptic Drug Therapy

The consultant pharmacist is reviewing the care of AN, who is a 79-year-old male resident of a long-term care facility. According to his records, he has received phenytoin and phenobarbital ever since suffering a stroke 12 years ago. There is no record of a seizure in his chart, and the nursing staff has not observed a seizure since he arrived at the facility 2 years ago. His family recalls that he had 1 seizure around the time of his stroke, but has not had any more seizures.

- Can his antiepileptic medications be discontinued?
- What additional information would be helpful to determine the possibility of discontinuing his antiepileptic drugs?
- If the antiepileptic drugs are stopped, how should they be discontinued?

Drug Interactions

AEDs are associated with many different drug interactions.[37–39] These interactions are primarily in relation to absorption, metabolism, and protein binding. Tube feedings and antacids are known to reduce the absorption of phenytoin and carbamazepine. Phenytoin, carbamazepine, and phenobarbital are potent inducers of various cytochrome P-450 (CYP450) isoenzymes, increasing the clearance of other drugs metabolized through these pathways (Table 27–4). In contrast, valproate is a CYP450 isoenzyme inhibitor and reduces the clearance of some drugs. Phenytoin and valproate are highly protein-bound and can be displaced when taken concurrently with other highly protein-bound drugs. For example, when phenytoin and valproate are taken together, there may be increased dose-related adverse effects within several hours of dosing. This can be avoided by staggering doses or giving smaller doses more frequently during the day. Whenever a change in a medication regimen occurs, drug interactions should be considered and appropriate adjustments in dose made.

Special Populations

❾ Children and women present special challenges in the management of epilepsy and use of AEDs. In children, developmental changes occur rapidly, and metabolic rates are greater than those seen in adults. When treating a child it is imperative to control seizures as quickly as possible to avoid interference with development of the brain and cognition. Antiepileptic drug doses are increased rapidly, and frequent changes in the regimen are made to maximize control of seizures. Due to the rapid metabolic rates seen in children, doses of AEDs are typically higher on a milligram-per-kilogram basis compared to those for adults, and serum concentrations are used more extensively to help ensure an adequate trial of a drug has been given.

For women, the treatment of epilepsy poses challenges, including teratogenicity, interactions between AEDs and hormonal contraceptives, and reduced fertility.[40,41] Recommendations for managing women of child-bearing potential and who are pregnant have been developed (Table 27–5). Several AEDs have been implicated in causing both minor and serious birth defects.[42] Of special concern are neural tube defects (e.g., spina bifida, microcephaly, and anencephaly), associated most commonly with valproate and possibly carbamazepine. All women of child-bearing potential who have epilepsy should be taking 1 to 4 mg daily of supplemental folic acid to reduce the risk of these defects. Even with drugs like valproate, more than 90% of pregnancies will produce a completely normal infant. Therefore, use of valproate is not contraindicated in women who may become pregnant, but it may be

TABLE 27–4. Common Drug Interactions with Antiepileptic Drug[36–38]

Enzyme	Substrate	Common Inducers	Common Inhibitors
CYP1A2	Carbamazepine	Carbamazepine Phenytoin Phenobarbital Rifampin	Cimetidine Ciprofloxacin Erythromycin Clarithromycin
CYP2C9	Phenobarbital[a] Phenytoin[a] Carbamazepine Valproate	Carbamazepine Phenytoin Phenobarbital Rifampin	Amiodarone Cimetidine Fluconazole Valproate
CYP2C19	Phenobarbital Phenytoin Valproate		Felbamate Ticlopidine Topiramate Zonisamide
CYP2D6	Zonisamide	Carbamazepine	
CYP3A4	Carbamazepine[a] Tiagabine[a] Zonisamide[a]	Carbamazepine Phenytoin Phenobarbital Rifampin	Amiodarone Erythromycin Propoxyphene Ketoconazole
Uridine diphosphate glucuronyl-transferase	Lamotrigine[a] Carbamazepine	Lamotrigine Phenobarbital Phenytoin	Valproate

[a]Primary route of metabolism.
CYP450, cytochrome P-450 isoenzyme.
Data from references 36, 37, 38.

TABLE 27–5. Management of Antiepileptic Drugs during Pregnancy

Give supplemental folic acid, 1–4 mg daily, to all women of child-bearing potential
Use monotherapy whenever possible
Use the lowest doses that control seizures
Continue pharmacotherapy that best controls seizures prior to pregnancy
Monitor antiepileptic drug serum concentrations at the start of pregnancy and monthly thereafter
Adjust antiepileptic drug doses to maintain baseline serum concentrations
Administer supplemental vitamin K during the eighth month of pregnancy to women receiving enzyme-inducing antiepileptic drugs
Monitor postpartum antiepileptic drug serum concentrations to guide adjustments of drug doses

advisable to start alternative AEDs, if appropriate, in women of child-bearing potential.

As noted above, many of the AEDs induce hepatic microsomal enzyme systems and thus reduce the effectiveness of hormonal contraceptives. Women taking AEDs that may reduce the effectiveness of hormonal contraceptives should be encouraged to also use other forms of birth control. Due to induction or inhibition of sex hormone metabolism and changes in binding of hormones to sex hormone binding globulin, some AEDs may reduce fertility. For example, valproate has been associated with a drug-induced polycystic ovarian syndrome. Women who experience difficulties with fertility should seek the advice of health care professionals with expertise in fertility.

Outcome Evaluation

Efficacy

- Seizure counts are the only reasonable and standard way to evaluate efficacy of treatment.
- Encourage patients to keep a seizure calendar that notes the time and day seizures occur and the type of seizure. Comparisons can then be made on a monthly basis to determine the level of seizure control.

Toxicity

- Monitor toxicity of AEDs at every clinic visit.
- Question patients about common adverse effects of the AEDs they are receiving. Weigh the impact of acute adverse effects against the extent of seizure control achieved. If it is determined that the adverse effects negatively impact a patient more than the extent of seizure control obtained benefits the patient, adjust the therapeutic regimen. Continuously monitor chronic adverse effects of AEDs.



Patient Encounter 4, Hormonal Contraceptives and Interactions with Antiepileptic Drugs

LJ, a 25-year-old-woman with complex partial seizures, presents a prescription to the pharmacy for a triphasic oral contraceptive containing ethinyl estradiol and norgestimate. A review of her medication profile shows that she is taking carbamazepine extended-release 1200 mg/day. Her last refill for this prescription was 2 weeks ago. She reports that she has not had a seizure for a year and that she just became engaged. She is planning to be married in 4 months.

- Is there an interaction between carbamazepine and the oral contraceptive?
- If so, what is the mechanism and clinical outcome of the interaction?
- If there is an interaction, how should it be managed?
- What AEDs interact with hormonal contraceptives?
- What are the clinical implications of these interactions? How should they be managed?



Patient Care and Monitoring

1. *Monitor the patient's seizure frequency and characteristics.* The only objective measure ofefficacy of AEDs is a count of seizure frequency. Ask patients to keep seizure calendars, noting the numbers and types of seizures that occur and have them bring the calendars to clinic at every visit for analysis and documentation of seizure frequency.
2. *Monitor for acute and chronic adverse effects of AEDs.* Acute adverse effects are best detected by a thorough neurologic examination at clinic visits. Instruct patients to report sedation, ataxia, rash, or other problems immediately. Monitor for chronic adverse effects including a loss of bone mineral density, which should be measured every 2 years in patients taking phenytoin, phenobarbital, carbamazepine, and valproate.
3. *Monitor for comorbid disease states at each clinic visit.* Evaluate for depression at every clinic visit.
4. *Take measures to ensure compliance with medications and access to care.* Compliance with medication regimens is a common problem for patients with epilepsy. Patients should be asked at every visit how they are taking their medications and if they missed any doses. Identify barriers to care, such as financial issues or transportation problems.
5. *Instruct patients, family members, and caregivers on first aid for seizures.* First aid for seizures consists primarily of keeping the patients from hurting themselves. They should be placed on the floor, if possible, and their heads cushioned. First responders to a seizure should never attempt to restrain them or force an item into their mouth. If a seizure lasts longer than 5 to 10 minutes, emergency medical assistance should be called.

ABBREVIATIONS

AAN:	American Academy of Neurology
AED:	antiepileptic drug
CBC:	complete blood cell count
CNS:	central nervous system
CYP450:	cytochrome P-450 isoenzymes
EEG:	electroencephalogram
GABA:	γ-aminobutyric acid
ILAE:	International League Against Epilepsy
JME:	juvenile myoclonic epilepsy
LFT:	liver function test
LGS:	Lennox-Gastaut syndrome
MRI:	magnetic resonance imaging
MTLE:	mesial temporal lobe epilepsy
PDS:	paroxysmal depolarizing shift

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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28 Status Epilepticus

Gretchen M. Brophy and Eljim P. Tesoro



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Discuss the pathophysiology of status epilepticus.
2. Explain the urgency of diagnosis and treatment of status epilepticus.
3. Recognize the signs and symptoms of status epilepticus.
4. Identify the treatment options available for termination of status epilepticus.
5. Formulate an initial treatment strategy for a patient in generalized convulsive status epilepticus.
6. Compare the pharmacotherapeutic options for refractory status epilepticus.
7. Describe adverse drug events associated with the pharmacotherapy of status epilepticus.
8. Recommend monitoring parameters for a patient in status epilepticus.

Key Concepts

❶ Status epilepticus is a neurologic emergency that can lead to permanent brain damage or death.

❷ Status epilepticus can be defined as any seizure lasting more than 30 minutes, with or without a loss of consciousness; or having recurrent seizures without regaining consciousness between seizure episodes. However, this definition does not provide any guidance for treatment strategies in the clinical setting where interventions begin within a few minutes of seizure onset. A more practical definition to guide treatment would be continuous seizure activity lasting more than 5 minutes or two or more seizures without complete recovery of consciousness.

❸ It is important to evaluate for possible etiologies of status epilepticus and treat any underlying causes in order to optimize seizure control.

❹ The goal of therapy is to arrest physical and electroencephalographic evidence of seizures, prevent recurrence of seizures, and minimize adverse drug events.

❺ The first-line treatment for status epilepticus is intravenous benzodiazepines. Diazepam, lorazepam, or midazolam may be used to rapidly control clinical signs of seizures. Lorazepam is currently considered the first-line agent by most clinicians.

❻ Antiepileptic drugs are used to prevent the recurrence of seizures. Intravenous phenytoin (or fosphenytoin) and phenobarbital are administered after benzodiazepines are given.

❼ Refractory status epilepticus is seizure activity that is not controlled by first-line and second-line therapies, including benzodiazepines and antiepileptic drugs.

❽ Midazolam, propofol, and pentobarbital infusions can be used for refractory status epilepticus but may require intensive monitoring and supportive care.

❶ ***Status epilepticus*** *(SE) is a neurologic emergency that can lead to permanent brain damage or death.* ❷ *SE can be defined as any seizure lasting more than 30 minutes, with or without a loss of consciousness; or having recurrent seizures without regaining consciousness between seizure episodes.*[1] *However, this definition does not provide any guidance for treatment strategies in the clinical setting where interventions begin within a few minutes of seizure onset.* ❷ *A more practical definition to guide treatment would be continuous seizures lasting more than 5 minutes or two or more seizures without complete recovery of consciousness.*[2] Refractory status epilepticus (RSE) can be defined as seizure activity that does not respond to first-line antiepileptic therapy.[3]

SE can present as non-convulsive status epilepticus (NCSE) or generalized convulsive status epilepticus (GCSE). NCSE is characterized by a persistent state of impaired consciousness and/or motor or sensory seizures without impaired consciousness. For patients with NCSE, **electroencephalography** (EEG) is the key to diagnosis. GCSE is characterized by full body motor seizures and involves the entire brain. This chapter will focus on GCSE, which is the most common type of SE and is associated with the greatest risk of neurologic and physical damage.

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Patient Encounter, Part 1

CH, a 42-year-old man, comes into the emergency department after his sister discovered him seizing at home. He has a history of hypertension, diabetes, epilepsy, and rheumatoid arthritis. His medications include hydrochlorothiazide, glyburide, phenytoin, and aspirin. He smokes one pack per day, drinks heavily on the weekends, and has a history of cocaine use. Upon further discussion with his sister, you discover that he stopped taking his phenytoin 4 days ago due to failure to obtain a refill from his doctor. He is currently unarousable since his last seizure 10 minutes ago.

- What initial assessments should be performed?
- What are some possible etiologies for his seizure?
- What interventions need to be performed at this time?

EPIDEMIOLOGY AND ETIOLOGY

There are an estimated 150,000 cases of SE each year in the United States, with approximately 55,000 associated deaths, and an estimated annual direct cost for inpatient admissions of $4 billion.[4,5] Status epilepticus occurs more frequently in African-Americans, children, and the elderly. Additional attention should be given to elderly individuals with SE, as other underlying disease states may complicate therapy and worsen prognosis.[6]

❸ *It is important to understand the underlying cause of SE, as this will guide the course of treatment, potentially shortening the duration of SE and improve outcomes.* The causes of SE can be categorized as acute or chronic. Acute changes that cause SE include metabolic disturbances; central nervous system (CNS) disorders, infections, or injuries; **hypoxia**; drug toxicity; or acute illness. Chronic processes that cause SE include preexisting **epilepsy**, chronic alcohol abuse, CNS tumors, and strokes.[3] In individuals diagnosed with epilepsy, the common causes of SE are anticonvulsant withdrawal or subtherapeutic anticonvulsant levels. Patients with SE due to chronic processes generally respond well to antiepileptic drug (AED) therapy.

PATHOPHYSIOLOGY

Status epilepticus occurs because the brain fails to stop an isolated seizure. The exact reason for this failure is unknown and probably involves many mechanisms. A seizure is likely to occur due to a mismatch of excitatory and inhibitory neurotransmitters in the brain. The primary excitatory neurotransmitter in the brain is **glutamate**. Glutamate stimulates postsynaptic N-methyl-D-aspartate (NMDA) receptors in the brain, causing an influx of calcium into the cells and depolarization of the neuron. Sustained depolarization may maintain SE and eventually cause neuronal injury and death.[7] The primary inhibitory neurotransmitter, **γ-aminobutyric acid** (GABA), opposes the excitatory response by stimulating $GABA_A$ receptors. $GABA_A$-receptor stimulation enhances the chloride inhibitory currents, producing hyperpolarization and inhibition of the postsynaptic cell membrane. The inhibitory ability of GABA is diminished as the duration of seizures increases. This may be due to a mechanistic shift in the functional properties of the $GABA_A$ receptors which causes a decrease in response to GABA-receptor agonists.[8,9] Seizure activity lasting more than 30 minutes can cause cerebral injury and neuronal loss in the hippocampal, cortical, and thalamic regions. These neurologic sequelae are related to the excessive electrical activity and alterations in cerebral metabolic demand. The clinical impact of the $GABA_A$-receptor changes on treatment response and the worsening degree of neuronal injury with prolongation of seizure activity highlights the urgency of rapid control of SE.

There are several systemic changes that occur during the course of SE. These changes can be divided into two phases. Phase I occurs during the first 30 minutes of seizure activity, and phase II occurs after 30 minutes of seizure activity.[10]

Phase I

During phase I, each seizure causes a sharp increase in autonomic activity with increases in epinephrine, norepinephrine, and steroid plasma concentrations, resulting in hypertension, tachycardia, hyperglycemia, hyperthermia, sweating, and salivation. Cerebral blood flow is also increased to preserve the oxygen supply to the brain during this period of high metabolic demand. Increases in sympathetic and parasympathetic stimulation with muscle hypoxia can lead to ventricular arrhythmias, severe acidosis, and rhabdomyolysis. These, in turn, could lead to hypotension, shock, hyperkalemia, and acute tubular necrosis.

Phase II

After approximately 30 minutes of continuous seizure activity, the patient enters phase II and there is loss of cerebral autoregulation, decreased cerebral blood flow, increased intracranial pressure, and systemic hypotension. Metabolic demand is still high; however, the body is no longer able to compensate. The systemic changes that may occur during this phase include hypoglycemia, hyperthermia, respiratory failure, hypoxia, respiratory and metabolic acidosis, hyperkalemia, hyponatremia, and uremia. It is important to note that during prolonged seizure activity, motor activity may not be clinically noticeable, but the electrical seizures may still persist. This is referred to as subclinical seizure activity and needs to be recognized and treated aggressively.

CLINICAL PRESENTATION AND DIAGNOSIS

History

❸ When a patient presents with seizures, a thorough history is needed to determine the type and duration of the seizure



Clinical Presentation of Status Epilepticus

General
The patient may present with or without clinically noticeable seizure activity.

Symptoms
- Impaired consciousness ranging from lethargy to coma
- Disorientation after cessation of GCSE
- Pain from associated injuries (e.g., tongue lacerations, dislocated shoulder, head trauma, facial trauma)

Signs

Phase I:	**Phase II (greater than 30 minutes of SE):**
Generalized convulsions	Respiratory failure with pulmonary edema
Hypertension, tachycardia	Cardiac failure (arrhythmias, shock)
Fever and sweating	Hypotension
Muscle contractions, spasms	Hyperthermia
Respiratory compromise	Rhabdomyolysis and multiorgan failure
Incontinence	

Laboratory Tests
- Hyperglycemia (phase I) and hypoglycemia (phase II) can occur
- Hyponatremia, hypernatremia, hyperkalemia, hypocalcemia, hypomagnesemia, and hypoglycemia can cause SE
- The white blood cell (WBC) count may slightly increase
- Abnormal arterial blood gases (ABGs) due to hypoxia and respiratory or metabolic acidosis
- Elevated serum creatinine will be present in renal failure patients
- Myoglobinuria can occur in patients with continuous seizures

Diagnostic Tests
Electroencephalography (EEG) will show seizure activity

activity. This will help guide therapy and identify which laboratory and diagnostic testing need to be conducted urgently. A diagnosis of status epilepticus will be made when a patient with a history of repeated seizures and impaired consciousness has a seizure witnessed by a health care professional.

Physical Examination

Upon admission and control of seizure activity, a neurologic exam should be conducted to evaluate level of consciousness (coma, lethargy, and somnolence), motor function and reflexes (rhythmic contractions, rigidity, spasms, and posturing), and pupillary response. A physical exam to identify secondary injuries from the SE should also be conducted.

Clinical Symptoms

Patients with SE usually present with generalized, convulsive tonic-clonic seizure activity that is unresponsive to initial AED treatment. They may also be hypertensive, tachycardic, febrile, and diaphoretic; however, these symptoms will resolve soon after the seizure is terminated. A loss of bowel or bladder function, respiratory compromise, and **nystagmus** may also be observed. When seizure activity is sustained for more than approximately 30 to 60 minutes, muscle contractions may no longer be visible, but the patient remains in SE. Twitching of the face, hands, or feet may be seen in these comatose patients with prolonged seizures.

Laboratory Parameters

❸ *It is important to obtain a serum chemistry profile to help identify the underlying cause of SE.* Abnormalities that can cause seizures include hypoglycemia, hyponatremia, hypernatremia, hypomagnesemia, hypocalcemia, and renal failure. In a febrile patient with an elevated WBC count, an active infection should be ruled out or treated appropriately. Cultures from the blood, cerebrospinal fluid (CSF), respiratory tract, and urine should be obtained once the seizures are controlled. Computed tomography (CT) or magnetic resonance imaging (MRI) can be done to rule out CNS abscesses, bleeding, or tumors, all of which may be a source for seizure activity. A blood alcohol level and urine toxicology screen for drugs of abuse should also be conducted to determine if a chronic alcoholic is having alcohol withdrawal seizures or if illicit drug use or a drug overdose could be the underlying cause of SE. Also,

drug levels should be obtained in a drug overdose situation to rule out toxicity as a cause of SE. ❸ *Knowing the source of SE will help to guide the initial antiepileptic therapy and increase the probability of halting seizure activity.*

In patients with a history of AED use, a baseline serum concentration may be useful to determine if the drug concentration is below the desired range and if a loading dose is needed. Albumin levels, renal function tests, and liver function tests can also be helpful when assessing antiepileptic therapy.

Hypoxia and respiratory or metabolic acidosis are common in patients with SE. Therefore, pulse oximetry and ABG measurements are useful to assess the patient's respiratory status and determine if airway protection or supplemental oxygen is needed. Metabolic acidosis typically corrects on its own after seizure activity stops, so pharmacologic treatment is not required.



Patient Encounter, Part 2

Physical exam and laboratory studies reveal the following additional information about CH.

PE

VS: blood pressure 148/87 mm Hg, pulse 115 beats per minute, respiratory rate 23/minute, temperature 39.0°C (102.2°F), Ht 180 cm (5′11″), Wt 80 kg (176 lbs)
CNS: Unresponsive, unarousable
CV: Sinus tachycardia; normal S_1, S_2; no murmurs, rubs, gallops
Pulm: Tachypneic; oxygen saturation 92% on room air; no rhonchi, wheezes, rales
Abd: Firm, non-tender, non-distended; (+) bowel sounds; no hepatosplenomegaly
Exts: Rhythmic tonic-clonic movements of all extremities
GU: Incontinent of urine and stool
HEENT: Persistent upward gaze

Labs

Sodium 130 mEq/L (130 mmol/L), WBC $12 \times 10^3/mm^3$ ($12 \times 10^9/L$)

Phenytoin 2.1 mcg/mL (8.3 µmol/L), albumin 3.5 g/dL (35 g/L)

Potassium 3.5 mEq/L (3.5 mmol/L), hemoglobin 14 g/dL (140 g/L or 8.7 mmol/L)

Chloride 100 mEq/L (100 mmol/L), hematocrit 42% (0.42 volume fraction)

Carbon dioxide 12 mEq/L (12 mmol/L), platelets $235 \times 10^3/mm^3$ ($235 \times 10^9/L$)

Blood urea nitrogen 10 mg/dL (3.6 mmol/L), prothrombin time 12 seconds

Serum creatinine 0.9 mg/dL (80 µmol/L), International Normalized Ratio 1.1

Glucose 189 mg/dL (10.5 mmol/L), activated partial thromboplastin time 28 seconds

- What is your assessment of the cause of this patient's condition?
- Identify your goals of therapy for this patient.
- What therapies must be instituted next?

Diagnostic Tests

The only way to determine if a comatose patient has SE is by EEG. EEG monitoring should be used for patients who remain unconscious after initial antiepileptic treatment, and for those who received a long-acting paralytic agent or require prolonged therapy for RSE. Treatment should never be delayed while awaiting EEG results. An electrocardiogram (ECG) should be obtained to rule out cardiac dysfunction when hypotension or an abnormal heart rate is observed.

TREATMENT

Desired Outcomes

❹ *The goals of treatment of status epilepticus include the cessation of any seizure activity, both clinical and subclinical, and the prevention of further seizures. Ideally, this is accomplished through directed pharmacotherapy with minimization of any side effects or adverse reactions. Complications of SE should also be treated.*

General Approach

The initial approach to SE involves first removing the patient from harmful surroundings and ensuring a safe airway to prevent respiratory collapse or aspiration. Benzodiazepines are the first medications administered, as they are the drugs of choice to stop acute seizure activity, followed by the initiation of an antiepileptic agent. Medications are typically given intravenously (IV) for immediate onset of action, but if no IV access is available, certain medications may be given intramuscularly (IM), rectally, buccally, or via an endotracheal tube. Once the seizures stop, clinicians must identify and treat the underlying cause of the seizures, such as toxins, hypoglycemia, or trauma. Patients with known seizure disorders should be evaluated for abrupt cessation of their medications or for history of non-compliance.

Nonpharmacologic Treatment

Non-drug interventions may include administration of oxygen or intubation for mechanical ventilation in cases of hypoxemia or body cooling for febrile seizures. All patients should receive glucose in case of hypoglycemia-induced SE. In patients with a history of alcohol abuse, thiamine 100 mg should be given prior to the administration of any glucose-containing solutions to prevent encephalopathy. Specialists in neurology or epileptology should be consulted as appropriate. Admission to an emergency department or intensive care unit (ICU) will allow appropriate monitoring during the seizure and in the postictal period.

Pharmacologic Treatment

Initial Treatment

Benzodiazepines

❺ *Initial drug therapy begins with the administration of an intravenous benzodiazepine since they are most effective in aborting seizure activity. Intravenous bolus doses of diazepam, lorazepam, and midazolam have all been used in status epilepticus because of their rapid effects at inhibiting GABA receptors in the CNS. Diazepam and lorazepam have historically been the more commonly used agents; however, most clinicians currently use lorazepam as the first-line agent.* When treating patients who are taking chronic benzodiazepines, clinicians should consider higher doses to overcome the effects of tolerance. Diazepam and lorazepam should be diluted with normal saline in a 1:1 ratio before parenteral administration via peripheral veins to avoid venous irritation from the propylene glycol diluent in the formulation.

Diazepam Being extremely **lipophilic**, diazepam penetrates quickly into the CNS, but can rapidly redistribute into body fat and muscle. This results in a faster decline in CNS levels and early recurrence of seizures. It is dosed at 5 to 10 mg (or 0.15 mg/kg) and infused no faster than 5 mg/minute. Repeated doses can be given every 5 minutes until seizure activity stops or toxicities are seen (e.g., respiratory depression). Diazepam can also be administered as a rectal suppository, making it possible for non-medical personnel to provide rapid therapy for seizures that develop at home or in public areas.[11] The adult dose is 10 mg given rectally and this dose may be repeated once if necessary. Diazepam is erratically absorbed via the intramuscular route; therefore, IM administration is not recommended.

Lorazepam Less lipophilic than diazepam, lorazepam has a longer redistribution half-life, resulting in longer duration of action and a decrease in the need for repeated doses. Both lorazepam and diazepam are effective in stopping seizures,[12] but lorazepam is currently the preferred agent due to its longer duration of action. Lorazepam is given as a single IV dose of 0.1 mg/kg (maximum dose is 4 mg) with a maximum rate of infusion of 2 mg/minute. It can be re-dosed every 10 to 15 minutes (up to a maximum cumulative dose of 8 mg) until seizure activity stops or side effects such as respiratory depression occur. It should not be given IM since it has slow and unpredictable absorption via the IM route.

Midazolam Midazolam is water-soluble and can be administered intravenously, intramuscularly,[13] buccally,[14,15] and nasally.[16,17] At physiologic pH, it becomes more lipophilic and can diffuse into the CNS. Compared to diazepam and lorazepam, it has fewer effects on the respiratory and cardiovascular systems. Its short half-life requires that it be re-dosed frequently or administered as a continuous infusion. Midazolam can be given at 0.2 mg/kg either intravenously or intramuscularly as a single dose.[18] The liquid or injectable formulation can be given buccally or intranasally (0.3 mg/kg) when IV access cannot be secured. Nasal administration in SE can be hindered by rapid breathing and increased nasal secretions.

Anticonvulsants

❻ Once the first dose of benzodiazepine is given, an antiepileptic drug must be started to prevent further seizures from occurring. AEDs must not be given as first-line therapy since they must be infused relatively slowly to avoid adverse effects, delaying their onset of action.

Once the loading dose of the AED is administered, it is important to remember to initiate maintenance doses to ensure that therapeutic levels are sustained. Chronic and idiosyncratic side effects as well as potential drug interactions should be considered if the patient will continue AED therapy indefinitely. All drug therapy should be adjusted for any hepatic or renal disease states. Table 28–1 summarizes the drug doses used in SE, and Table 28–2 provides an example of an algorithm for the treatment of patients in SE. Published studies comparing these treatment strategies are summarized in Table 28–3.

Phenytoin The most widely used antiepileptic agent is phenytoin, which is administered IV as a loading dose (for patients previously not on phenytoin) of 15 to 20 mg/kg. The loading dose must be modified in those patients who are taking phenytoin and have subtherapeutic levels in order to avoid toxic serum concentrations. The loading dose is infused no faster than 50 mg/minute due to potential risks of hypotension or arrhythmias. Continuous monitoring of ECG and blood pressure is recommended. Maintenance dosing can be started 12 hours after the loading dose. Phenytoin should not be infused with other medications because of stability concerns (it is soluble in propylene glycol and compatible only in 0.9% sodium chloride solutions). It should not be given via the IM route due to its alkaline nature. **Extravasation** of the drug can cause local discoloration, edema, pain, and sometimes necrosis (purple glove syndrome). Although phenytoin comes in a variety of enteral preparations, oral loading is not recommended in SE due to the delay in absorption.

Fosphenytoin Fosphenytoin is a water-soluble, phospho-ester prodrug of phenytoin that is rapidly converted to phenytoin in the body. It is compatible with most IV solutions and is well tolerated as an IM injection, even with the large volumes associated with loading doses (20 to 30 mL).[19] It is dosed in phenytoin equivalents (PE), and it can be infused three times as fast as phenytoin, up to 150 mg PE/minute. The loading dose for patients not taking phenytoin is 15 to 20 mg PE/kg. It can be an advantage to use IM fosphenytoin when IV access cannot be obtained immediately and in patients with poor venous access. Although it has fewer cardiovascular side

TABLE 28–1. Parenteral Medications Used in Status Epilepticus in Adults

Drug Name (Brand Name)	Loading Dose	Administration Rate	Therapeutic Level	Side Effects	Comments
Diazepam (Valium)	0.15 mg/kg	5 mg/minute (IVP)	N/A	Hypotension, respiratory depression	Rapid redistribution rate; can be given rectally
Lorazepam (Ativan)	0.1 mg/kg	2 mg/minute (IVP)	N/A	Hypotension, respiratory depression	May be longer-acting than diazepam
Midazolam (Versed)	0.2 mg/kg	2 mg/minute (IVP)	N/A	Sedation	Can also be given IM, buccally, intranasally; expensive
Phenytoin (Dilantin)	15–20 mg/kg	Up to 50 mg/minute	10–20 mcg/mL (39.6–79.2 µmol/L)	Arrhythmias, hypotension,	Hypotension, especially in elderly
Fosphenytoin (Cerebyx)	15–20 mg PE/kg	Up to 150 mg PE/minute	10–20 mcg/mL	Paresthesias, hypotension	Can be given IM; less CV side effects than phenytoin; expensive
Phenobarbital (Luminal)	20 mg/kg	50–100 mg/minute	15–40 mcg/mL (64.7–172.4 µmol/L)	Hypotension, sedation, respiratory depression	Long-acting
Valproate sodium (Depacon)	15–20 mg/kg (up to 40 mg/kg)	3–6 mg/kg per minute	50–150 mcg/mL (346.5–1039.5 µmol/L)		Less CV side effects than phenytoin
Propofol (Diprivan)	1–2 mg/kg	Approximately 40 mg every 10 seconds	N/A (typically titrated to EEG)	Hypotension, respiratory depression	Requires mechanical intubation; high lipid load (increased calories); propofol infusion syndrome
Pentobarbital (Nembutal)	10–15 mg/kg	Up to 50 mg/minute	10–20 mcg/mL (typically titrated to EEG)	Hypotension, respiratory depression, cardiac depression, infection, ileus	Requires mechanical intubation, pressors, hemodynamic monitoring

CV, cardiovascular; EEG, electroencephalogram; IM, intramuscular; IVP, intravenous push; N/A, not applicable; PE, phenytoin equivalents.

effects than phenytoin, clinicians should still continuously monitor blood pressure, ECG, and heart rate. Maintenance doses are begun 12 hours after the loading dose. A common side effect is **paresthesias**, especially around the lips and in the groin, which typically resolve within a few minutes and should not necessitate stopping the infusion. If a post-load serum level is desired, it should be obtained 2 hours after an IV load or 4 hours after an IM load. Fosphenytoin is more expensive than phenytoin, making it difficult to justify its use in many institutions.[20]

Phenobarbital If phenytoin or fosphenytoin fails to prevent seizure recurrence, phenobarbital can be administered. However, emerging evidence suggests that phenobarbital may not be effective if SE persists after giving benzodiazepines and phenytoin. This may be due to the progressive resistance of the $GABA_A$ receptor, at which the barbiturates also act.[21] It is dosed as an IV load of 15 to 20 mg/kg with a maximum rate of administration of 100 mg/minute. Adverse reactions of phenobarbital include sedation, hypotension, and respiratory depression; therefore, patients who receive a rapid IV loading dose of phenobarbital should have hemodynamic monitoring and be mechanically ventilated. Its long half-life makes it a popular agent for both acute treatment and chronic maintenance therapy.

Valproate Sodium Valproate sodium is an older AED that was released as an intravenous preparation (Depacon®) in 1996. Although it is not FDA-approved for SE, its use has been documented in various types of SE including generalized tonic-clonic, myoclonic, and non-convulsive SE.[22,23] Reports indicate



Patient Encounter, Part 3

Treatment Failure

It has been forty-five minutes since CH's arrival, and he has been given lorazepam 4 mg twice and loaded with 1500 mg of phenytoin. He received another 400 mg dose of phenytoin 15 minutes ago, but is still unarousable. His jerking movements have slowed down, but his temperature is now 39.9°C (103.8°F), and his blood pressure has dropped to 124/62 mm Hg. His oxygen saturation is 91% on 4 L oxygen via nasal cannula. Bilateral crackles are heard upon auscultation of his lungs. A CT scan of his head is obtained which shows no evidence of hemorrhage, tumor, or mass effect.

- What is your assessment of this patient's condition?
- What possible treatment options exist at this time?
- How would you optimize this patient's outcome?

TABLE 28–2. Algorithm for Status Epilepticus in Adults

Time (minutes)	Assessment/Monitoring	Treatment
0	Vital signs (HR, RR, BP, T) Assess airway Monitor cardiac function (ECG) Pulse oximeter Check blood glucose Check laboratory tests: complete blood count serum chemistries liver function tests arterial blood gas blood cultures serum anticonvulsant levels urine drug/alcohol screen	Stabilize airway (intubate if necessary) Administer oxygen Secure IV access and start fluids Give thiamine (100 mg) + glucose (50 mL of 50% solution) if hypoglycemic
0–10	Vital signs Physical exam Patient history including medications (prescription, OTC, and herbals)	Lorazepam 0.1 mg/kg (maximum 4 mg) IVP at 2 mg/minute (may repeat in 10–15 minutes to maximum of 8 mg if no response) If no IV access, can give: diazepam 10 mg PR (may repeat in 10 minutes if no response); midazolam 0.2 mg/kg IM (may repeat in 10 minutes if no response)
10–30	Vital signs Review laboratory results and correct any underlying abnormalities CT scan (if seizures controlled)	Phenytoin 15–20 mg/kg IV at a maximum rate of 50 mg/minute (or fosphenytoin 15–20 mg PE/kg IV at a maximum rate of 150 mg/minute) If no IV access, can give fosphenytoin IM Treat for possible infection
30–60	Vital signs Consult neurologist/epileptologist Consider admission to ICU Consider EEG	If seizures continue: additional phenytoin bolus 5–10 mg/kg (or fosphenytoin 5–10 mg PE/kg) **OR** start phenobarbital at 20 mg/kg IV at a maximum rate of 100 mg/minute
Greater than 60 *refractory status epilepticus*	Vital signs Transfer to ICU Obtain EEG Consider MRI when controlled	If seizures continue: repeat boluses of phenobarbital 10 mg/kg until seizures stop **OR** valproate sodium 20 mg/kg at 6 mg/kg per minute max followed by 1–4 mg/kg per hour CI **OR** midazolam 2 mg/kg bolus followed by 0.05–2 mg/kg per hour CI or propofol 1 mg/kg bolus followed by 2–15 mg/kg per hour CI **OR** pentobarbital 10–15 mg/kg bolus over 1–2 hours followed by 0.5–4 mg/kg per hour; Consider intubation and/or pressor support if needed

BP, blood pressure; CI, continuous infusion; CT, computed tomography; ECG, electrocardiogram; EEG, electroencephalography; HR, heart rate; ICU, intensive care unit; IV, intravenous; IVP, intravenous push; OTC, over the counter; MRI, magnetic resonance imaging; PE, phenytoin equivalents; PR, per rectum; RR, respiratory rate; T, temperature.
Adapted from Phelps SJ, Hovinga CA, Boucher BA. Status epilepticus. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1054, with permission.

TABLE 28–3. Randomized, Prospective Trials Comparing Treatments for Status Epilepticus in Adults

Study	Treatment	Outcome	Adverse Events	Comments
Leppik (1983)[44]		Seizure control		Onset did not differ between two groups
	Diazepam 10 mg	76%	12%	
	Lorazepam 4 mg	89%	13%	
Shaner (1988)[45]		Time spent in SE	Incidence of intubation, hypotension, and arrhythmias similar in both groups	Unblinded study
Goal: Time to seizure control	Diazepam + phenytoin	9 minutes		
	Phenobarbital +/– phenytoin	5 minutes		
Treiman (1998)[46]		Seizure control	Resp/cardiac events	Patients with subtle GCSE fared worse than patients with overt GCSE
Goal: Seizure control within 20 minutes and no recurrence within 60 minutes	Diazepam 0.15 mg/kg + phenytoin 18 mg/kg	55.8%	2.1–31.6%	
	Lorazepam 0.1 mg/kg	64.9%	7.2–25.8%	
	Phenobarbital 15 mg/kg	58.2%	3.3–34.1%	
	Phenytoin 18 mg/kg	43.6%	6.9–27%	
Alldredge (2001)[47]		Seizure control	Resp/cardiac events	Higher doses used in hospital for SE
Goal: Seizure control on arrival to ED	Lorazepam 2 mg	59.1%	10.6%	
	Diazepam 5 mg	42.6%	10.3%	
	Placebo	21.1%	22.5%	
Misra (2006)[48]		Seizure control	Resp/cardiac events	As second line agent, valproate controlled more seizures than phenytoin (79% vs 25%)
Goal: Seizure control after infusion	Sodium valproate 30 mg/kg	66%	4%/0%	
	Phenytoin 18 mg/kg	42%	14%/14%	

ED, emergency department; GCSE, generalized convulsive status epilepticus; SE, status epilepticus.

a good response rate (80%) and a relatively benign side-effect profile compared to phenytoin and phenobarbital. It can be considered when the use of phenytoin and phenobarbital are precluded due to allergies or intolerance. Valproate sodium can be loaded intravenously at 15 to 20 mg/kg and infused at a rate of up to 3 mg/kg per minute. Higher doses (up to 30 to 40 mg/kg) have also been used to attain serum levels of 100 to 150 mcg/mL in less responsive cases of SE.[24]

Treatment of Refractory Status Epilepticus

❼ *Seizure activity that does not respond to benzodiazepines (first-line) and antiepileptics (second-line) or persists beyond 60 minutes in duration can be considered refractory status epilepticus (RSE).*[25] It can occur in up to 30% of patients with SE and has a mortality rate approaching 50%. Patients in RSE are unlikely to return to their baseline state, even if the seizures are eventually controlled. As RSE progresses, clinical signs may become subtle, and in certain patients, an EEG is required to detect ongoing seizure activity. ❶ *Even patients without clinical signs of seizing are at risk for brain damage or even death.*

The optimal therapy for RSE has not been determined. Clinicians must aggressively investigate and treat possible causes including infection, tumors, drugs or toxins, metabolic disorders, liver failure, or fever.[26] In general, patients with RSE are managed in an ICU where hemodynamic and respiratory support are available and frequent monitoring can be performed. Continuous EEG monitoring is desirable to document cessation of seizure activity, but treatment should not be delayed if continuous EEG monitoring is not immediately available or while waiting for results. ❽ *Treatment of RSE consists of continuous intravenous infusions of benzodiazepines (midazolam), anesthetic agents (propofol), or barbiturates (pentobarbital) to suppress all clinical and electrographic evidence of seizures.*[27] These agents are typically titrated to achieve "burst suppression" on the EEG, although no strong evidence exists to support this as the universal goal.[28] Any AEDs that were started before treatment for RSE should be continued and their serum levels optimized in order to minimize any breakthrough or withdrawal seizures. Patients should be intubated and mechanically ventilated before initiating these treatment strategies for RSE. Consultation with a neurologist or epileptologist is highly recommended in these cases.

Midazolam

A loading dose of 0.2 mg/kg (repeated up to a maximum of 2 mg/kg) followed by a continuous infusion of 0.05 to 2 mg/kg per hour is recommended in RSE.[29–31] The dose must be adjusted during prolonged infusions, especially in patients with renal impairment, as the active metabolite can accumulate.[32] Breakthrough seizures are common with midazolam infusions and usually respond to a bolus and a 20% increase in the rate. Despite this, tachyphylaxis can occur and the patient should be switched to another agent if seizure activity continues.

Propofol

The anesthetic agent propofol can be started with loading doses of 1 mg/kg repeated every 3 to 5 minutes until a clinical

response is achieved, after which the infusion can be initiated at 2 to 4 mg/kg per hour. Propofol can cause hypotension, especially with loading doses. Long-term, high-dose (greater than 5 mg/kg per hour) propofol infusions are associated with rhabdomyolysis, acidosis, and cardiac arrhythmias (propofol infusion syndrome), especially in children.[33] Propofol has a very short serum half-life and should be tapered off slowly to avoid withdrawal seizures. High-dose propofol infusions can also provide a considerable amount of calories (1 kcal/mL of the 1% solution) over time, so other sources of nutrition may have to be adjusted accordingly.

Pentobarbital

Barbiturate infusions have been reported to be highly successful in treating RSE,[34] but their side effects are considerable. They can cause significant hypotension, myocardial and respiratory depression, ileus, and infection (especially gram-positive organisms). As a result, patients often require mechanical ventilation, intravenous **vasopressor** therapy, invasive hemodynamic monitoring, and total parenteral nutrition while undergoing "barbiturate coma." On the other hand, barbiturates are beneficial if elevated intracranial pressure (ICP) is present, as they are effective in decreasing ICP.

Pentobarbital is commonly loaded at a dose of 10 to 15 mg/kg over 1 to 2 hours, followed by a continuous infusion of 0.5 to 4 mg/kg per hour. Therapy can be tapered off after 12 to 24 hours of seizure control as evident on the EEG.[35] One meta-analysis reported a lower incidence of treatment failure with pentobarbital (3%) when compared to midazolam (21%) or propofol (20%), although the risk of hypotension requiring vasopressor therapy was higher when pentobarbital was used.[36] This relative efficacy for pentobarbital must be considered together with its complications when determining which agent to use. Patients who fail midazolam and/or propofol infusions should be switched over to pentobarbital therapy.

Other Agents

Ketamine,[37] topiramate, and inhaled anesthetics are newer modalities that have been used to treat RSE. Ketamine is an NMDA receptor antagonist that has been given orally[38] and intravenously[39] for RSE in children. Topiramate is a newer oral antiepileptic agent with multiple mechanisms of action that may have some benefit in RSE. The dose in adults ranges from 300 to 1600 mg/day.[41] Children have also been administered topiramate at a starting dose of 2 to 3 mg/kg per day and titrated to a maintenance dose of 5 to 6 mg/kg per day.[41] The inhaled anesthetics, desflurane and isoflurane,[42] are normally delivered in an operating room, and require special equipment for administration in an ICU. Future studies will determine their place in therapy.

Special Populations

Certain patient populations require special considerations due to their altered metabolism, unique volume of distribution, or increased risk for side effects.[43] Although many of these patients are excluded from clinical trials in SE, the standard algorithm for SE still applies for these patients in terms of immediate care, assessment, and drugs (see Table 28–2).

Pediatrics

The treatment approach of SE in children is similar to that in adults with a few exceptions (Table 28–4). The doses are also weight-based but are typically higher than those used in adults due to higher clearance by the liver. It may be difficult to rapidly obtain IV access in children, so alternate methods of

TABLE 28–4. Drugs Used in Pediatric Status Epilepticus

Drug	Dose	Comments
Diazepam (Valium injection, Diastat rectal gel)	IV: 0.2–0.3 mg/kg over 2–5 minutes	Maximum dose in children less than 5 y: 5 mg Maximum dose in children greater than 5 y: 15 mg
	PR: 2–5 years: 0.5 mg/kg 6–11 years: 0.3 mg/kg greater than 12 years: 0.2 mg/kg	A second rectal dose can be given 4–12 hours after the first dose if necessary
Lorazepam (Ativan)	0.05–0.1 mg/kg IV over 2–4 minutes	May redose twice in 10–15 minutes if necessary
Midazolam (Versed)	0.2 mg/kg IV bolus followed by 0.05–0.6 mg/kg per hour continuous infusion	Bolus dose may also be given intranasally, buccally, or intramuscularly
Phenytoin (Dilantin)	15–20 mg/kg IV at 1–3 mg/kg per minute *max*	
Fosphenytoin (Cerebyx)	15–20 mg PE/kg IV at 3 mg/kg per minute *max*	Dose can be given intramuscularly
Phenobarbital (Luminal)	15–20 mg/kg IV at 100 mg/minute *max*	
Valproate sodium (Depacon)	15–20 mg/kg IV at 1.5–3 mg/kg per minute	May have fewer cardiovascular side effects than other agents
Propofol (Diprivan)		Not recommended due to adverse events (e.g., rhabdomyolysis)
Pentobarbital (Nembutal)	10–15 mg/kg IV over 1–2 hours followed by continuous infusion at 1 mg/kg per hour	Titrated to EEG

PR, per rectum; EEG, electroencephalograph; IV, intravenous; PE phenytoin equivalent.

drug administration have been studied, including intranasal, buccal, rectal, and IM.

Geriatrics

The elderly are prone to injury and toxicity from multiple concomitant disease states and polypharmacy. Seizures in the elderly can easily arise from metabolic disorders, drug interactions, or even incorrect dosing of medications in patients with impaired renal and hepatic function and decreased protein binding. Clinicians treating elderly patients presenting with SE should investigate drug- and disease state–induced causes, since treating these etiologies alone may terminate seizures. Acute treatment with benzodiazepines and AEDs is no different in the elderly, but elderly patients may have a more pronounced reaction to these medications in terms of their sedative and cardiorespiratory side effects. Phenytoin and fosphenytoin loading doses should be carefully calculated in the elderly, as their weights may be overestimated, and they may not tolerate the commonly ordered 1-g dose. They should also be infused at slower rates to minimize hypotension and arrhythmias. Phenobarbital may cause respiratory depression earlier in the elderly, especially after benzodiazepines are administered. Clinicians should consider using smaller doses and should evaluate these patients for renal and hepatic insufficiency if repeated doses are to be given.

Pregnancy

The main concern in the treatment of pregnant females in SE is the safety of the fetus which is at risk of hypoxia during periods of prolonged seizures. Although many of the agents used in SE are **teratogenic**, clinicians should still use them as acute measures to stop the seizures and consider alternative agents as maintenance therapy. The volume of distribution and clearance of many drugs are typically increased during pregnancy, and this should be considered when calculating doses.

OUTCOME EVALUATION

❹ *The success of treatment is measured by the early termination of seizures, without adverse drug effects or brain injury.* Therefore, it is essential to start pharmacologic treatment as soon as possible. First-line treatment for SE should halt seizure activity within minutes of administration. In patients who are unarousable following treatment, an EEG should be done to rule out continued excessive electrical brain activity and confirm termination of seizures. A physical exam and evaluation of the patient's laboratory results can help determine if the cause or complications of seizure activity are being appropriately treated.

Once seizure activity has ceased and the patient has stabilized, review the patient's therapeutic regimen. Evaluate and monitor the serum trough concentrations of AEDs with defined target ranges to determine patient-specific therapeutic ranges. If there is a known cause of SE, simplify the treatment regimen once the underlying cause has been treated. In patients with RSE on multiple AEDs, slowly decrease the dose of one drug at a time while continuing to evaluate the patient for seizure activity. Base the titration schedule on the half-life of the drug and individual patient response. The optimal treatment regimen is one that uses the least medications to prevent seizure recurrence and does not cause adverse drug reactions.

Continue to monitor AED serum trough concentrations approximately every 3 to 5 days until the AEDs have reached steady-state concentrations. Give additional loading doses or hold doses as needed to maintain trough concentrations in the patient's therapeutic range. Be sure to evaluate the time the sample was drawn to assure it is a trough level.

Frequently monitor the patient for signs of drug toxicity and seizures until the patient's drug concentrations have stabilized. Drug interactions are likely when patients are on more than one AED; therefore, closely evaluate the patient's entire medication profile, and change medications or doses to minimize the interaction, if possible.



Patient Care and Monitoring

1. Obtain a seizure history from the patient or family members, including precipitating factors and duration of seizure activity.
2. Identify the underlying cause of the seizures and correct the cause, if possible. Does the patient have any laboratory abnormalities? Is there a positive toxicology screen for alcohol or drugs?
3. Obtain a thorough history of non-prescription, prescription, and alternative or herbal drug use. Determine adherence with the medication regimen and whether barriers to care exist. Does the patient have the financial ability and transportation to obtain their prescriptions?
4. Assess the AED serum concentration and adjust therapy as needed for agents with a defined therapeutic range (e.g., phenytoin, carbamazepine, valproic acid, and phenobarbital). Drug levels can also be used to determine adherence to medication regimens for agents that do not have defined ranges.
5. Evaluate the patient for adverse drug reactions, IV site extravasation and allergic reactions. What alternative AEDs should be used if a drug allergy is identified?
6. Determine whether there are any drug interactions with the patient's current or home medication regimens. Do you need to adjust the dose of any medications for toxic or subtherapeutic concentrations from the drug interaction?
7. Maintain adequate cardiovascular support, nutrition, and electrolyte and glucose serum concentrations to prevent recurrence of seizure activity.
8. Continue to evaluate the patient for seizure activity and adjust therapy as needed to control seizures and optimize quality of life.

ABBREVIATIONS

ABG:	arterial blood gas
AED:	antiepileptic drug
CNS:	central nervous system
CSF:	cerebrospinal fluid
CT:	computerized tomography
ECG:	electrocardiogram
EEG:	electroencephalography
GABA:	γ-aminobutyric acid
GCSE:	generalized convulsive status epilepticus
ICP:	intracranial pressure
ICU:	intensive care unit
IM:	intramuscular
IV:	intravenous
MRI:	magnetic resonance imaging
NCSE:	non-convulsive status epilepticus
NMDA:	N-methyl-D-aspartate
PE:	phenytoin equivalent
RSE:	refractory status epilepticus
SE:	status epilepticus
WBC:	white blood cell

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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29 Parkinson's Disease

Mary L. Wagner



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Explain the etiology of Parkinson's disease.
2. Explain the pathologic and biochemical changes in patients with Parkinson's disease.
3. Identify motor and non-motor symptoms of Parkinson's disease as well as symptoms that indicate disease progression.
4. Explain the desired therapeutic goals for patients with Parkinson's disease.
5. Recommend lifestyle modifications and pharmacotherapy interventions for treating motor symptoms of patients with Parkinson's disease.
6. Recommend drug and non-drug interventions for treating the non-motor symptoms of patients with Parkinson's disease.
7. Develop a monitoring plan to assess effectiveness and adverse effects of nonpharmacologic therapy and pharmacotherapy for Parkinson's disease.
8. Educate patients about the disease state, appropriate lifestyle modifications, and drug therapy required for effective treatment.

Key Concepts

❶ Patients with Parkinson's disease display both motor and non-motor symptoms. The non-motor symptoms may precede the motor symptoms.

❷ The most useful diagnostic tool is the clinical history, including both presenting symptoms and associated risk factors. The Unified Parkinson's Disease Rating Scale (UPDRS) is used to define the degree of disability.

❸ The goals of treatment are to maintain patient independence, activities of daily living (ADL), and quality of life (QOL) by alleviating the patient's symptoms, minimizing the development of response fluctuations, and limiting medication-related adverse effects.

❹ The treatment of Parkinson's disease is categorized into three phases:

- Lifestyle changes, nutrition, and exercise
- Pharmacologic intervention, primarily with drugs that enhance dopamine concentrations
- Surgical treatments for those who fail pharmacologic interventions

❺ The best time to initiate dopaminergic therapy is controversial and patient-specific. Generally, medication is started when the patient's physical impairment affects quality of life.

❻ Medication schedules should be individualized. The doses are divided throughout the day to maximize on and minimize off periods.

❼ The treatment of non-motor symptoms should be based on whether they are worse during an off state or if they could be related to other neurotransmitter dysfunction.

❽ As the disease progresses, most patients develop response fluctuations. Treatment is based on optimizing the pharmacokinetic and pharmacodynamic properties of Parkinson's disease medications.

❾ Patient monitoring should involve a regular systematic evaluation of efficacy and adverse events, referral to appropriate specialists, and patient education.

Parkinson's disease (PD) is a slow, progressive, neurodegenerative disease of the extrapyramidal motor system. Dopamine neurons in the substantia nigra are primarily affected, and degeneration of these neurons causes a disruption in the ability

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Patient Encounter, Part 1

MW, a 65-year-old man with a 2-year history of mild depression comes for an initial visit to evaluate his symptoms of tremor and slowness. The tremor started in his right hand about 6 months ago, and he does not remember how long he has been slower at completing his tasks. His wife reports that for the last 4 months he has been slower and that he kicks her while they are sleeping.

- Identify the motor and non-motor symptoms of Parkinson's disease.
- What additional information would you collect before creating this patient's treatment plan?

to generate body movements. There is no cure for PD and treatment is aimed at controlling symptoms and slowing disease progression.

EPIDEMIOLOGY AND ETIOLOGY

PD affects approximately one million Americans (1% of people over 60 years of age). The average age of onset is 60 years of age, and PD is fairly uncommon in those under age 40. The etiology of PD is unknown, but genetic predisposition, environmental factors, or combinations of these have been proposed to explain why nerve cells in the substantia nigra deteriorate. About 15% of patients with PD have a first-degree relative with the disease. The pathogenesis of cell death (neuron degeneration) may be due to oxidative stress, mitochondrial dysfunction, increased concentrations of excitotoxic amino acids and inflammatory cytokines, immune system disorders, trophic factor deficiency, signal-mediated apoptosis, and environmental factors. Conditions that may promote oxidative stress include increased monoamine oxidase B metabolism or decreased glutathione clearance of free radicals which can promote cell dysfunction and death. Environmental toxins include 1-methyl-4-phenyl-1-2-5-6-tetrahydropyridine (MPTP), carbon monoxide, manganese, methanol, hydrogen sulfide, petrochemicals and pesticides, but they have never been clearly proven as causative. Drugs that deplete central dopamine, such as some antipsychotics, amoxapine, antinausea drugs (i.e., prochlorpromazine) and metoclopramide, worsen Parkinson's symptoms.[1,2,3]

Pathology studies of patients with PD indicated that there is a loss of pigmented cells in the substantia nigra that make and store dopamine. When patients are diagnosed with PD, they have lost 50% to 60% of their dopamine neurons in the substantia nigra, and the remaining neurons may not function well, as they have lost about 80% of their activity in the striatum. There may be cortical **Lewy bodies** along with Lewy neurites seen in microscopic samples from the medial temporal, limbic, and frontal areas of the brain, gastrointestinal tract, and peripheral autonomic nervous system that may explain some of the non-motor symptoms of PD.[2–4]

PATHOPHYSIOLOGY

The extrapyramidal motor system controls muscle movement through a system of pathways and nerve tracts that connect the cerebral cortex, basal ganglia, thalamus, cerebellum, reticular formation, and spinal neurons. Patients with PD lose dopamine neurons in the **substantia nigra**, which is located in the midbrain within the brain stem. The substantia



Clinical Presentation of Parkinson's Disease

❶ *Patients with PD display both motor and non-motor symptoms. The non-motor symptoms may precede the motor symptoms.*

Motor Symptoms (TRAP)[7]

T = Tremor at rest ("pill rolling")
R = Rigidity (stiffness and cogwheel rigidity)
A = **Akinesia or bradykinesia**
P = Postural instability and gate abnormalities

Non-motor Symptoms (SOAP)

S = Sleep disturbances (insomnia, rapid eye movement sleep behavioral disorder, restless legs syndrome)
O = Other miscellaneous symptoms (problems with nausea, fatigue, speech, pain, **dysesthesias**, vision, seborrhea)
A = Autonomic symptoms (drooling, constipation, sexual dysfunction, urinary problems, sweating, orthostatic hypotension, dysphagia)
P = Psychological symptoms (anxiety, psychosis, cognitive impairment, depression)

Response Fluctuations (MAD)

M = motor fluctuations (delayed peak, wearing off, random off, freezing)
A = **akathisia**
D = **dyskinesias** (chorea, dystonia, diphasic dyskinesia)

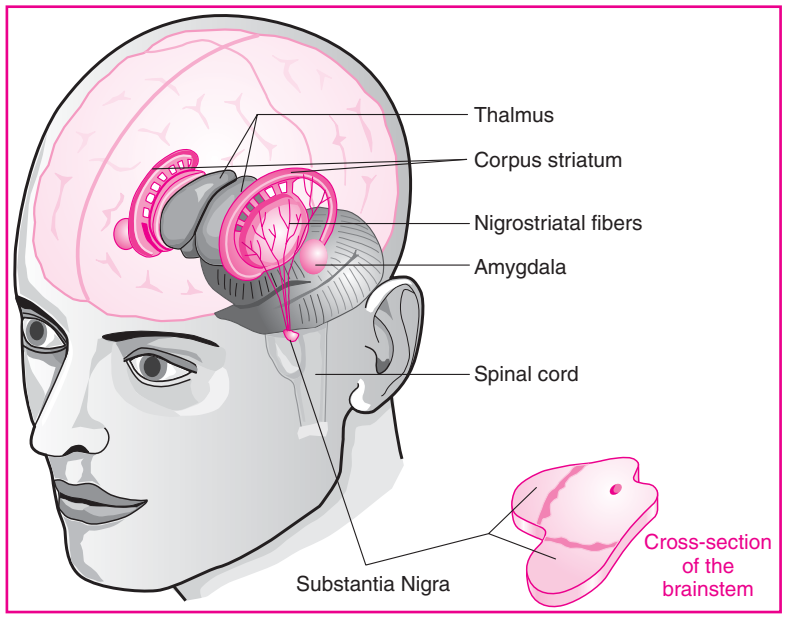


FIGURE 29–1. Anatomy of the extrapyramidal system. The extrapyramidal motor system controls muscle movement through a system of pathways and nerve tracts that connect the cerebral cortex, basal ganglia, thalamus, cerebellum, reticular formation, and spinal neurons. Patients with Parkinson's disease have a loss of dopamine neurons in the substantia nigra in the brain stem that leads to depletion of dopamine in the corpus striatum. The corpus striatum is made up of the caudate nucleus and the lentiform nuclei that are made up of the putamen and the globus pallidus.

nigra sends nerve fibers up to the corpus striatum, which is part of the **basal ganglia** in the cerebrum. The corpus striatum is made up of the caudate **nucleus** and the lentiform nuclei that consist of the pallidum (globus pallidus) and putamen (Fig. 29–1). As dopamine neurons die, dopamine-relayed messages cannot communicate to other motor centers of the brain and patients develop motor symptoms. A variety of chemicals are active in the basal ganglia including acetylcholine, histamine, glutamate, serotonin, dopamine, norepinephrine, epinephrine, γ-aminobutyric acid (GABA), enkephalins, substance P, and adenosine. Some of these neurotransmitters also decrease in concentration as other brain regions degenerate resulting in degeneration of norepinephrine neurons in the locus ceruleus and acetylcholine neurons in the nucleus basalis as well as selected neurons of the dorsal motor nucleus of the vagus, spinal cord, and peripheral autonomic system. Decreases in these neurotransmitters may explain some of the non-motor symptoms of PD.[3] For example, loss of dopamine and norepinephrine neurons in the limbic system has been associated with depression and anxiety, and neuron loss in the hippocampus and amygdala of the limbic system is associated with cognitive impairment.[5,6]

CLINICAL PRESENTATION AND DIAGNOSIS

As the onset of PD is insidious, patients are likely to rationalize other causes for their symptoms. A thorough patient history including past and present medications, family history, environmental exposure, and a detailed description of symptom onset is essential in making an accurate diagnosis. Patients feel slowed down or trapped in their body unable to move. The tremor of PD occurs during rest and disappears with purposeful movement. Tremor usually affects the hands or feet, but may occur in other body parts such as in the lip and chin. The hand tremor can appear as if the patient is rolling a pill between their fingers. Patients describe rigidity as stiffness. Upon physical exam, it feels like uniform resistance as the muscles seem to be in a constant state of increased tone. It is defined as cogwheel rigidity when the examiner extends or flexes the patient's extremities and feels as if they are rhythmically hitting a series of teeth on the rim of a wheel, or a gear that is meshing with another gear with teeth. Bradykinesia is noted when there is hesitancy in movement initiation, slowness in movement performance, or rapid fatiguing during movement. Patients may have a decrease in automatic movements, such as blinking, a decrease in facial expressions (often termed masked facies), or a decrease in arm swing while walking. Postural instability is a result of the loss of reflexes necessary to maintain balance when standing or ambulating. Patients may report a feeling of unsteadiness. Gait abnormalities may be evidenced by shuffling, leg dragging, **festination**, propulsion, retropulsion, or freezing. Rigidity and bradykinesia may make handwriting difficult as evidenced by **micrographia**.[2,8]

Non-motor Symptoms

Non-motor symptoms are due to multiple neurotransmitter abnormalities throughout the brain, and some symptoms may be aggravated by PD medications. Sleep disturbance can affect more than 70% of PD patients and includes insomnia, sleep

fragmentation, rapid eye movement sleep behavioral disorder (RBD), vivid dreams, nightmares, night terrors, hallucinations, restless legs syndrome (RLS), and sleep walking. Speech problems may be exhibited as a decrease in normal volume, slurring, monotone speech, rapid speech, or stammering. Visual problems such as reading problems, double vision, perceptual changes, decreased blink, burning eyes, or itchy eyes are the result of impaired function of the muscles that move the eyeball and decreased retinal dopamine.[7–11]

As the autonomic system is disturbed in patients with PD, orthostatic hypotension and gastrointestinal, urinary, sexual, and dermatologic symptoms are common. Patients with orthostatic hypotension may experience dizziness, lightheadedness, or fainting upon standing. Gastrointestinal symptoms include constipation and **dysphagia** due to a slowing of the automatic pattern of contraction and relaxation of the throat muscles. These swallowing difficulties may lead to weight loss, **sialorrhea**, and aspiration. Genitourinary symptoms include urinary incontinence, urgency, and frequency related to overactivity of the bladder emptying reflex. Symptoms may be worse at night, causing nocturia. Sexual dysfunction includes decreased libido, erectile dysfunction, and delayed ejaculation. Skin symptoms include sweating, and intolerance to heat and cold.[7,8,11,12]

Psychological symptoms may be exaggerated during the patient's off periods and include psychosis, dementia, impaired **cognitive function**, depression, and anxiety. Psychosis can occur in nearly 30% of PD patients and is exhibited as vivid dreams, hallucinations (usually visual), paranoia, and delusions. Hallucinations may be more common when the patient is in dim light, falling asleep, or awakening. Dementia occurs in 20% to 44% of patients, and is described as problems with cognitive function. Depression occurs in 30% to 70% of PD patients and may appear as apathy, psychomotor slowing, memory problems, irritability, or sadness. It may be associated with agitation and sleep disturbances. Some features of PD, such as the decreased facial expression and bradykinesia, may make the diagnosis of depression more difficult. Anxiety may present as panic attacks, phobia, or generalized anxiety and occurs in 30% of patients. Anxiety was noted in 66% of patients with motor fluctuations and is often comorbid with depression.[7–9,11,13,14]

Response Fluctuations

Response fluctuations occur with disease progression as the patient's dopamine reserves are depleted in the brain and as a complication of PD treatment. Motor fluctuations include delayed peak response, early wearing off, random unpredictable on-off, and freezing. Dyskinesias include **chorea**, **dystonia**, and diphasic dyskinesia. Wearing off can be visualized by imagining the therapeutic window of dopamine narrowing over time. The therapeutic window is defined as the minimum effective concentration of dopamine required to control PD symptoms (on without dyskinesia) and the maximum concentration before experiencing side effects from too much dopamine (on with dyskinesia). Early in the disease, a dose of levodopa is administered and the plasma concentrations are supplemented by the brain's supply of dopamine. Thus, although the plasma half-life of levodopa is 1.5 to 2 hours, the therapeutic effect lasts about 5 hours, and the patient experiences no dopamine side effects. As the disease progresses over time, the therapeutic window narrows because the brain can no longer supplement each levodopa dose with additional dopamine. Thus, during advanced disease, each dose lasts 2 to 3 hours and patients experience dopamine side effects in order to be in an on state.[15–16]

❷ *The most useful diagnostic tool is the clinical history, including both presenting symptoms and associated risk factors. The UPDRS is used to define the degree of disability in motor and some non-motor symptoms.*



Patient Encounter, Part 2: The Medical History, Physical Exam, and Diagnostic Tests

Chief Complaint
MW complains of stiffness, slow movements, and mild tremor that worsens his handwriting

PMH
Depression for 2 years

SH
After owning a dry cleaning store for 40 years, he is thinking about retiring because he does not enjoy visiting with the customers anymore; he does not smoke or drink alcohol

Meds
Fluoxetine 10 mg every morning for 2 years
Gen: Pessimistic attitude, apathetic, looks older than stated age, slow movements, thin

PE
VS: Blood pressure: sitting 130/80 mm Hg, standing 110/80 mm Hg (with orthostatic symptoms); pulse 78 beats per minute, respiratory rate 16/minute, Wt 65 kg (143 lbs)
CV: RRR, normal S_1, S_2; no murmurs, rubs, gallops
Abd: Soft, non-tender, non-distended; (+) bowel sounds, no hepatosplenomegaly
Skin: Scalp itchy, oily, and flaky silverish scales
Exts: Tremor in right hand and foot while sitting, cogwheel rigidity in right elbow
Neuro: Steady gait, sensory function intact, alert, normal mental status, UPDRS = 10 while "on"

Labs
Within normal limits

- Assess the patient's condition.
- Identify treatment goals for the patient.
- Describe nonpharmacologic and pharmacologic treatments that are available for the patient.

The patient's degree of disability should be evaluated by using the UPDRS which has six parts. The scale combines patient history and a physical examination that is performed on both sides of the body, as symptoms may appear asymmetric in early disease. It evaluates mentation, behavior, and mood (Part 1); activities of daily living (ADL, Part 2); PD motor symptoms (Part 3); complications of therapy (Part 4); modified Hoehn and Yahr stage of disease (Part 5); and Schwab and England ADL (Part 6). The modified Hoehn and Yahr staging scale defines eight stages of PD ranging from no symptoms to wheelchair or bed bound. A copy of the exam can be obtained at http://www.mdvu.org/pdf/updrs.pdf.[17]

TREATMENT

Desired Outcomes

❸ *The goals of treatment are to maintain patient independence, ADL, and QOL by alleviating the patient's symptoms, minimizing the development of response fluctuations, and limiting medication-related adverse effects.*

General Approach to Treatment

❹ *The treatment of PD is categorized into three phases:*

- *Lifestyle changes, nutrition, and exercise*
- *Pharmacologic intervention, primarily with drugs that enhance dopamine concentrations*
- *Surgical treatments for those who fail pharmacologic interventions*

The initial therapeutic modality selected depends in part on the patient's age, risk of psychiatric adverse effects, and degree of physical impairment. The current approach to treatment is to delay medication therapy until the symptoms begin to interfere with the patient's ability to function or impact their QOL.

Nonpharmacologic Therapy

Lifestyle Modifications

Lifestyle modifications should be started early and continued throughout treatment because they may improve ADL, gait, balance, and mental health. The most common interventions include maintaining good nutrition, physical condition, and social interactions. Patients should avoid medications that block central dopamine, as they may worsen PD.[1,18] A multidisciplinary approach using the expertise of nutritionists, speech therapists, physical therapists, occupational therapists, and social workers may optimize care but may not be covered by insurance. Patients should maintain regular visits with their optometrist or ophthalmologist and their dentist. The dentist should be informed that the patient has PD, as PD medications that decrease saliva flow may increase the risk of dental caries.

Dietary modification can improve constipation, nausea, erratic drug absorption, and minimize the risk of aspiration and weight loss. Patients should eat a balanced diet and take a daily multivitamin if they do not eat well. Nutritionists can help with meal selection, products to boost calories, and suggestions for arranging the proper protein content of meals so as not to interfere with medication absorption. Speech therapy may improve swallowing, articulation, and the force of speech. The therapist can perform swallowing studies that assess the patient's risk of aspiration.

An exercise program and increased activity during the day should minimize daytime sleepiness, possibly improve sleep at night, and may be neuroprotective. Maintaining a daily routine that allows patients to remain as independent as possible is of psychological and physical importance. Stretching, strengthening, and balance training should be encouraged, as well as programs that enhance cardiovascular fitness. Therapists can teach patients skills that would improve motion and reduce the risk of falling. Patient's PD symptoms improve with physical therapy and return to baseline when physical therapy is stopped.[1,8,19]

Occupational therapy may improve confidence and ability to stay active. Therapists can provide information about adaptive equipment for the home, specialized clothing, and personal training that can maximize a patient's independence, safety, and ADLs. They can help improve handwriting and train patients to use special computer programs that enhance communication.

Maintaining social interactions helps overall well being; thus, patients should resist the temptation to withdraw from activities. Maintaining good communication with a spouse regarding sexual issues may prevent conflicts, and clinicians should remind patients of this. Social workers help patients and their families cope with their condition and handle problems related to disease progression. They can provide family counseling and help arrange for special community assistance programs.

Surgery

Surgical treatment is for patients with persistent and disabling motor fluctuations despite maximizing medications. Patients need an intact cognition as determined by neuropsychological testing. Surgical procedures include ablative lesioning such as pallidotomy or thalamotomy, and deep brain stimulation. Pallidotomy helps mostly tremors and drug-induced dyskinesia, whereas thalamotomy is beneficial to tremor only. Deep brain stimulation has become the surgery of choice, as it is less traumatic and may be individualized to treat patient-specific symptoms. It involves the implantation of a high-frequency device that provides electrical stimulation of the globus pallidus and subthalamic nucleus. Patients can expect a 40% to 75% decrease in symptoms.[2,20,21]

Pharmacologic Therapy

❺ *The best time to initiate dopaminergic therapy is controversial and patient-specific. Generally, medication is started when the patient's physical impairment affects QOL.*

❻ *Medication schedules should be individualized. The doses should be divided throughout the day to maximize on and minimize off periods.*

Pharmacologic options include anticholinergic drugs, amantadine, MAO inhibitors, dopamine agonists, levodopa/carbidopa, and catechol-o-methyltransferase (COMT) inhibitors. Medications help relieve symptoms, improve QOL, and may lengthen life expectancy, but they are not curative, as treated PD patients still die earlier than controls.[1] Medications primarily work by enhancing the concentration of dopamine in the brain. Knowing how dopamine is metabolized and how drugs affect dopamine metabolism is important in understanding the pharmacology of PD medications (Fig. 29–2). Which medication to select for initial therapy is also controversial, but the American Academy of Neurology and the Movement Disorder Society determined that it is reasonable to start with levodopa or a dopamine agonist. Starting treatment with a dopamine agonist rather than levodopa may help to delay the onset of dyskinesias and the on/off fluctuations commonly seen with long-term levodopa use. The use of a dopamine agonist in preference to levodopa/carbidopa may result in less motor benefit and greater risk of hallucinations or somnolence. Levodopa results in greater motor improvement and should be used as initial therapy in the elderly (greater than 75 years of age) and in those with cognitive impairment. There is no preference for using controlled-release over immediate-release levodopa as initial therapy. There are insufficient data to recommend initiating treatment with both levodopa and a dopamine agonist. Initiating treatment with anticholinergic medications, amantadine, or selegiline are only for patients who have mild symptoms, as they are not as effective as dopamine agonists.[1,22,23]

Medications should be started at the lowest dose and increased gradually based on the patient's symptoms (Table 29–1). When interviewing patients, ask the following questions for each scheduled dose before adjusting the dose or timing of medications:

- When did the dose start to work and how long did it last?
- How did you feel just before the dose, and during the dosing period?

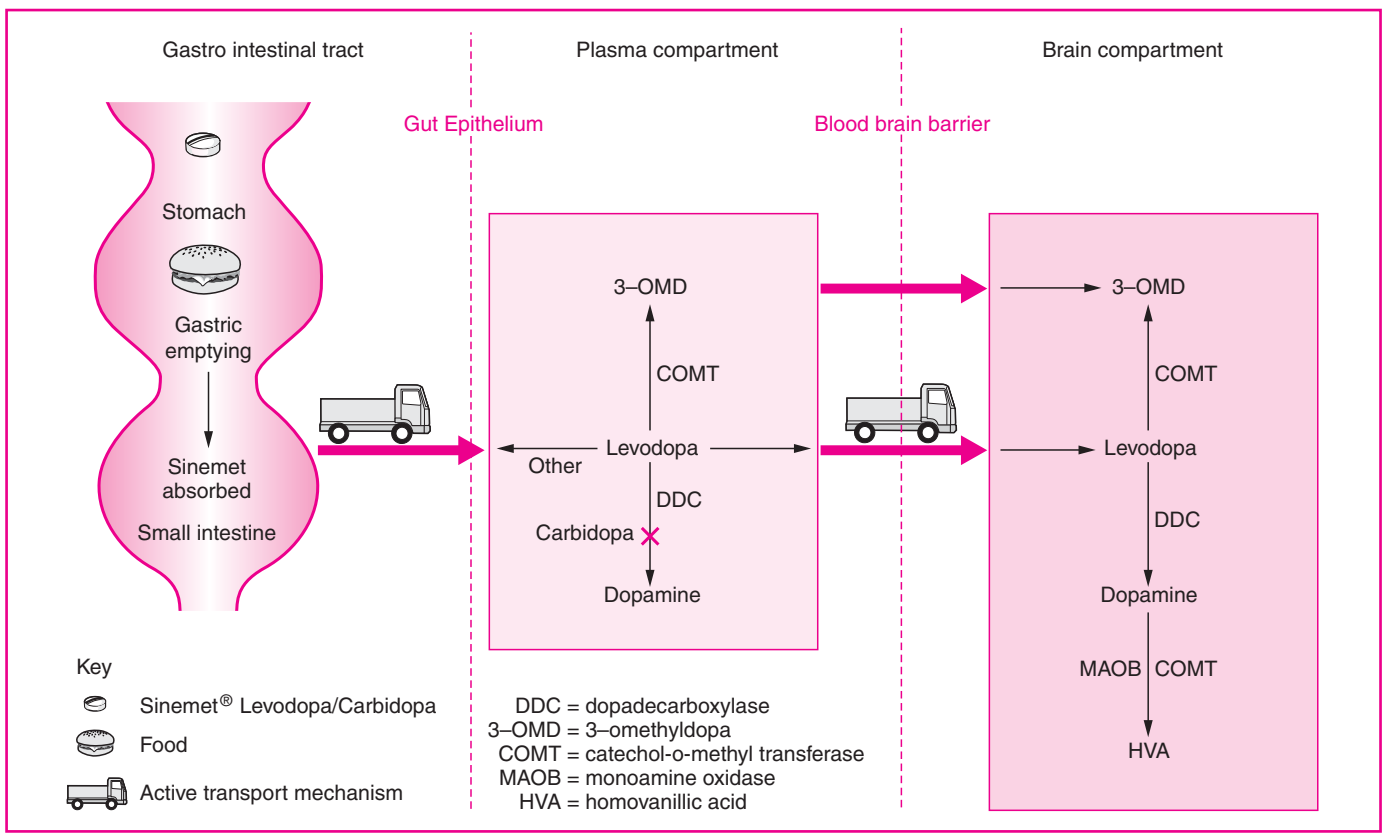


FIGURE 29–2. Levodopa absorption and metabolism. Levodopa is absorbed in the small intestine and is distributed into the plasma and brain compartments by an active transport mechanism. Levodopa is metabolized by dopa decarboxylase, monoamine oxidase, and catechol-O-methyltransferase. Carbidopa does not cross the blood–brain barrier. Large, neutral amino acids in food compete with levodopa for intestinal absorption (transport across gut endothelium to plasma). They also compete for transport across the brain (plasma compartment to brain compartment). Food and anticholinergics delay gastric emptying resulting in levodopa degradation in the stomach and a decreased amount of levodopa absorbed. If the interaction becomes a problem, administer levodopa 30 minutes before or 60 minutes after meals.

TABLE 29–1. Mechanism of Action and Dosing of Medications to Treat Parkinson's Disease[1,2,16,25,29,31,36]

Generic Name (Trade Name)	Mechanism of Action and Receptor Specificity	Dosing
Levodopa (Larodopa®, Dopar®) Carbidopa (Lodosyn®)	LD metabolized to DA CD blocks peripheral conversion of LD to DA and increases LD CNS penetration	Start with Sinemet® $^1/_2$ tab (100 mg LD, 25 mg CD) twice daily for 1 week, then $^1/_2$ tab three times daily; then, increase by $^1/_2$ tab daily every week; usual MD is 300–2000 mg daily; since the duration of LD is 2 to 3 hours, patients may require doses every 2 hours
Levodopa/Carbidopa (Sinemet®) (Parcopa™ with phenylalanine) (Sinemet CR®)	Standard, immediate-release LD Rapid-dissolving LD Controlled-release LD	Sinemet CR: Start with 1 tab (100 mg LD, 25 mg CD) two or three times daily; as symptoms increase, use 200 mg LD tab 2–4 times daily; usual MD is 200–2200 mg daily
Apomorphine (Apokyn®)	Activate postsynaptic D1 and D2 DA receptors	Start an antiemetic for 3 days, then give apomorphine 2 mg SC injection (1 mg if outpatient) while monitoring blood pressure; then increase by 1 to 2 mg every 2 or more hours; usual MD is 2–6 mg 3–5 times daily for off periods
Pergolide (Permax®)	Activate postsynaptic D1 and D2 DA receptors	Start with 0.05 mg daily and increase by 0.05–0.15 mg daily every few days over several weeks to a usual MD of 0.5–1 mg three times daily (maximum 5 mg daily)
Bromocriptine (Parlodel®)	Activate postsynaptic D2 and blocks D1 DA receptors	Start with 1.25 mg daily at bedtime, then 1.25 mg twice daily; on week 2, increase to 2.5 mg twice daily, then increase by 2.5 mg daily every 2–4 weeks up to 15–45 mg daily divided 2–3 times daily
Pramipexole (Mirapex®)	Activate postsynaptic D2 DA receptors	Start with 0.125 mg three times daily; increase about weekly by 0.375–0.75 mg/day to a MD of 0.5–1.5 mg three times daily; dosage reduction needed in patients with creatinine clearance less than 60 mL/minute
Ropinirole (Requip®)	Activate postsynaptic D2 DA receptors	Start with 0.25 mg three times daily; increase about weekly by 0.75–1.5 mg daily to a MD dose of 3–8 mg three times daily
Selegiline (Eldepryl®)	Blocks MAO_B metabolism and presynaptic reuptake of DA in the brain	Start with 5 mg in the morning; if symptoms continue, add 5 mg at noon; 5 mg daily may be as clinically effective as 10 mg daily with fewer side effects
(Zelapar® with phenylalanine)	Rapid-dissolving selegiline	Start with 1.25 mg every morning before breakfast; if symptoms continue after 6 weeks, increase dose to 2.5 mg every morning. Avoid food or liquid for 5 minutes before or after the dose
Rasagaline (Azilect®)	Blocks MAO_B metabolism	Start with 0.5 mg daily if symptoms continue, increase to 1 mg daily
Tolcapone (Tasmar®)	Peripherally blocks COMT metabolism of DA; some central activity	Start with 100 mg with first Sinemet® dose once daily; if symptoms continue, increase to 2 and then 3 times daily, then to 200 mg each dose; usual MD is 100 three times daily to minimize risk of side-effects
Entacapone (Comtan®)	Peripherally blocks COMT metabolism of DA	Take a 200-mg tab with each Sinemet® dose up to 8 tabs daily; usual MD is 200 mg 3–4 times daily; decrease dose by 50% with hepatic impairment
CD/LD/Entacapone (Stalevo®)	See CD, LD, and entacapone	Usual MD is 300–1200 mg LD daily; the largest strength tab contains 150 mg LD and 200 mg entacapone; patients requiring larger LD doses will need additional LD medication; titrate as with LD
Amantadine (Symmetrel®)	NMDA-receptor antagonist that blocks glutamate transmission, promotes DA release, and blocks Ach	Start with 100 mg daily at breakfast; after 1 week, add 100 mg daily in the early afternoon; decrease dose as creatinine clearance decreases less than
Anticholinergics (various, including trihexyphenidyl, benztropine)	Block Ach, decrease Ach: DA ratio	80 mL/minute

Ach, acetylcholine; CNS, central nervous system; CD, carbidopa; COMT, catechol-O-methyltransferase; D1, a class of dopamine receptors which includes D_1 and D_5 subtypes; D2, a class of dopamine receptors which includes D_2, D_3, and D_4 subtypes; DA, dopamine; LD, levodopa; MAO, monoamine oxidase; MD, maintenance dose; NMDA, N-methyl-D-aspartate.

If the dose did not last long enough, consider adding another dose each day, higher individual doses, an additional agent, or changing to a longer-acting dosage form. If the patient experiences side effects related to excessive dopamine concentrations (i.e., dyskinesia), consider decreasing the dose, increasing the time interval between doses, or decreasing the use of concomitant medications that augment dopamine concentrations. A sample diary for monitoring symptoms can be found at www.sinemetcr.com/cross_site/DiaryChart.shtml.

Anticholinergics

Anticholinergics may minimize resting tremor and drooling, but they are not as good as other agents in controlling rigidity, bradykinesia, and gait problems. Anticholinergics should be discontinued gradually to avoid withdrawal effects or worsening of PD symptoms. Side effects of anticholinergics include dry mouth (decreased saliva), blurred vision, constipation, cognitive impairment (forgetfulness, confusion, and hallucinations), urinary retention, orthostatic hypotension, temperature sensitivity, and sedation. They are usually avoided or used with caution in patients older than 70 years of age because of an increased risk of cognitive impairment. Use of anticholinergics is associated with an increased incidence of amyloid plaques and neurofibrillary tangles in patients with PD that may translate to an increased risk of Alzheimer's disease.[1,2,7,8,24–27]

Amantadine

Amantadine improves PD symptoms in mildly affected patients and reduces motor fluctuations in patients with more advanced disease. Amantadine may minimize or delay the development of motor complications, as levodopa's pulsatile stimulation of dopamine receptors is associated with N-methyl-D-aspartate receptor changes and resultant motor complications. Patients who develop tolerance to amantadine's effects may benefit from a drug holiday. Doses need to be reduced in patients with renal impairment. When stopping amantadine, gradually discontinue the drug to minimize potential withdrawal effects. Side effects include nausea, dizziness, livedo reticularis (purple mottling of the skin), peripheral edema, orthostatic hypotension, hallucinations, restlessness, and anticholinergic effects (confusion and sedation). Its stimulant action may worsen insomnia, so amantadine should not be dosed in the evening. It should be avoided in the elderly who cannot tolerate its anticholinergic effects. It should be used cautiously with memantine, as there may be an increased risk of psychosis.[1,2,7,8,16,18,22,24–26,28]

MAO_B Inhibitors

MAO_B inhibitors include selegiline and rasagaline. They may provide mild symptomatic benefit for those patients who choose to delay dopaminergic medications. Combining selegiline or rasagaline with levodopa in early treatment may delay motor complications. In patients with advanced disease, they decrease off time and improve wearing-off symptoms in patients with motor fluctuations.

Side effects of selegiline include nausea, confusion, hallucinations, headache, jitteriness, and orthostatic hypotension. Selegiline is metabolized to amphetamines which may cause insomnia, and should not be dosed in the afternoon or evening. Doses are limited to 10 mg daily, as MAO_B selectivity may be lost at higher doses increasing the risk of adverse effects and drug interactions. Rasagaline is not metabolized to amphetamine; thus, there is less risk of insomnia, and it may be neuroprotective. Treatment-limiting side effects in clinical trials included diarrhea, weight loss, hallucinations, and rash. The MAO_B selectivity of rasagaline in humans and sensitivity to tyramine has not been well defined. Therefore, the manufacturer recommends that patients restrict the intake of tyramine-containing foods and medications that contain amines. Dyskinesias can be minimized by decreasing the levodopa dose when adding either of these agents. Patients should avoid or use these medications cautiously with narcotic analgesics, antidepressants, or sympathomimetic amines (cold and weight loss products). Drugs that inhibit CYP1A2, such as ciprofloxacin, will increase serum rasagaline concentrations.[1,2,7,8,16,18,22,25]

Dopamine Agonists

Dopamine agonists are useful as initial therapy, as they can delay the need to start levodopa and can decrease the risk of developing motor fluctuations by two- to threefold during the first 4 to 5 years of treatment. After a few years, dopamine agonists inadequately control the patient's symptoms and levodopa needs to be started. In advanced disease, dopamine agonists can be added to levodopa because they have a longer duration of action, minimize fluctuations in dopamine blood concentrations, decrease off-time, improve wearing-off symptoms, allow a reduction in levodopa dose, and improve ADLs.[1–3,16,22,23,26]

Dopamine agonists include the ergot derivatives (pergolide, bromocriptine, and cabergoline) and the non-ergot derivatives (rotigotine, pramipexole, ropinirole, and apomorphine). Rotigotine is an investigational once-daily skin patch. Generally, all are equally effective except bromocriptine, which is the least effective. There are five subtypes of dopamine receptors that are divided into two classes called D1 (D_1 and D_5 subtypes) and D2 (D_2, D_3, and D_4 subtypes). Receptor selectivity may result in subtle differences between the products, as pramipexole is thought to have an antidepressant effect because it has greater D_3 receptor affinity. Ropinirole and pergolide may also have higher D_3 specificity, but less than pramipexole. Pergolide and apomorphine are also D1 agonists which may optimize their effect. Cabergoline, a very long-acting agonist, is effective for PD, but it is approved for hyperprolactinemia instead of PD. If patients fail one dopamine agonist, another can be tried. Although not well established, it appears that bromocriptine 30 mg, ropinirole 15 mg, pramipexole 4.5 mg, and pergolide 3 mg are equivalent and can be a guide when switching agents.[16,25,29]

Common side effects include nausea, vomiting, sedation (highest with apomorphine), pedal edema, orthostatic hypotension (highest with pramipexole and cabergoline), and

psychiatric effects that are greater than with levodopa (nightmares, confusion, and hallucinations). Obsessive-compulsive behaviors such as pathologically excessive gambling, shopping, sexual desire, or eating may occur. Reducing or eliminating the agonist will usually resolve the problem.[26,30,31] Ergot side effects are uncommon but include painful reddish discoloration of the skin over the shins and pleuropulmonary, retroperitoneal, and cardiac fibrosis.[1,16,25]

In addition, pergolide, and possibly other ergot dopamine agonists, may cause a thickening and restriction in cardiac valves in 33% of patients. As of March 2007, the manufacturers of pergolide voluntarily withdrew their drug from the market because of this risk. It may remain available under an Investigational New Drug Application. It is hypothesized that ergot derivatives stimulate 5-HT_{2B} serotonin receptors that promote fibrotic lesions. While there are no specific guidelines, many specialists obtain a baseline echocardiogram when starting pergolide, or get one as soon as possible if the patient is already receiving pergolide. If there are no specific abnormalities of concern, the echocardiogram should be repeated yearly while the patient receives pergolide. If valvular regurgitation is detected, and determined to be significant by the cardiologist, pergolide should be discontinued. The risk is greater in patients receiving doses higher than 5 mg/day.[1,2,29,32]

Excessive daytime sleepiness occurs in 15% to 20% of PD patients and can be aggravated by all dopaminergic drugs. Sleep attacks without warning may occur in up to 6% of patients. Patients at greatest risk of sleep attacks are those with an Epworth Sleepiness Scale score more than 10 (http://jama.amaassn.org/cgi/content/full/287/4/455/TABLEJOC10367T1), long duration of PD, and those taking dopamine agonists with levodopa. Sleepiness may also be due to the pathology of PD or co-existing conditions such as sleep disturbances or depression.[10,11,32–34] Adding modafinil (100 to 200 mg twice daily) or possibly selegiline can improve alertness.[35] Patients who are still driving need to be aware of this potentially dangerous effect. Occupational therapists can evaluate the patient's driving ability by using a simulated driver's test.

All dopamine agonists are metabolized by the liver except pramipexole, which is eliminated unchanged in the urine by active tubular secretion and requires dose reduction in renal insufficiency (creatinine clearance less than 60 mL/minute). Drug interactions may occur if it is given concurrently with other agents that are eliminated by active tubular secretion, such as procainamide, trimethoprim, and cimetidine. Ropinirole is metabolized by cytochrome P-450 oxidation in the liver and subject to drug-drug interactions with drugs that induce or inhibit CYP1A2 such as ciprofloxacin, fluvoxamine, and mexiletine.[31]

Apomorphine is approved for acute off episodes in patients with advanced stages of PD. The onset of effect is within 10 to 20 minutes and the duration of effect is about 60 minutes. It requires premedication with an antiemetic because it causes nausea and vomiting. Antiemetics that block central dopamine worsen the symptoms of PD, and 5-HT_3 antagonists, such as ondansetron, can aggravate PD-related hypotension. Trimethobenzamide (300 mg three times daily) should be started 3 days prior to starting apomorphine and continued for 2 months or until tolerance to the nausea develops. It should be used with caution in patients receiving antihypertensives or drugs that increase the QT interval. Patients who are allergic to sulfites may be allergic to apomorphine.[36]

Levodopa/Carbidopa

Levodopa, a dopamine precursor, is the most effective agent for PD. Patients experience a 40% to 50% improvement in motor function. It is absorbed in the small intestine and peaks in the plasma in 30 to 120 minutes. A stomach with excess acid, food, or anticholinergic medications will delay gastric emptying time and decrease the amount of levodopa absorbed. Antacids decrease stomach acidity and improve levodopa absorption. Levodopa requires active transport by a large, neutral amino acid transporter protein from the small intestine into the plasma and from the plasma across the blood–brain barrier into the brain (Fig. 29–2). Levodopa competes with other amino acids, such as those contained in food, for this transport mechanism. Thus, in advanced disease, adjusting the timing of protein-rich meals in relationship to levodopa doses may be helpful. Levodopa also binds to iron supplements and administration of these should be spaced by at least 2 hours from the levodopa dose.[1,8,16,25]

The controlled-release (CR) formulation is more slowly absorbed and longer acting than immediate-release tablets. Patients need to increase the total daily dose by 30%, as it is not as bioavailable as the immediate-release levodopa/carbidopa. The CR formulation has a delayed onset (45 to 60 minutes) compared to the standard formulation (15 to 30 minutes). Thus, patients may also need to take immediate-release tablets or even a liquid formulation when they want a quicker onset of effect, such as with the first morning dose.[1,8,25]

Carbidopa, a dopa-decarboxylase inhibitor, is added to the levodopa in order to decrease the peripheral conversion of levodopa to dopamine. It does not cross the blood–brain barrier and does not interfere with levodopa conversion in the brain. Concomitant administration of carbidopa and levodopa allows for lower levodopa doses and minimizes levodopa peripheral side effects such as nausea, vomiting, anorexia, and hypotension. For most patients, at least 75 to 100 mg daily of carbidopa is required to adequately block dopamine decarboxylase in the peripheral metabolism of levodopa in most patients. Taking extra carbidopa may reduce nausea related to initiating levodopa.[8,16]

Side effects include dyskinesias, orthostatic hypotension, dizziness, nausea, insomnia, sleep attacks, pathologic gambling, discoloration of urine/sweat, and psychiatric effects (confusion, hallucinations, nightmares, and altered behavior). Dyskinesias caused by adding other PD drugs to levodopa may be improved by decreasing the levodopa dose. Motor complications occur in about 40% of patients within 4 to 6 years of starting levodopa.[1,8,24,25,37]

Patients with severe dyskinesias and off periods may achieve more constant blood concentrations (lower peak and higher trough concentrations) by taking a liquid formulation of levodopa with carbidopa. Each day patients make a 1 mg/mL levodopa

solution made with water and ascorbic acid or with a carbonated beverage, which allows patients to take a precisely adjusted dose every 30 to 90 minutes.[25,38]

COMT Inhibitors

Catechol-O-methyltransferase inhibitors are used in conjunction with levodopa/carbidopa. They minimize peak and trough levodopa fluctuations by prolonging the half-life and area under the curve of levodopa. They may allow for a decrease in daily levodopa doses while increasing on time, decreasing wearing off, and improving ADLs in patients with motor fluctuations. Some clinicians believe that a COMT inhibitor should be added when levodopa is first introduced in an effort to promote more continuous dopamine stimulation, potentially minimizing long-term complications associated with the more pulsatile effect of intermittent levodopa administration. However, starting multiple drugs at the same time increases the risk of side effects. Side effects include diarrhea, nausea, vomiting, anorexia, dyskinesias, urine discoloration, daytime sleepiness, sleep attacks, orthostatic hypotension, and hallucinations. Dyskinesias should improve with a decrease in the levodopa dose.[24,25,29]

Tolcapone has been associated with several cases of severe liver failure, including fatalities, and has been removed from the market in some countries. Thus, it should only be used in patients who cannot take or do not respond to entacapone. Serum alanine aminotransferase and aspartate aminotransferase concentrations should be monitored at baseline, then every 2 to 4 weeks for 6 months, and then periodically for the remainder of therapy. Patients who fail to show symptomatic benefit after 3 weeks should discontinue tolcapone. Entacapone has not been associated with liver damage, so monitoring of liver enzymes is not currently recommended.[24,25,29]

Herbs and Supplements

Clinicians should ask patients if they take any herbs and supplements, as they may not volunteer this information. The most common herbs and supplements that patients ask about are vitamins, melatonin, valerian, and coenzyme Q_{10}. There is very little support for using creatinine, gingko, ginseng, green tea, ginger, yohimbine, and St John's wort in patients with PD. Patients should be cautioned that supplements and herbs are not well controlled by the FDA and may not contain the amounts indicated on the label. Melatonin and valerian may improve insomnia, but they are not commonly used because there is insufficient information in PD patients.[39]

There is usually no need to supplement with specific vitamins. Patients should be encouraged to eat a well balanced diet and should also take a multivitamin and mineral supplement. Some clinicians recommend vitamins C and E for their antioxidant properties; however, no significant improvements have been shown compared to placebo. Encourage patients to eat a diet rich in vitamin C and E (i.e., bright colored fruits and vegetables, nuts, and whole grains). Metabolism of levodopa may cause elevated homocysteine concentrations that may be associated with an increased risk of vascular disease, dementia, and depression. Administering levodopa with a COMT inhibitor may minimize the increase in homocysteine. Vitamin B is involved in maintaining normal homocysteine concentrations; thus, PD patients may have a greater requirement of B vitamins than patients not receiving levodopa. Eating foods rich in B vitamins (i.e., wheat germ, beans, and whole grains) and taking a multivitamin should be sufficient; however, B vitamin supplements may be warranted in patients with elevated homocysteine concentrations. Excess pyridoxine (vitamin B_6) may decrease the effect of levodopa, so limit doses to less than 50 mg per day.[8,40,41]

Coenzyme Q_{10} is an antioxidant essential for mitochondrial function. A dose of 1200 mg daily was associated with a slower decline in UPDRS scores than patients not receiving coenzyme Q_{10}. Lower doses were no better than placebo, but the drug continues to be studied in doses up to 2400 mg daily. Many formulations contain vitamin E, and patients should not exceed recommended daily allowances of this vitamin, as bleeding times may be prolonged.[42,43]

Treatment of Non-motor Symptoms

❼ *The treatment of nonmotor symptoms should be based on whether they are worse during an off state or if they could be related to other neurotransmitter dysfunction.*

The treatment of non-motor symptoms, such as psychological conditions, sleep disorders, and autonomic dysfunction, should include both pharmacologic and nonpharmacologic approaches. Patients should be given suggestions for maintaining ADLs, a positive self-image, family communication, and a safe environment.

Psychological Symptoms

Patients should report vivid dreams or nightmares, as these may herald psychosis. Neuropsychometric testing may be a helpful diagnostic tool. Other potential causes of psychosis, dementia, or depression, such as infections, metabolic changes, or toxic exposures should be ruled out. Psychological symptoms may be alleviated by the presence of a night light or correction of vision and hearing deficits. PD therapy should be adjusted to decrease off periods when depression and anxiety may be more likely to occur. Low-efficacy PD medications should be gradually decreased and stopped in patients with psychosis. Patients should be encouraged to participate in tasks that improve cognition, such as puzzles or reading. Some patients and their families may benefit from professional counseling. Some antidepressants may be used for anxiety, panic, or depression. Low-dose quetiapine (12.5 to 200 mg) or clozapine (6.25 to 150 mg) at bedtime can improve psychosis although clozapine requires at least monthly blood monitoring for agranulocytosis. Dementia symptoms may improve with acetylcholinesterase inhibitor or memantine. Electroconvulsive therapy can be considered in patients who fail medications.[2,7–9,11,13,14,44,45]

Sleep Problems

Sleep problems and fatigue are common in PD and may be due to medications, uncontrolled PD symptoms, or many other medical and psychological causes. The patient's bed partner can provide useful information on the patient's quality of sleep. Patients may benefit from instruction on good sleep hygiene, adjustment of therapy to control nighttime PD symptoms, or cognitive behavioral therapy. Referral to a sleep specialist may be necessary. Amantadine and selegiline may worsen insomnia, selegiline and tricyclic antidepressants may worsen RBD, and some antidepressants and antipsychotics may worsen RLS. Short-acting benzodiazepines and sedating antidepressants are used for short periods to help insomnia. Ramelteon may prove beneficial in patients with circadian sleep disorders. Pramipexole, melatonin, and clonazepam are recommended for RBD. In addition to dopaminergic medications, iron, gabapentin, and opioids are recommended for RLS. A nighttime dose of a COMT inhibitor may also help RLS. Benzodiazepines may increase the risk of falling. Iron may decrease the absorption of levodopa and increase constipation.[2,10,11,44,45]

Autonomic and Other Problems

Drooling may be accompanied by speech problems and dysphagia. Anticholinergics, botulinum toxin injections, and sublingual atropine can decrease drooling. A speech therapist can perform a swallowing study to assess the risk of aspiration, and a nutritionist can help optimize diet. Patients at high risk of aspiration or poor nutrition may require placement of a percutaneous endoscopic gastrostomy tube. Nausea can be improved by having patients take their PD medications with meals or pharmacologic therapy (domperidone from Canada or trimethobenzamide). Sexual dysfunction or urinary problems may need a urologic evaluation. Improvement of PD therapy to increase on time, removal of drugs that decrease sexual response, and pharmacologic therapy (sildenafil or yohimbine) may be helpful to treat sexual dysfunction. Patients with urinary frequency may find a bedside urinal along with a decrease in evening fluids helpful. Improvement in PD control can also benefit, but worsening symptoms may require catheterization or pharmacologic measures (oxybutynin, tolterodine, propantheline, imipramine, hyoscyamine, or nocturnal intranasal desmopressin). Anticholinergic drugs could cause urinary retention as well as constipation. Constipation can be helped with increased fluid and fiber-rich diet intake and physical activity. Patients should avoid cathartic laxatives and use stool softeners, osmotic or bulk-forming laxatives, glycerin suppositories, or enemas. Dyskinesia-related sweating may respond to PD therapy adjustment or β-blockers. Orthostasis may respond to removal of offending drugs (tricyclic antidepressants, PD medications, alcohol, and antihypertensives) increasing carbidopa doses, or addition of salt or fluids to the diet, compression stockings, fludrocortisone, indomethacin, or mitodrine. Seborrhea usually responds to over-the-counter dandruff shampoos or topical steroids.[2,7,8,11,12,44,45]

Treatment of Response Fluctuations

As the disease progresses, most patients develop response fluctuations. Management of these is based on optimizing the pharmacokinetic and pharmacodynamic properties of PD medications.

Treatment includes adjusting or adding medications to maximize the patient's on time, minimize the time on with dyskinesia, and minimize off time (Table 29–2). Use various

TABLE 29–2. Management of Motor Complications in Advanced Disease[2,15,16,44–46]

I. Motor Fluctuations
- A. Suboptimal or delayed peak response
  1. Take Sinemet® on an empty stomach
  2. Use rapid-dissolving tablet (Parcopa™), crush Sinemet®, or make liquid Sinemet®
  3. Decrease dietary protein around the dose that is delayed
  4. Substitute standard Sinemet® for some of the Sinemet CR®
- B. Optimal peak but early wearing off
  1. Decrease dose and increase frequency of standard Sinemet®
  2. Substitute Sinemet CR® for some of the standard Sinemet®
  3. Add other PD medications (dopamine agonist, selegiline, amantadine, or COMT inhibitor)
- C. Optimal peak but unpredictable offs
  1. Adjust time with meals and avoid high-protein meals or redistribute the protein in meals
  2. Substitute or add rapid-dissolving tablet form or liquid form of Sinemet®
  3. Rescue with a dopamine agonist (apomorphine) given with domperidone or trimethobenzamide
  4. Sinemet® via intraduodenal tube
  5. Deep brain stimulation procedure
- D. Freezing
  1. Gait modifications (use visual cues such as walk over lines, tapping, rhythmic commands, rocking; use rolling walker)
  2. Difficult to treat so adjust current medication up or down based on other PD symptoms
  3. Treat anxiety with benzodiazepine

II. Dyskinesias
- A. Peak dose chorea
  1. Decrease risk by lowering Sinemet® dose when adding other PD medications
  2. Smaller doses more frequently (liquid Sinemet®)
  3. Decrease Sinemet® dose and add dopamine agonist
  4. Amantadine
  5. Add propranolol, fluoxetine, buspirone, or clozapine
  6. Deep brain stimulation
- B. Off period dystonia in the early morning (i.e., foot cramping)
  1. Add Sinemet® CR or dopamine agonist at bedtime if having nighttime offs
  2. Morning Sinemet® dose should be immediate-release with or without CR
  3. Selective denervation with botulinum toxin
- C. Diphasic dyskinesia
  1. Avoid controlled-release preparations; consider liquid Sinemet®
  2. Add dopamine agonist, amantadine, or COMT inhibitor
  3. Deep brain stimulation

III. Akathisia
1. Benzodiazepine
2. Propranolol
3. Dopamine agonists
4. Gabapentin

COMT, catechol-O-methyltransferase.



Patient Encounter, Part 3: Creating a Care Plan

Create a care plan for MW that includes:

- The goals of therapy.
- A list of problems and how well each is controlled.
- A therapeutic plan that includes non-drug and drug therapy.
- A protocol for monitoring efficacy and adverse effects.
- A definition of your outcome variables.

dosage plans to minimize suboptimal or delayed peak levodopa concentrations by adding longer-acting medications to minimize wearing off periods, adding or adjusting medications to stop an unpredicted off period, and providing treatments that decrease freezing episodes. It also involves adjusting or adding medications to decrease chorea, dystonia, diphasic dyskinesias, or akathisia. Patients should schedule activities when they are on. Patients can also keep an extra dose of medication with them when they are away from home in case their medication wears off.[2,15,16,44–46]

OUTCOME EVALUATION

Evaluate the clinical outcomes of treatment by using the UPDRS. In addition, periodically ask patients to record the amount of on and off time they have with and without dyskinesias in a diary. There are a variety of scales that can be used to assess QOL, depression, anxiety, and sleep disorders. Patients with PD cannot be cured; but treatment can delay the progression of symptoms and improve QOL. Delaying the patient's admission into a nursing home is a good outcome.



Patient Encounter, Part 4: Evaluation of the Outcomes

At the last visit, MW's fluoxetine was changed to bupropion, pergolide was started and gradually increased to 0.25 mg three times daily, and a dandruff shampoo was started. Since that time his skin condition, attitude, apathy, stiffness, rigidity, handwriting, tremor, slowness, and kicking have improved. The UPDRs score is 5 while "on".

- Do you agree with this therapeutic plan?
- Have therapeutic goals been achieved?
- What additional questions would you ask the patient?



Patient Care and Monitoring

❾ *Patient monitoring should involve a regular systematic evaluation of efficacy and adverse events, referral to appropriate specialists, and patient education.*

1. Determine type of symptoms, frequency, and exacerbating factors. Does the patient have any PD treatment-related complications? Assess the patient's symptoms to determine if therapy should be adjusted or maintained, or if referral for more extensive evaluation is needed.
2. Review any available diagnostic data to determine status, motor ability, dyskinesias, and non-motor symptoms.
3. Obtain a thorough history of prescription, non-prescription, and complementary/alternative medication use. Determine what treatments have been helpful to the patient in the past. Is the patient taking any medications that may increase PD symptoms?
4. Educate the patient about lifestyle modifications that will improve symptoms and sustain independence.
5. Is the patient taking the appropriate dose of PD medication to maximize on time and minimize adverse effects? If not, why?
6. Determine if polytherapy treatment is necessary and/or adequate.
7. Assess improvement in QOL measures.
8. Evaluate the patient for the presence of drug adverse reactions, allergies, and interactions.
9. Recommend a therapeutic regimen that is easy for the patient to follow. Educate the patient on how to use medications, and allow the patient to adjust medications for fluctuations in response.
10. Educate patients regarding PD, including lifestyle modifications and drug therapy, including:
    - When and how to take medications.
    - The potential adverse effects that may occur.
    - Which drugs may interact with therapy (give patients a list).
    - Warning signs to report to the physician.
    - Where they can obtain further information such as books and Web sites (e.g., http://www.apdaparkinson.org; http://www.parkinson.org)
11. Refer patients to a local PD support group where they can obtain educational materials as well as empathy and social support from fellow PD patients. Support groups that include patients with advanced disease may upset patients with early disease; therefore, the advantages and disadvantages of attending should be explained to the patient.

ABBREVIATIONS

ADL: activities of daily living
COMT: catechol-O-methyltransferase
CR: controlled-release
GABA: γ-aminobutyric acid
MAO: monoamine oxidase
MPTP: 1-methyl-4-phenyl-1-2-5-6-tetrahydropyridine
NMDA: N-methyl-D-aspartate
PD: Parkinson's disease
RBD: rapid eye movement sleep behavioral disorder
RLS: restless legs syndrome
UPDRS: Unified Parkinson's Disease Rating Scale

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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30 Pain Management

Christine K. O'Neil



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Identify characteristics of the types of pain: nociceptive, inflammatory, neuropathic, and functional.
2. Explain the mechanisms involved in pain transmission.
3. Select an appropriate method of pain assessment.
4. Recommend an appropriate choice of analgesic, dose, and monitoring plan for a patient based on type and severity of pain and other patient-specific parameters.
5. Perform calculations involving equianalgesic doses, conversion of one opioid to another, rescue doses, and conversion to a continuous infusion.
6. Educate patients and caregivers about effective pain management, dealing with chronic pain, and the use of nonpharmacologic measures.

Key Concepts

❶ Pain is an unpleasant subjective experience that is the net effect of a complex interaction of the ascending and descending nervous systems involving biochemical, physiologic, psychological, and neocortical processes.
❷ Following initial assessment of pain, reassessment should be done as needed based on medication choice and the clinical situation.
❸ Effective treatment involves an evaluation of the cause, duration, and intensity of the pain and selection of an appropriate treatment modality for the pain situation.
❹ Whenever possible, the least potent oral analgesic should be selected.
❺ Equianalgesic doses should be used when converting from one opioid to another.

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[1] ❶ *Pain is an unpleasant subjective experience that is the net effect of a complex interaction of the ascending and descending nervous systems involving biochemical, physiologic, psychological, and neocortical processes.* Pain can affect all areas of a person's life including sleep, thought, emotion, and activities of daily living. Since there are no reliable objective markers for pain, the patients are the only ones to describe the intensity and quality of their pain.

Pain is the most common symptom prompting patients to seek medical attention and is reported by more than 80% of individuals who visit their primary care provider.[1] Despite the frequency of pain symptoms, individuals often do not obtain satisfactory relief of pain. This has led to recent initiatives in health care to make pain the fifth vital sign, thus making pain assessment equally important as obtaining a patient's temperature, pulse, blood pressure, and respiratory rate.

EPIDEMIOLOGY AND ETIOLOGY

Prevalence of Pain

Most people experience pain at some time in their lives, and pain is a symptom of a variety of diseases. For some, pain may be mild to moderate, intermittent, easily managed, and has minimal effect on daily activities. For others, pain may be chronic, severe or disabling, all consuming, and be treatment resistant. Thus, identifying the exact prevalence of pain is a difficult task. According to the American Pain Foundation, more than 50 million people in the United States suffer from

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chronic pain, and an additional 25 million experience acute pain from injury or surgery.[2] About 20% of adults, mostly women and the elderly, experience chronic pain such as back pain, headache, and joint pain.

Prevalence rates for a variety of different types of pain have been described. The annual incidence of moderate-intensity back pain is 10% to 15% in the adult population with a point prevalence of 15% to 30%.[3] Migraine affects more than 25 million Americans, and 90% of Americans report some other types of headaches (e.g., tension or sinus) each year.[4] Pain resulting from fibromyalgia affects 4 million Americans.[5] Cancer is commonly associated with both acute and chronic pain, and about 70% of those diagnosed with cancer will experience significant pain.[6]

The prevalence of **neuropathic pain** is unknown because of the lack of epidemiologic studies. Current estimates suggest that approximately 1.5% of the population in the United States may be affected by neuropathic pain.[7] However, this figure is probably an underestimate and will likely increase due to the increase in disorders associated with neuropathic pain in the ever-growing older population. Approximately 25% to 50% of all pain clinic visits are related to neuropathic pain.[8] Central neuropathic pain is estimated to occur in 2% to 8% of all stroke patients.[9]

The elderly, defined as people 65 years of age and over, bear a significant burden of pain, and pain continues to be underrecognized and undertreated in this population. The prevalence of pain in people over the 60 years of age is twice that in those younger than 60 years of age.[10] Studies suggest that 25% to 50% of community-dwelling elderly suffer pain. Pain is quite common among nursing home residents. It is estimated that pain in 45% to 80% of nursing home patients contributes to functional impairment and a decreased quality of life.[11]

The financial impact of pain is considered to be significant. The National Institute for Occupational Safety and Health (NIOSH) estimated that the cost of low back pain alone was between $50 billion and $100 billion per year.[12] The American Productivity Audit of the United States workforce, conducted from 2001 to 2002, revealed that the cost of lost productivity due to arthritis, back pain, headache, and other musculoskeletal pain was approximately $ 80 billion per year.[13]

The Undertreatment of Pain

Despite the growing emphasis on pain management, pain often remains undertreated and continues to be a problem in hospitals, long-term care facilities, and the community. In one series of reports, 50% of seriously ill hospitalized patients reported pain; however, 15% were dissatisfied with pain control, and some remained in pain after hospitalization.[14,15]

Misconceptions about pain management, both from patients and health care providers, are among the most common causes of analgesic failure. Some clinicians may be hesitant to treat pain because they do not believe the patient's reports of pain or feel the patient is exaggerating symptoms in order to obtain medications. Inadequate clinical knowledge of available pain management strategies, including pharmacologic, nonpharmacologic, and alternative therapy options, also often leads to suboptimal pain management. In one survey, approximately three-fourths of physicians cited low competence in pain assessment as the major barrier to effective pain management.[16] Concerns about opiate misuse, abuse, and diversion also contribute to less than optimal pain management and cause providers to exercise caution when prescribing opiates for pain. Misunderstandings about the terms addiction, physical dependence, tolerance, and pseudoaddiction are additional obstacles to optimal pain management.

Patients may present barriers to pain management by not reporting pain symptoms because of fear of becoming addicted or because of cultural beliefs. Elderly patients may not report pain for a variety of reasons including belief that pain is something they must live with, fear of consequences (e.g., hospitalization or loss of independence), or fear that the pain may be forecasting impending illness, inability to understand terminology used by health care providers, or a belief that showing pain is unacceptable behavior.

PATHOPHYSIOLOGY

Types of Pain

Several distinct types of pain have been described: nociceptive, inflammatory, neuropathic, and functional.[17] **Nociceptive pain** is a transient pain in response to a noxious stimulus at nociceptors that are located in cutaneous tissue, bone, muscle, connective tissue, vessels, and viscera. Nociceptors may be classified as thermal, chemical, or mechanical. The nociceptive system extends from the receptors in the periphery to the spinal cord, brain stem, and to the cerebral cortex where pain sensation is perceived. This system is a key physiologic function that prevents further tissue damage due to the body's autonomic withdrawal reflex. When tissue damage occurs despite the nociceptive defense system, inflammatory pain ensues. The body now changes focus from protecting against painful stimuli to protecting the injured tissue. The inflammatory response contributes to pain hypersensitivity that serves to prevent contact or movement of the injured part until healing is complete, thus reducing further damage.

Neuropathic pain is defined as spontaneous pain and hypersensitivity to pain associated with damage to or pathologic changes in the peripheral nervous system as in painful diabetic peripheral neuropathy (DPN), acquired immunodeficiency syndrome (AIDS), polyneuropathy, post-herpetic neuralgia (PHN); or pain originating in the central nervous system (CNS), that which occurs with spinal cord injury, multiple sclerosis, and stroke. Functional pain, a relatively newer concept, is pain sensitivity due to an abnormal processing or function of the central nervous system in response to normal stimuli. Several conditions considered to have this abnormal sensitivity or hyperresponsiveness include fibromyalgia and irritable bowel syndrome.

Mechanisms of Pain

Pain Transmission

The mechanisms of nociceptive pain are well-defined and provide a foundation for the understanding of other types of pain.[18] Following **nociceptor** stimulation, tissue injury causes the release of substances (bradykinin, serotonin, potassium, histamine, prostaglandins, and substance P) that may further sensitize and/or activate nociceptors. Nociceptor activation produces action potentials (transduction) that are transmitted along myelinated A-δ fibers and unmyelinated C fibers to the spinal cord. The A-δ fibers are responsible for first, fast, sharp pain and release excitatory amino acids that activate α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors in the dorsal horn. The C fibers produce secondary pain which is described as dull, aching, burning, and diffuse. These nerve fibers synapse in the dorsal horn of the spinal cord, where several neurotransmitters are released including glutamate, substance P, and calcitonin gene-related peptide. Transmission of pain signals continues along the spinal cord to the thalamus, which serves as the pain relay center, and eventually to the cortical regions of the brain where pain is perceived.

Pain Modulation

Modulation of pain (inhibition of nociceptive impulses) can occur by a number of processes. Based on the gate control theory, pain modulation may occur at the level of the dorsal horn.[19] Since the brain can process only a limited number of signals at one time, other sensory stimuli at nociceptors may alter pain perception. This theory supports the effectiveness of counterirritants and transcutaneous electrical nerve stimulation (TENS) in pain management. Pain modulation may result through several other complex processes. The endogenous opiate system consists of endorphins (enkephalins, dynorphins, and β-endorphins) that interact with μ, δ, and κ receptors throughout the CNS to inhibit pain impulses and alter perception. The CNS also includes inhibitory descending pathways from the brain that can attenuate pain transmission in the dorsal horn. Neurotransmitters involved in this descending system include endogenous opioids, serotonin, norepinephrine, γ-aminobutyric acid (GABA) and neurotensin. The perception of pain involves not only nociceptive stimulation but physiologic and emotional input that contributes to the perception of pain. Consequently, cognitive behavioral treatments such as distraction, relaxation, and guided imagery can reduce pain perception by altering pain processing in the cortex.

Peripheral Sensitization, Central Sensitization, and Wind-Up

Under normal conditions, a balance generally exists between excitatory and inhibitory neurotransmission. Changes in this balance can occur both peripherally and centrally resulting in exaggerated responses and sensitization such as that observed in inflammatory, neuropathic, or functional chronic pain. Pain in these settings may occur spontaneously without any stimulus or may be evoked by a stimulus. Evoked pain may arise from a stimulus that normally does not cause pain (**allodynia**) such as a light touch in neuropathic pain. **Hyperalgesia**, an exaggerated and/or prolonged pain response to a stimulus that normally causes pain, can also occur as a result of increased sensitivity in the CNS.

During normal pain transmission, the AMPA receptors are activated, but the N-methyl-D-aspartate (NMDA) receptor is blocked by magnesium.[16] Repeated nerve depolarization causes release of the magnesium block allowing the influx of calcium and sodium and results in excessive excitability and amplification of signals. Continued input from C fibers and subsequent increases in substance P and glutamate causes the activation of the NMDA receptor, a process referred to as wind-up. Wind-up increases the number and responsiveness of neurons in the dorsal horn irrespective of the input from the periphery. Recruitment of neurons not normally involved in pain transmission or spread occurs leading to allodynia, hyperalgesia, and spread to uninjured tissues.[20] The wind-up phenomenon supports the observation that untreated acute pain can lead to chronic pain and the belief that pain processes are plastic and not static.

CLINICAL PRESENTATION AND DIAGNOSIS

Classification of Pain

Pain has always been described as a symptom. However, recent advances in the understanding of neural mechanisms have demonstrated that unrelieved pain may lead to changes in the nervous system known as neural plasticity. Since these changes reflect a process that influences a physiologic response, pain, particularly chronic pain, may be considered a disease unto itself.

Pain can be divided into two broad categories: acute and chronic or persistent pain. Acute pain is also referred to as adaptive pain since it serves to protect the individual from further injury or promote healing.[17] However, chronic pain has been called maladaptive, a pathologic function of the nervous system or pain as a disease.

Acute Pain

Acute pain is pain that occurs as a result of injury or surgery and is usually self-limited, subsiding when the injury heals. Untreated acute pain can produce physiologic symptoms including tachypnea, tachycardia, and increased sympathetic nervous system activity, such as pallor, diaphoresis, and pupil dilation. Furthermore, poorly treated pain can cause psychological stress and compromise the immune system due to the release of endogenous corticosteroids. This situation accompanied by decreased range of motion and decreased lung capacity can delay recovery from the initial injury. Somatic acute pain arises from injury to skin, bone, joint, muscle, and connective tissue, and it is generally localized to the site of injury.

Visceral pain involves injury to nerves on internal organs (e.g., intestines or liver) and can present as diffuse, poorly differentiated, and often referred pain. Acute pain should be treated aggressively, even before the diagnosis is established, except in conditions of head or abdominal injury where pain may assist in the differential diagnosis.

Chronic Pain

Chronic pain persists beyond the expected normal time for healing and serves no useful physiologic purpose. Chronic pain may be nociceptive, inflammatory, neuropathic, or functional in origin; however, all forms share some common characteristics. Chronic pain can be episodic or continuous, or both. Physiologic responses observed in acute pain are often absent in chronic pain; however, other symptoms may predominate. There are four main effects of chronic pain, and these include: 1) effects on physical function, 2) psychological changes, 3) social consequences, and 4) societal consequences. Effects of chronic pain on physical function include impaired activities of daily living and sleep disturbances. Psychological components of chronic pain may include depression, anxiety, anger, and loss of self-esteem. As a result of physical and psychological changes, social consequences may ensue such as changes in relationships with friends and family, intimacy, and isolation. On a societal level, chronic pain contributes to increased health care costs, disability, and lost productivity. Management of chronic pain should be multimodal and may involve cognitive interventions, physical manipulations, pharmacologic agents, surgical intervention, and regional or spinal anesthesia.

Chronic Malignant Pain

Chronic malignant pain is associated with a progressive disease that is usually life-threatening such as cancer, AIDS, progressive neurologic diseases, end-stage organ failure, and dementia.[21] The goal is pain alleviation and prevention, often through a systematic and stepwise approach. Tolerance, dependence, and addiction are often not a concern due to the terminal nature of the illness.

Chronic Non-malignant Pain

Pain not associated with a life-threatening disease and lasting longer than 6 months beyond the healing period is referred to as chronic non-malignant pain. Pain associated with low back pain, osteoarthritis, previous bone fractures, peripheral vascular disease, genitourinary infection, rheumatoid arthritis, and coronary heart disease is considered non-malignant. The numerous causes of this type of chronic pain make treatment complex and involves a multidisciplinary approach. Treatment is initially conservative but may involve the use of more potent analgesics including opiates in psychologically healthy patients.[22]

Neuropathic Pain

Neuropathic pain may be considered to be a type of chronic non-malignant pain involving disease of the central and peripheral nervous systems. Neuropathic pain may be broadly categorized as peripheral or central in nature. Examples of neuropathic pain include PHN, which is pain associated with acute herpetic neuralgia or an acute shingles outbreak. Peripheral or polyneuropathic pain is associated with the distal polyneuropathies of diabetes, human immunodeficiency virus (HIV), and chemotherapeutic agents. Types of **central pain** include central stroke pain, trigeminal neuralgia, and a complex of syndromes known as complex regional pain syndrome (CRPS). Complex regional pain syndrome includes both reflex sympathetic dystrophy and **causalgia**, both of which are neuropathic pain associated with abnormal functioning of the autonomic nervous system. One of the newest categories of neuropathic pain is neuropathic low back pain.

The symptoms of neuropathic pain are characterized as tingling, burning, shooting, stabbing, electric shock–like quality, or radiating pain. The patient may describe either a constant dull throbbing or burning pain, or an intermittent pain that is stabbing or shooting. Frequent damage to the peripheral nerves may be referred to the body region innervated by those nerves.

Traditionally neuropathic pain has been difficult to treat and involves a variety of therapeutic modalities. Rational choice of treatment options may be accomplished through evaluation of the neuropathy and its relationship to peripheral or central nerve damage. Targeting the mechanistic points in the pain pathway is another rationale for treating neuropathic pain. For example, certain opioids, such as methadone, are characterized by NMDA receptor antagonist activity and are effective in treating pain. Anticonvulsant drugs are able to block sodium channels in the peripheral afferent nerve fibers. Agents such as tricyclic antidepressants, bupropion, and venlafaxine block the release of monoamines targeting dorsal horn inhibitory mechanisms.



Clinical Presentation of Pain

General

Patients may be in acute distress (acute pain) or have no signs or symptoms of suffering (chronic pain).

Symptoms

Pain is described based on the following characteristics: onset, duration, location, quality, severity, and intensity. Other symptoms may include anxiety, depression, fatigue, anger, fear, and insomnia.

Signs

Acute pain may cause hypertension, tachycardia, diaphoresis, mydriasis, and pallor.

Diagnosis

The patient is the only person who can describe the intensity and quality of their pain. There are no laboratory tests that can diagnose pain.

Pain Assessment

Effective pain management begins with a thorough and accurate assessment of the patient. Even though pain is a common presenting complaint, lack of regular assessment and reassessment of pain remains a problem and contributes to the undertreatment of pain.[23]

Pain Assessment Guidelines and Regulations for Specific Practice Settings

Screening for pain should be a part of a routine assessment, and this has led several organizations such as the Veterans Health Administration (VHA) and the American Pain Society (APS) to declare pain the fifth vital sign. Many states have adopted a bill of rights for patients in pain. In 2001, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) incorporated pain as the fifth vital sign in its accreditation standards. [24] According to the JCAHO, patients have a right to appropriate assessment and management of their pain and education regarding their pain. ❷ *Following initial assessment of pain, reassessment should be done as needed based on medication choice and the clinical situation.*

Methods of Pain Assessment

A patient-oriented approach to pain is essential, and methods do not differ greatly from those used in other medical conditions. A comprehensive history (medical, family, and psychological) and physical exam are necessary to evaluate underlying disease processes for the source of pain and other factors contributing to the pain.[20] A thorough assessment of the characteristics of the pain should be completed including questions about the pain (onset, duration, location, quality, severity, and intensity), pain relief efforts, and efficacy and side effects of current and past treatments for pain. A common mnemonic for pain assessment is PQRST (Palliative/Provocative, Quality, Radiation, Severity, and Temporal).[25] Some clinicians have suggested the addition of U (you) to this mnemonic.[26] During the pain interview, the impact of the pain on the patient's functional status, behavior, and psychological states should also be assessed. Evaluation of psychological status is especially important in patients with chronic pain since depression and affective disorders may be common comorbid conditions. A history of drug and alcohol use should be elicited due to the potential for addiction in patients who may require opiates or other pain medications with a potential for abuse. Other conditions such as renal or hepatic dysfunction, diabetes, and conditions that affect bowel function can influence therapy choices and goals. A discussion of the patient's expectations and goals with respect to pain management (level of pain relief, functional status, and quality of life) should also be part of any pain interview.

Pain Assessment Tools

Pain, particularly acute pain, may be accompanied by physiologic signs and symptoms, and there are no reliable objective markers for pain. Many tools have been designed for assessing the severity of pain including rating scales and multidimensional pain assessment tools.

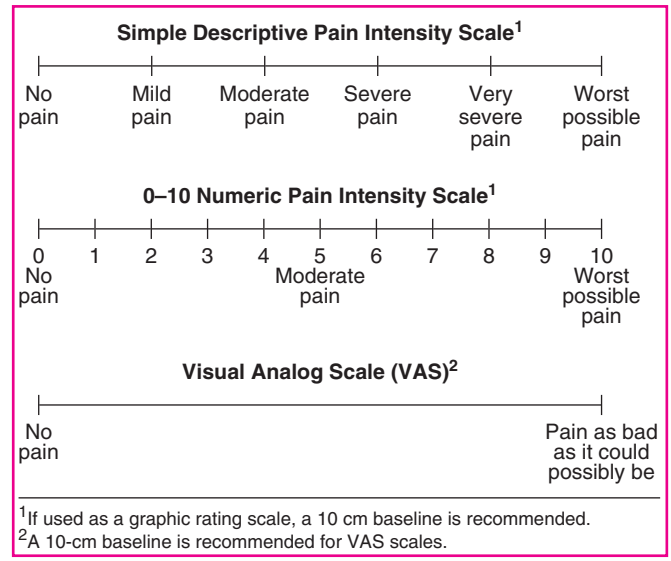


FIGURE 30–1. Pain rating scales.[27]

Rating scales provide a simple way to classify the intensity of pain, and should be selected based on the patient's ability to communicate (Fig. 30–1).[27] Numeric scales are widely used and ask patients to rate their pain on a scale of 0 to 10, with 0 indicating no pain and 10 being the worst pain possible. Using this type of scale, 1 to 3 is considered mild pain, 4 to 6 is moderate pain, and 8 to 10 is severe pain. The visual analog scale (VAS) is similar to the numerical scale in that it requires patients to place a mark on a 10-cm line where one end is no pain, and the worst possible pain is on the other end. For patients who have difficulty assigning a number to their pain, a categorical scale may be an option to communicate the intensity of the pain experience. Examples of this include a simple descriptive list of words and the Wong-Baker FACES of Pain Rating Scale.[28]

Multidimensional assessment tools obtain information about the pain and impact on quality of life, but are often more time-consuming to complete. Examples of these types of tools include the Initial Pain Assessment Tool, Brief Pain Inventory, McGill Pain Questionnaire, the Neuropathic Pain Scale, and the Oswestry Disability Index.[29–33]

Pain Assessment in Challenging Populations

Children Pain interviews may be conducted with children as young as 3 or 4 years of age; however, communication may be limited by vocabulary.[34] Terms familiar to children such as "hurt," "owie," or "boo boo" may be used to describe pain. The VAS is best used with children older than 7 years of age. Other scales based on numbers of objects (e.g., poker chips), increasing color intensity, or faces of pain may be helpful for children between 4 and 7 years of age. In children younger than 3 to 4 years of age, behavioral or physiologic measures, such as pulse or respiratory rate, may be more appropriate. Pain assessment in newborns and infants relies on behavioral observation for such clues as vocalizations (crying and fussing), facial expressions,

body movements (flailing of limbs and pulling legs in), withdrawal, and change in eating and sleeping habits.[35] Preschool children experiencing pain may become clingy, lose motor and verbal skills, and start to deny pain because treatment may be linked to discomfort or punishment. School-age children may exhibit aggressiveness, nightmares, anxiety, and withdrawal when in pain, while adolescents may respond to pain with oppositional behavior and depression.

Elderly Most of the previously discussed pain scales can be used in older persons that are cognitively intact or with mild dementia. The pain thermometer and FACES of pain have been studied in older persons. In persons with moderate to severe dementia or those who are nonverbal, observation of pain behaviors, such as guarding or grimacing, provides an alternative for pain assessment. The Pain Assessment in Advanced Dementia (PAINAD) tool may be used to quantify signs of pain and involves observing the older adult for 15 minutes for breathing, negative vocalizations, facial expression, body language, and consolability.[36] Regardless of which pain assessment tool is used, the practitioner should first determine if the patient understands the concept of the scale to ensure reliability of the instrument.



Patient Encounter, Part 1

HPI
BA is a 58-year-old male recently diagnosed with lung cancer. Following surgery he was placed on morphine patient-controlled analgesia (PCA). He has been using 120 mg of morphine/24 hours with adequate pain control.

PMH
Hypertension × 18 years

FH
Non-contributory

SH
Lives with wife; has four grown children; smoked 2 packs of cigarettes per day × 40 years (quit with diagnosis of lung cancer)

Meds
Hydrochlorothiazide 25 mg every day

Pain assessment: Patient rates pain as 8 on a scale of 1 to 10.

- The physician would like to convert him to a combination preparation of oxycodone and acetaminophen. What dosing regimen would you suggest?
- Six months later, BA's pain is controlled with the escalating doses of the combination product; however, he has reached the maximum dose of acetaminophen. What would you suggest at this time?

TREATMENT

General Approach to Treatment

❸ *Effective treatment involves an evaluation of the cause, duration, and intensity of the pain and selection of an appropriate treatment modality for the pain situation.* Depending on the type of pain, treatment may involve pharmacologic or nonpharmacologic therapy or both. General principles for the pharmacologic management of pain are listed in the section on patient care and monitoring. Two common approaches to the selection of treatment are based on severity of pain and the mechanism responsible for the pain (Fig. 30–2). Clinical practice guidelines for pain management are available from the APS, the Agency for Healthcare Research and Quality (AHRQ), the American Geriatrics Society (AGS), and the American Society of Anesthesiologists (ASA).

Selection of Agent Based on Severity of Pain

❹ *Whenever possible, the least potent oral analgesic should be selected.*

Guidelines for the selection of therapeutic agents based on pain intensity are derived from the World Health Organization (WHO) analgesic ladder for the management of cancer pain (Table 30–1).[37] Mild to moderate pain is generally treated with non-opioid analgesics. Combinations of medium-potency opioids and acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) are often used for moderate pain. Potent opioids are recommended for severe pain. Throughout this progression adjuvant medications are added as needed to manage side effects and to augment analgesia. While these guidelines can be useful for initial therapy, the clinical situation (type of pain); cost and pharmacokinetic profile of available drugs; and patient-specific factors (age, concomitant illnesses, previous response, and other medications) must also be considered. Pain medications may also be used in the absence of pain in anticipation of a painful event such as surgery to minimize peripheral and central sensitization.

Mechanistic Approach to Therapy

Current analgesic therapy is aimed at controlling or blunting pain symptoms. However, diverse mechanisms contributing to the various types of pain continue to be further elucidated. An understanding of these new mechanisms of pain transmission may lead to improvement in pain management, as pharmacologic management of pain becomes more mechanism-specific. Use of NSAIDs for inflammatory types of pain is an example of a mechanistic approach. Since several mechanisms of pain often co-exist, a polypharmacy approach seems rational to target each mechanism.

Two current foci in pain management are to identify the mechanisms that are responsible for pain hypersensitivity and to prevent this initial hypersensitivity. Therefore, the goal of pain therapy is to reduce peripheral sensitization and subsequent central stimulation and amplification associated with wind-up, spread, and central sensitization.[17]

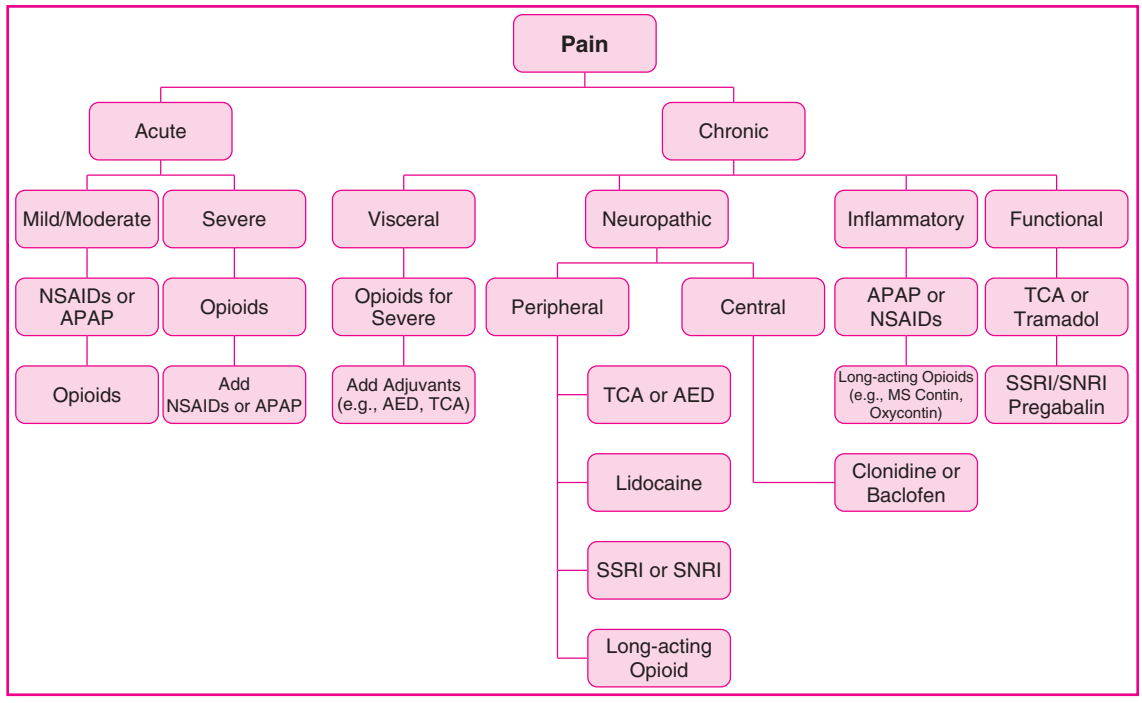


FIGURE 30–2. Pain algorithm. AED, antiepileptic drug; APAP, acetaminophen; NSAID, non-steroidal antiinflammatory drug; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Nonpharmacologic Therapy

Nonpharmacologic therapies (psychological interventions and physical therapy) may be used in both acute and chronic pain. Psychological interventions can reduce pain as well as the anxiety, depression, fear, and anger associated with pain. Psychological interventions helpful in management of acute pain are imagery (picturing oneself in a safe, peaceful place) and distraction (listening to music or focusing on breathing). Chronic pain patients may benefit from relaxation, biofeedback, cognitive-behavioral therapy, psychotherapy, support groups, and spiritual counseling. Biofeedback teaches patients to control physiologic responses to pain and has been effective in headache and chronic low back pain. Cognitive therapy encourages patients to monitor their perceptions of pain, reducing stress and negativism. Psychotherapy is very useful for patients with chronic pain, and it can also assist in treatment of psychiatric comorbidities and help patients to deal with terminal illnesses.[38] The patient should be educated about what to expect regarding pain and its treatment whether pain is acute (i.e., preoperative explanations of

TABLE 30–1. Selection of Analgesics Based on Intensity of Pain[37]

Pain Intensity	Corresponding Numerical Rating	WHO Therapeutic Recommendations	Examples of Initial Therapy	Comments
Mild	1–3/10	Non-opioid analgesic; regular scheduled dosing	Acetaminophen 1000 mg every 6 hours; Ibuprofen 600 mg every 6 hours	Consider adding an adjunct or using an alternate regimen if pain is not reduced in 1–2 days
Moderate	4–6/10	Add an opioid to the non-opioid for moderate pain; regular scheduled dosing	Acetaminophen 325 mg + codeine 60 mg every 4 hours; Acetaminophen 325 mg + oxycodone 5 mg every 4 hours	Consider step-up therapy if pain is not relieved by greater than or equal to 2 or more different drugs
Severe	7–10/10	Switch to a high-potency opioid; regular scheduled dosing	Morphine 10 mg every 4 hours; Hydromorphone 4 mg every 4 hours	

WHO, World Health Organization.

expected postsurgical pain) or chronic (patient and family education in hospice care).

Physical therapy is an essential part of many types of pain situations. Treatment modalities include heat, cold, water, ultrasound therapy, TENS, massage, and therapeutic exercise. Heat and cold therapy are utilized in a variety of musculoskeletal conditions (muscle spasms, low back pain, fibromyalgia, sprains, and strains). Heating modalities include local hot packs, paraffin wrap, hydrotherapy, and deep-heating methods (ultrasound). Cold treatments may be delivered via cold packs, ice massage, cold water immersion, or coolant sprays. TENS therapy is based on the theory that electrical stimulation of a nerve in a particular area can block pain impulses originating from that area. TENS is also believed to release endogenous endorphins and enkephalins. Massage therapy is used to relieve muscle tension and stiffness and is also felt to increase endogenous endorphins. Therapeutic exercise improves not only strength, endurance, and range of motion, but also provides cardiovascular, psychological, and other health benefits.

Pharmacologic Therapy

Non-opioid Analgesics

Acetaminophen

Acetaminophen, an analgesic and antipyretic, is often selected as initial therapy for mild to moderate pain and is considered first-line in several pain situations such as low back pain and osteoarthritis.[39] Mechanistically, acetaminophen is believed to inhibit prostaglandin synthesis in the CNS and block pain impulses in the periphery. Acetaminophen is well-tolerated at usual doses and has few clinically significant drug interactions except causing increased hypoprothrombinemic response to warfarin in patients receiving acetaminophen doses of more than 2000 mg per day. The maximum recommended dose for patients with normal renal and hepatic function is 4000 mg per day. Hepatotoxicity has been reported with excessive use and overdose and the risk of this adverse effect increases in those with hepatitis or chronic alcohol use, as well as those who binge drink or are in a fasting state. Regular chronic use of acetaminophen has been associated with chronic renal failure, but reports are conflicting. For these reasons, the maximum dose should be reduced by 50% to 75% in patients with renal dysfunction or hepatic disease and in those who engage in excessive alcohol use.

Aspirin and Other Salicylates

Aspirin, non-acetylated salicylates, and other NSAIDs have analgesic, antipyretic, and anti-inflammatory actions. These agents inhibit cyclooxygenase (COX-1 and COX-2) enzymes, thereby preventing prostaglandin synthesis, which results in reduced nociceptor sensitization and an increased pain threshold. NSAIDs are the preferred agents for mild to moderate pain in situations that are mediated by prostaglandins (e.g., rheumatoid arthritis and osteoarthritis, menstrual cramps, and postsurgical pain) and in the management of pain from bone metastasis, but they are of minimal use in neuropathic pain.

Aspirin is effective for mild to moderate pain; however, the risk of gastrointestinal irritation and bleeding limits frequent use of this drug for pain management. Direct effects of aspirin on the gastrointestinal mucosa and irreversible platelet inhibition contribute to this risk which can occur even at low doses. Hypersensitivity reactions are also possible and may occur in 25% of patients with co-exsiting asthma, nasal polyps, or chronic urticaria. Of additional concern is the potential for cross-sensitivity of other NSAIDs in this group of patients. Non-acetylated salicylates (choline magnesium salicylate and sodium salicylate) have a reduced risk of gastrointestinal effects and platelet inhibition and may be used in aspirin-sensitive patients. Diflunisal, a salicylic acid derivative, is associated with fewer gastrointestinal (GI) complaints compared to aspirin, but platelet inhibition does increase the risk of GI bleeding.

Non-steroidal Anti-Inflammatory Drugs

NSAIDs provide analgesia equal to or better than that of aspirin or acetaminophen combined with codeine, and they are very effective for inflammatory pain and pain associated with bone metastasis.[18] These agents may be classified by their chemical structures (fenamates, acetic acids, propionic acids, pyranocarboxylic acids, pyrrolizine carboxylic acids, and COX-2 inhibitors). While only some members of this class have approval for treatment of pain, it is likely that all of them have similar analgesic effects. All members of this class appear to be equally effective, but there is great intrapatient variability in response. After an adequate trial of 2 to 3 weeks with a particular agent, it is reasonable to switch to another member of the class. NSAIDs demonstrate a flat dose-response curve, with higher doses producing no greater efficacy than moderate doses, but resulting in an increased incidence of adverse effects (gastrointestinal irritation, hepatic dysfunction, renal insufficiency, platelet inhibition, sodium retention, and CNS dysfunction).

Patients at increased risk of NSAID-induced gastrointestinal adverse effects (e.g., dyspepsia, peptic ulcer formation, and bleeding) include the elderly, those with peptic ulcer disease, coagulopathy, and patients receiving high doses of concurrent corticosteroids. Nephrotoxicity is more common in the elderly, patients with creatinine clearance values less than 50 mL/minute, and those with volume depletion or on diuretic therapy. NSAIDs should be used with caution in patients with reduced cardiac output due to sodium retention and in patients receiving antihypertensives, warfarin, and lithium.

NSAIDs are classified as non-selective (they inhibit COX-1 and COX-2) or selective (they inhibit only COX-2) based on degree of cyclooxygenase inhibition. COX-2 inhibition is responsible for anti-inflammatory effects, while COX-1 inhibition contributes to increased GI and renal toxicity associated with non-selective agents. Since the antiplatelet effect of non-selective NSAIDs is reversible, concurrent use may reduce the

cardioprotective effect of aspirin due to competitive inhibition of COX-1. For this reason, administration of aspirin prior to the NSAID is recommended.[40] The cardiovascular safety of the COX-2 inhibitors has been questioned due to increased risk of myocardial infarction and stroke seen in several trials.[41–43] The Food and Drug Administration (FDA) Committees on Arthritis and Drug Safety and Risk Management convened in February 2005 to evaluate the published studies and manufacturer information about the cardiovascular adverse events associated with COX-2 inhibitors.[44] As a follow-up to the committee's recommendations, the FDA took regulatory action in April 2005, announcing that the increased risk of cardiovascular events was likely a class effect of NSAIDs. A boxed warning highlighting the potential for increased risk of cardiovascular events and GI bleeding is now required for all prescription non-selective NSAIDs and celecoxib. Stronger warnings about these adverse events are also required on non-prescription NSAIDs. As a result of the data and subsequent events, two members of this class, rofecoxib and valdecoxib, have been withdrawn from the market. Future COX-2 inhibitors and non-selective NSAIDs will likely have to undergo cardiovascular safety studies before receiving FDA approval. When an NSAID is needed in a patient with cardiovascular risk, the benefits of therapy must outweigh the risk and the lowest effective dose of NSAID is recommended.

Opioid Analgesics

Opioids are considered the agents of choice for the treatment of severe acute pain and moderate to severe pain associated with cancer.[45] For chronic pain, their use was once highly controversial; however, use of opioids in chronic pain is now gaining acceptance.[46] Opioids may be classified by their activity at the receptor site, usual pain intensity treated, and duration of action (short- versus long-acting).

Selection and Dosing

The opioids exert their analgesic efficacy by stimulating opioid receptors (μ, κ, and δ) in the CNS. There is a wide variety of potencies among the opioids, with some used for moderate pain (codeine, hydrocodone, tramadol, and partial agonists) and others reserved for severe pain (morphine and hydromorphone). Pure agonists (morphine) bind to μ receptors to produce analgesia that increases with dose without a ceiling effect. Pure agonists are divided into three chemical classes: phenanthrenes or morphine-like, phenylpiperidine or meperidine-like, and diphenylheptane or methadone-like. Partial agonists/antagonists (butorphanol, pentazocine, and nalbuphine) partially stimulate the μ receptor and antagonize the κ receptors. This activity results in reduced analgesic efficacy with a ceiling dose, reduced side effects at the μ receptor, psychotomimetic side effects due to κ antagonism, and possible withdrawal symptoms in patients who are dependent on pure agonists.

Selection of the agent and route depend on individual patient-related factors including severity of pain, individual perceptions, weight, age, opioid tolerance, and concomitant disease (renal or hepatic dysfunction). Since pure agonists are pharmacologically similar, choice of agent may also be guided by pharmacokinetic parameters and other drug characteristics. Hepatic impairment can decrease the metabolism of most opioids, particularly methadone, meperidine, pentazocine,



Patient Encounter, Part 2: Converting to Different Drugs and Adjusting Doses

Two years following his diagnosis of lung cancer, BA has been diagnosed as having bone metastases. Pain has been controlled with the following medications: hydromorphone (Dilaudid) 10 mg IV every hour and levorphanol (Levodromoran) 10 mg orally every 4 hours. He is currently receiving hydrochlorothiazide 25 mg daily, senna two tablets twice daily, and docusate sodium 100 mg twice daily. As the home care pharmacist, you are asked to convert this patient to a morphine infusion.

Morphine equivalents (based on 10 mg parenteral morphine) (Table 30–2):

Hydromorphone 1.5 mg is equivalent to 10 mg of morphine.

Levorphanol 4 mg is equivalent to 10 mg of morphine.

- Based on BA's opioid requirement, recommend an initial infusion rate (in milligrams per hour) of parenteral morphine.
- Which adjuvant therapy could be considered for BA?
- Recommend a monitoring plan for this patient.
- How would you assess pain response?

TABLE 30–2. Equianalgesic Doses of Selected Opioids[26,45,49,51]

	Dose Equianalgesic to 10 mg of Parenteral Morphine (mg)	
Opioid	**Parenteral (mg)**	**Oral (mg)**
Mild-Moderate Pain		
Codeine	120	200
Hydrocodone	N/A	30
Oxycodone	N/A	20
Meperidine (Demerol)	100	400
Propoxyphene (Darvon)	N/A	65–130
Moderate-Severe Pain		
Morphine	10	30
Hydromorphone (Dilaudid)	1.5	7.5
Oxymorphone	1	N/A
Levorphanol	2	4
Fentanyl (Duragesic)	0.1–0.2	N/A[a]
Methadone (Dolophine)	10[b]	3–5[b]

[a]Transdermal: 100 mcg/hour = 2–4 mg/hour of IV morphine.
[b]Dosage calculations when converting from morphine to methadone are not linear. The equianalgesic dose of methadone will decrease progressively as the morphine equivalents increase (Table 30-4).

and propoxyphene. Furthermore, the clearance of meperidine, propoxyphene, and morphine and their metabolites is reduced in renal dysfunction.

Table 30–3 provides a summary of opiate side effects, but several drugs warrant further discussion. Normeperidine, the active metabolite of meperidine, can produce tremors, myoclonus, delirium, and seizures. Due to the potential for accumulation of normeperidine, meperidine should not be used in the elderly, those with renal impairment, in patients using patient-controlled analgesia devices, or for more than 1 to 2 days of continuous dosing with intermittent dosing. Propoxyphene also has an increased risk of seizures and cardiac conduction abnormalities and should be avoided in the elderly. Despite its popularity, propoxyphene has proven to be no more effective than acetaminophen, aspirin, or codeine alone.[18] Methadone is unique among the opiates since it has several mechanisms (μ agonist, NMDA receptor antagonist, and inhibition of reuptake of serotonin and norepinephrine) that makes it an interesting choice for chronic pain. The long half-life of methadone (30 hours) permits extended dosing intervals; however, the potential for accumulation with repeated dosing often results in challenging dose conversions. Tramadol is a synthetic opioid with a dual mechanism of action (μ agonist and inhibition of serotonin and norepinephrine reuptake), and efficacy and safety similar to that of equianalgesic doses of codeine plus acetaminophen. Tramadol has been evaluated in several types of neuropathic pain and may have a place in the treatment of chronic pain. Tramadol is associated with an increased risk of seizures in patients with a seizure disorder, those at risk for seizures, and those taking medications that can lower the seizure threshold. Doses greater than 500 mg have also been associated with seizures. Use of tramadol with other serotonergic drugs [e.g., selective serotonin reuptake inhibitors (SSRIs)] may precipitate serotonin syndrome. While originally thought to be non-habit forming, dependence may occur with tramadol.

TABLE 30–3. Managing Opioid Side Effects[27,45,49]

Adverse Effects	Drug Treatment/Management
Excessive sedation	Reduce dose by 25% or increase dosing interval
Constipation	Casanthranol-docusate 1 cap at bedtime or twice daily; senna 1–2 tabs at bedtime or twice daily; bisacodyl 5–10 mg daily + docusate 100 mg twice daily
Nausea and vomiting	Prevention: hydroxyzine 25–100 mg (PO/IM) every 4–6 hours as needed; diphenhydramine 25–50 mg (PO/IM) every 6 hours as needed; ondansetron 4 mg IV or 16 mg PO Treatment: prochlorperazine 5–10 mg (PO/IM) every 3–4 hours as needed or 25 mg per rectum twice daily; ondansetron 4–8 mg IV every 8 hours as needed
Gastroparesis	Metoclopramide 10 mg (PO/IV) every 6–8 hours
Vertigo	Meclizine 12.5–25 mg PO every 6 hours as needed
Urticaria/itching	Hydroxyzine 25–100 mg (PO/IM) every 4–6 hours as needed; diphenhydramine 25–50 mg (PO/IM) every 6 hours as needed
Respiratory depression	Mild: Reduce dose by 25% Moderate-severe: naloxone 0.4–2 mg IV every 2–3 minutes (up to 10 mg) for complete reversal; 0.1–0.2 mg IV every 2–3 minutes until desired reversal for partial reversal; may need to repeat in 1–2 hours depending on narcotic half-life
CNS irritability	Discontinue opioid; treat with benzodiazepine

CNS, central nervous system; IM, intramuscular; IV, intravenous; PO, orally.

About 70% of individuals will experience significant analgesia from 10 mg/70 kg (154 lbs) of body weight of intravenous morphine or its equivalent.[18] For severe pain in opiate-naïve patients, a usual starting dose is 5 to 10 mg of morphine every 4 hours. In the initial stages of severe pain, medication should be given around the clock. Rescue doses should be made available in doses equivalent to 10% to 20% of the total daily opioid requirement and administered every 2 to 6 hours if needed. Alternatively one-sixth of the total daily dose or one-third of the 12-hourly dose may be used. Doses should be titrated based on the degree of pain. One method involves adjustment of the maintenance dose based on the total 24-hour rescue dose requirement. Utilizing dose escalation, doses should be increased by 50% to 100% or 30% to 50% of the current dose, for those in severe and moderate pain, respectively. Once pain relief is achieved, and if treatment is necessary for more than a few days, conversion to a controlled-release or long-acting opioid should be made with an equal amount of agent. Several sustained-release products are available containing morphine, oxycodone, and fentanyl. Some clinicians will reduce the total daily dose of the long-acting dosage form by 25% when initiating a sustained-release product to reduce the likelihood of oversedation. The dose of a pure agonist is limited only by tolerability to side effects. Tolerance may develop to analgesic effects necessitating increasing doses to achieve the same level of pain relief. Physical dependence will also occur with long-term use of opioids. However, addiction or psychological dependence is unlikely in legitimate pain patients unless there are predisposing risk factors. Pain patients who are undertreated may appear to be drug-seeking (pseudoaddiction); however, effective pain management resolves the behaviors. When opioids are used for chronic pain, use of informed consent for chronic opioid therapy and medication management agreements or pain contracts may be appropriate to monitor the use (prescribing and dispensing) of controlled substances.

Opioids may be administered in a variety of routes including oral (tablet and liquid), sublingual, rectal, transdermal, transmucosal, intravenous, subcutaneous, and intraspinal. While the oral and transdermal routes are most common, the method of administration is based on patient needs (severity of pain) and characteristics (swallowing difficulty and preference). Oral opioids have an onset of effect of 45 minutes, so intravenous or subcutaneous administration may be preferred if more rapid relief is desired. Intramuscular injections are not recommended because of pain at the injection site and wide fluctuations in drug absorption and peak plasma concentrations achieved. More invasive routes of administration such as PCA and intraspinal (epidural and intrathecal) are primarily used postoperatively, but may also be used in refractory chronic pain situations. PCA delivers a self-administered dose via an infusion pump with a preprogrammed dose, minimum dosing interval, and maximum hourly dose. Morphine, fentanyl, and hydromorphone are commonly administered via PCA pumps by the intravenous route, but less frequently by the subcutaneous or epidural route.

Epidural analgesia is frequently used for lower extremity procedures and pain (e.g., knee surgery, labor pain, and some abdominal procedures). Intermittent bolus or continuous infusion of preservative-free opioids (morphine, hydromorphone, or fentanyl) and local anesthetics (bupivacaine) may be used for epidural analgesia. Opiates given by this route may cause pruritus that is relieved by naloxone. Adverse effects including respiratory depression, hypotension, and urinary retention may occur. When epidural routes are used in narcotic-dependent patients, systemic analgesics must also be used to prevent withdrawal since the opioid is not absorbed and remains in the epidural space. Doses of opioids used in epidural analgesia are 10 times less than intravenous doses, and intrathecal doses are 10 times less than epidural doses (i.e., 10 mg of IV morphine is equivalent to 1 mg epidural morphine and 0.1 mg of intrathecally administered morphine).[45]

Combination Analgesics

Combinations of opioids and non-opioids often result in enhanced analgesia and lower dose of each. Combination analgesics are frequently used in moderate pain. However, in severe pain, the non-opioid component reaches maximum dosage, and thus, the usefulness of non-opioids in this situation is limited. Additionally, the combination products are short-acting and often not suitable for chronic therapy. Single agents offer greater dosing flexibility than combination products.

Opioid Allergy

True narcotic allergies are rare and should not be confused with pruritus associated with opiate use. Cross-sensitivity between morphine-like, meperidine-like, and methadone-like agents is unlikely. Therefore, when an individual is allergic to one drug in a chemical class of opioids, it is reasonable to select an agent in another chemical class. For the purpose of drug selection in patients with allergies, mixed antagonists should be treated as morphine-like agents.

Tapering of Opioids

Tapering of opioids may be necessary once the painful situation has resolved in patients receiving doses greater than 160 mg/day of oral morphine (or the equivalent) or in those with prolonged opioid use. In these situations the dose should be reduced by 15% to 20% each day to avoid withdrawal symptoms.

Managing Opioid Side Effects and Drug Interactions

Side effects common to all opioids include sedation, hallucinations, constipation, nausea and vomiting, urinary retention, myoclonus, and respiratory depression. In terms of medication management, the most frequent are sedation, nausea, and constipation. Sedation and nausea are common when initiating therapy and when increasing doses. Nausea can be prevented with a centrally-acting antiemetic (Table 20–3). Sedation usually improves with continued therapy but may become intractable at high doses, and stimulants may be needed. Respiratory depression is a serious adverse effect, and usually occurs after acute administration in opioid-naïve patients. Tolerance to respiratory depression develops rapidly with repeated doses and is rarely a clinically significant problem in pain patients, even those with respiratory impairment. Constipation is a significant adverse effect to which tolerance does not develop, and prophylaxis with stimulant laxatives (e.g., senna or bisacodyl) and stool softeners, such as docusate, is recommended.

Codeine, hydrocodone, morphine, methadone, and oxycodone are substrates of the cytochrome P-450 isoenzyme CYP2D6.[47] Inhibition of CYP2D6 results in decreased analgesia of codeine and hydrocodone due to decreased conversion to the active metabolites (e.g., morphine and hydromorphone, respectively) and increased effects of morphine, methadone, and oxycodone. Methadone is also a substrate of CYP3A4, and its metabolism is increased by phenytoin and decreased by cimetidine. CNS depressants may potentiate the sedative effects of opiates.

Opioid Rotation

Opioid rotation is the switch from one opioid to another to achieve a better balance between analgesia and treatment-limiting adverse effects. This practice is often used when escalating doses (greater than 1 g of morphine per day) become ineffective. In some settings opioid rotation is utilized routinely to prevent the development of analgesic tolerance.[48]

Equianalgesic Dosing of Opioid Analgesics

Conversion from one dosage form to another or from one opioid to another may be necessary in situations such as ineffective pain control, emergence of side effects, change in patient status, and in formulary restrictions. ❺ *Equianalgesic doses should be used when converting from one opioid to another.* Clinicians

should be familiar with the equianalgesic dosing and conversion strategies to avoid analgesic failure. Equianalgesic tables serve as a guide for selection of the dosage of the new opioid, but have limitations, as they are often based on single-dose studies and clinical observations.[32] Opioid potency is compared using a reference standard of 10 mg of parenteral morphine. Switching from one dosage form to another of the same opioid (i.e., IV to PO) is relatively simple. The current total daily dose is calculated and the total of the new dosage form is determined using a ratio of the equianalgesic doses. This result is then adjusted based on the usual dosing frequency of the new form. When converting to a sustained-release form of the same opioid, dosage may be reduced by 25% to avoid initial sedation; however, the specific product literature should also be consulted.

The first step in an opioid rotation is to calculate the patient's total daily dose of opioid based on the regularly scheduled dose and the total amount of rescue dose needed in 24 hours. This total is then converted to morphine dosing equivalents using equianalgesic doses (Table 30–2). The total daily morphine dose is then used to calculate the daily dose of the new opioid using dosing equivalents from an equianalgesic table. Since cross-tolerance may not be complete between opioids, some references suggest that the calculated equianalgesic dose be reduced by 25% to 50%.[49] If the opioid switch is due to uncontrolled pain, a dosage reduction may not be needed. The equianalgesic dose may need to be reduced more in the medically frail and when converting to methadone.[50] Using the commonly cited equianalgesic dose of morphine to methadone (10 mg morphine/10 mg methadone), methadone doses should be reduced by 75% to 80%. However, this ratio is not applicable even in patients tolerant to low doses of morphine.[51] Methadone appears to be much more potent than once believed, and morphine/methadone ratios vary according to the total dose of morphine taken at the time of making the conversion to methadone (Table 30–4).[52,53] Conversion to methadone is a complex process, and several different strategies have been proposed including a switch of the entire dose in one day or a gradual conversion over 3 days.

Adjuvant Agents for Chronic Pain

The role of NSAIDs and opioids in chronic non-malignant pain has been discussed; however, a review of adjuvant agents for chronic pain, particularly neuropathic pain, is warranted. Adjuvant analgesics are drugs that have indications other than pain but are useful as monotherapy or in combination with non-opioids and opioids. Common adjuvants include antiepileptic drugs (AEDs), antidepressants, antiarrhythmic drugs, local anesthetics, topical agents (e.g., capsaicin), and a variety of miscellaneous drugs (e.g., NMDA antagonists, clonidine, and muscle relaxants).

There is little consensus as to the optimal management of neuropathic pain, because much of the evidence for treatment effectiveness consists of anecdotal reports or poorly designed trials. Published guidelines have been suggested for the general management of neuropathic pain.[54] Suggestions for first-line therapy include gabapentin, lidocaine patch, or tricyclic antidepressants (TCAs) (Table 30–5).[54–58] Newer antidepressants, such as the SSRIs, have fewer side effects but appear to be less effective than the TCAs for neuropathic pain. However, serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., duloxetine and venlafaxine) have been used successfully for painful DPN.

TABLE 30–4. Methadone Dose Conversions[53]

Total Daily Dose Oral Morphine	Morphine: Methadone Factor
Less than 100 mg	3:1 3 mg morphine: 1 mg methadone
101–300 mg	5:1
301–600 mg	10:1
601–800 mg	12:1
801–1,000 mg	15:1
Greater than 1,000 mg	20:1

Data from reference 53 with permission.

TABLE 30–5. Selected Adjuvant Analgesics and Suggested Dosing[54–58]

Agent	Dosing Guidelines	FDA-Approved Indication
Amitriptyline (Elavil)	10–25 mg at bedtime with weekly increments to a target dose of 25–150 mg of amitriptyline or an equivalent dose of another TCA	
Duloxetine (Cymbalta)	60 mg daily	DPN
Gabapentin (Neurontin)	Initially, 300 mg three times daily up to a maximum of 3600 mg daily, in divided doses[a]	PHN
Pregabalin (Lyrica)	DPN: Initially, 50 mg three times daily; may be increased to 100 mg three times daily within 1 week based on efficacy and tolerability[a] PHN: Initially 75 mg twice daily or 50 mg three times daily; may be increased to 100 mg three times daily within 1 week based on efficacy and tolerability[a]	DPN and PHN
Lidocaine 5% (Lidoderm patch)	Up to three patches may be applied directly over the painful site once daily; patches are applied using a regimen of 12 hours on and 12 hours off	PHN

[a]Dosing for creatinine clearance of 60 mL/minute or greater.
DPN, diabetic peripheral neuropathy; PHN, post-herpetic neuralgia; TCA, tricyclic antidepressant.

A stepwise approach is suggested for managing the patient with neuropathic pain, beginning with the least invasive effective therapeutic choice and proceeding to the rational use of multiple drug regimens. To guide the choice of pharmacologic agents, patients may be identified as candidates for AEDs, TCAs, or opioids based on the presence of peripheral or central nerve pain and description of symptoms (Fig. 30–2). Choice of agent may also depend on dosing frequency and comorbidities. Data on combination therapy are lacking, and the use of combined treatment is empirical based on additive therapeutic benefit. Scheduled medication regimens instead of "as needed" dosing should be employed when treating chronic pain, and the effectiveness of therapy should be reassessed regularly. If patients are managed on a multiple drug regimen and changes are indicated, changing only one drug at a time is suggested. Topical agents (e.g., capsaicin) may be added to a regimen to reduce the oral medication load, particularly if adverse effects are a problem or if pain is not relieved.

Complementary and Alternative Medicine

Complementary and alternative medicine (CAM) is a term used to encompass a variety of therapies (e.g., acupuncture, chiropractic, botanical and non-botanical dietary supplements, and homeopathy) not typically taught in medical and allied health schools. Painful conditions are among the most common reasons individuals seek relief from CAM. In a recent survey, neck pain, joint pain, arthritis, and headache were among the top ten reasons for use of CAM, and low back pain ranked the number one reason for CAM therapies. A variety of dietary supplements have been suggested for painful conditions, such as S-adenosylmethionine (SAM-e), ginger, fish oil, feverfew, γ-linoleic acid, glucosamine, and chondroitin. Of these, glucosamine and chondroitin are the most popular and have the most evidence of efficacy. Glucosamine in doses of 1500 mg/day is effective in reducing pain of osteoarthritis by repair of cartilage and is recommended by the American Pain Society.

OUTCOME EVALUATION

Individualize treatment goals at the beginning of treatment. Utilize information obtained during the pain interview to create goals that are consistent with the patient's expectations. Prevention, reduction, or elimination of pain are important goals for treatment of acute pain. With chronic pain, elimination of pain may not be possible, and goals may focus on improvement or maintenance of functional capacity and quality of life. Thus, for example, pain goals may include "pain scale less than 3," "be able to play a game with grandchildren, " or "be able to knit again." Assess patients periodically, depending on the method of analgesia and pain condition, for achievement of pain goals. Evaluate the patient for the presence of adverse drug reactions, drug allergies, and drug interactions.



Patient Care and Monitoring

1. Identify the source of pain.
2. Assess the level of pain using a pain intensity scale.
3. Base the initial choice of analgesic on the severity and type of pain, as well as on the patient's medical condition and concurrent medications.
4. Use the least potent oral analgesic that provides adequate pain relief and causes the fewest side effects.
5. Titrate the dose to one that achieves an adequate level of pain control.
6. Use a dosing schedule versus as-needed dosing.
7. Assess the patient for analgesic effectiveness and for side effects at each visit or more frequently, depending on the acuity of the patient's condition.
8. Avoid excessive sedation.
9. Adjust the route of administration if the patient is unable to take oral medications.
10. Use equianalgesic doses as a guide when switching opioids.

ABBREVIATIONS

AED:	Antiepileptic drug
AGS:	American Geriatrics Society
AHRQ:	Agency for Healthcare Research and Quality
AIDS:	acquired immunodeficiency syndrome
AMPA:	α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid
APAP:	acetaminophen
APS:	American Pain Society
ASA:	American Society of Anesthesiologists
CAM:	complementary and alternative therapy
CNS:	central nervous system
COX:	cyclooxygenase
CRPS:	complex regional pain syndrome
CYP:	cytochrome P-450 isoenzyme
DPN:	diabetic peripheral neuropathy
FDA:	Food and Drug Administration
GABA:	γ-aminobutyric acid
GI:	gastrointestinal
HIV:	human immunodeficiency virus
IASP:	International Association for the Study of Pain
IM:	intramuscular
IV:	intravenous
JCAHO:	Joint Commission on Accreditation of Healthcare Organizations
NIOSH:	National Institute for Occupational Safety and Health
NMDA:	N-methyl-D-aspartate
NSAID:	non-steroidal anti-inflammatory drug
PAINAD:	Pain Assessment in Advanced Dementia (tool)

PCA:	patient-controlled analgesia
PHN:	postherpetic neuralgia
PO:	oral
PQRST:	Palliative/precipitating, Quality, Radiation, Severity, and Time
SAM-e:	S-adenosylmethionine
SNRI:	serotonin-norepinephrine reuptake inhibitor
SSRI:	selective serotonin reuptake inhibitor
TCA:	tricyclic antidepressant
TENS:	transcutaneous electrical nerve stimulation
VAS:	visual analog scale
VHA:	Veterans Health Administration
WHO:	World Health Organization

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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31 HEADACHE

Leigh Ann Ross and Brendan S. Ross



LEARNING OBJECTIVES

UPON COMPLETION OF THE CHAPTER, THE READER WILL BE ABLE TO:

1. Differentiate among types of headaches based on symptoms and signs.
2. List underlying causes and precipitating factors of different types of headache disorders.
3. Recommend appropriate nonpharmacologic measures for headache treatment and prevention.
4. Based on patient-specific data, determine when pharmacologic therapy is indicated for headache.
5. Propose individualized pharmacologic treatment regimens for the acute and chronic management of headache syndromes.
6. Construct therapeutic and adverse-effect monitoring plans for patients with headache.
7. Discuss pertinent patient education points for patients with headache disorders.

KEY CONCEPTS

❶ Headache may be a primary, or a secondary disorder due to an underlying medical condition.
❷ Primary headaches are classified as migraine, tension-type, or cluster and other trigeminal autonomic cephalalgias.
❸ The pain experienced with headache is likely due to overactivity in the trigeminovascular system of the brain.
❹ Migraine is further classified as migraine with aura and migraine without aura.
❺ The short-term goal of headache therapy is pain relief and a return to normal activities.
❻ The long-term goal of therapy is the prevention of headache recurrence.
❼ Pharmacologic treatment of acute headache should be started early to improve the response to therapy.
❽ Prophylaxis is indicated if headaches are frequent or severe, lead to significant disability, or require the use of pain-relieving medications two or more times per week.
❾ Regimens for headache disorders should be individualized based on the pattern of occurrence, response to therapy, medication tolerability, and comorbid medical conditions.

Headaches are common and have a significant impact on quality of life. ❶ *They can be classified as primary or secondary, causally related to an underlying medical disorder.* Primary headaches are more common and will be the focus of this chapter. Patients may seek evaluation of headache from a variety of health care providers. Therefore, all clinicians must be familiar with the types of headache, their diagnostic criteria, red flags indicating need for urgent intervention or specialist referral, and nonpharmacologic and pharmacologic options for treatment. ❷ *The International Headache Society (IHS) classifies primary headaches as migraine, tension-type, or cluster and other trigeminal autonomic cephalalgias.*[1] Tension-type headaches appear to be more common than migraine, and both are more common in women than in men. Cluster is a less common chronic headache syndrome that affects predominantly men.

EPIDEMIOLOGY OF HEADACHE DISORDERS

Migraine Headache

Migraine is a primary headache disorder that is estimated to affect 10% to 15% of adults in the United States.[2] Less than one-half of headaches meeting the diagnostic criteria for migraine are appropriately diagnosed. Migraine prevalence depends on age and gender. In children less than 12 years of age, migraines are more prevalent in males. After age 12, this

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prevalence shifts markedly to women. The evolution in this gender difference is brought on by the hormonal changes of **menarche**.[3] Onset typically occurs between the ages of 10 and 30 years, but the prevalence is highest in the age range of 35 to 45 years.[4] Migraines significantly impact patient function, with over one-half of sufferers reporting severe disability requiring bed rest during an attack. The economic burden of migraine due to direct and indirect costs is substantial. Migraines are the leading cause of employee absenteeism and decreased workplace productivity.[5]

Tension-Type Headache

Tension-type headache (TTH) is the most common primary headache disorder. It is often underrepresented in clinical practice, as many patients do not present for care.[6] The term "tension-type headache" is used to describe all headache syndromes in which muscle contraction is the most significant factor in the pathogenesis of pain. The 1-year prevalence of TTH in the population ranges from 30% to 90%.[6] It is more common in adult females. Environmental factors, as opposed to genetic predisposition, play a more central role in their development. Tension-type headaches can be further divided into episodic or chronic; the mean frequency of attacks is 3 days per month in episodic disorders, and chronic TTH is defined as 15 or more attacks in a 1-month period.[7] The estimated prevalence of chronic TTH is less than 5%.[6] Some researchers believe that chronic TTHs represent a continuum of headache severity with migraine headache.[8] When severe headaches are difficult to differentiate clinically, treatment should initially target TTH.

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

Cluster headache disorders are the most uncommon and severe primary headache syndromes.[9] The estimated point prevalence is less than 1%. Unlike migraine and TTH, cluster headaches occur more frequently in men. Onset commonly occurs prior to age 30.[6] A genetic predisposition seems apparent, although affected individuals often provide a history of tobacco use and alcohol abuse.[6] Attacks consist of debilitating, unilateral head pains that occur in series lasting up to months at a time, but that remit over months to years between occurrences. In rare instances, cluster headache can be a chronic disorder without remissions.[4]

ETIOLOGY AND PATHOPHYSIOLOGY OF HEADACHE DISORDERS

Migraine Headache

The mechanism by which headache pain occurs in **migraineurs** is not confirmed, but competing pathoetiologic theories exist: tissue pain generated by vascular reactivity or neuronal imbalance accompanied by **trigeminovascular** system overactivity.[10] The vascular hypothesis suggests that intracerebral vasoconstriction leads to neural ischemia and is followed by reflex extracranial vasodilation and pain. Recent **neuroimaging** evidence and the effectiveness of medications with no vascular properties do not support this theory, and ischemia alone is no longer accepted as the primary cause of migraine distress.[6] A neuronal etiology has emerged as the leading mechanism of the development of migraine.[11] Depressed neuronal electrical activity spreads across the brain, which produces transitory neural dysfunction.[12] ❸ *The pain experienced with headache is likely due to compensatory overactivity in the trigeminovascular system of the brain.* Activation of trigeminal sensory nerves leads to the release of vasoactive peptides [e.g., calcitonin gene-related peptide (CGRP), neurokinin A, and substance P] that produce a sterile inflammatory response around vascular structures in the meninges of the brain, which leads to pain.[11] Continued sensitization of central nervous system sensory neurons can potentiate and intensify headache pain as an attack progresses.[12] Bioamine pathways projecting from the brain stem regulate activity within the trigeminovascular system. Thus, the pathogenesis of migraine may be due to an imbalance in the modulation of nociceptors and blood vessel tone by serotonin and norepinephrine neurons.[13]



Patient Encounter, Part 1

GC, a 28-year-old woman, complains of a "terrible headache that won't go away." She describes the pain as "on one side and throbbing." The pain began yesterday morning and caused her to leave work. She reports a history of similar headaches since the age of 16, but none that lasted this long. In the past, her headaches were relieved with the use of over-the-counter non-steroidal anti-inflammatory drugs (NSAIDs). She often has to take analgesics multiple times per week.

- What type of headache is the patient most likely experiencing?
- What characteristics of the headache support this diagnosis?
- What are possible causes or triggers of headache in this patient?
- What additional information is needed to formulate a treatment plan?

Tension-Type Headaches

The pathophysiologic mechanisms of TTH are not clearly understood. The pain is thought to originate in the myofascial tissues of the head, but central brain processing is believed to be an important modulator of pain perception.[14]

Chronic TTH syndromes may evolve from recurrent episodic headaches as central nociception becomes sensitized.[15]

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

Cluster headache is one of a group of disorders referred to as trigeminal autonomic **cephalalgias**.[16] The **autonomic** dysfunction is characterized by sympathetic underactivity and parasympathetic activation. Similar to migraine, the pain of a cluster headache is believed to be the result of vasoactive peptide release and neurogenic inflammation. The exact cause of trigeminal activation is not clear.[9] A leading hypothesis is that hypothalamic dysfunction, occasioned by diurnal or seasonal changes in neurohumoral balance, are responsible for headache periodicity.[6] Serotonin affects neuronal activity in the hypothalamus and trigeminal system and may play a role in the pathophysiology of cluster headache. The precipitation of cluster headache by high altitude exposure also implicates hypoxemia in the pathogenesis of trigeminal autonomic cephalalgias.[17]

CLINICAL PRESENTATION OF HEADACHES

Migraine Headache

Migraine presents as a recurrent headache that is severe enough to interfere with daily functioning. ❹ *Migraine headaches are classified as migraine with aura and migraine without aura.*[6] The correlating terms of "classic" and "common" migraine are no longer employed. Aura is defined as a transient focal neurologic symptom, which can be positive or negative, and can occur prior to or during an attack.[18] Examples of positive symptoms include the visual perception of flickering lights, spots, or wavy lines; whereas a partial loss of vision is a classic negative symptom of an aura. The International Classification of Headache Disorders (ICHD) outlines diagnostic criteria that differentiate migraine with and without aura.[6] The pain of a migraine headache is typically described as moderate to severe, throbbing, unilateral, and retro-orbital in location. The pain is accompanied by nausea, sensitivity to light and sound, and difficulty concentrating.[19] Untreated migraines can last from 4 to



Patient Encounter: Part 2: Medical History, Physical Exam and Diagnostic Tests

Further evaluation of GC reveals the following:

Past Medical History
- Mild persistent asthma
- Gastroesophageal reflux disease (GERD)
- Generalized anxiety disorder

Family History
- Father living, age 58 years; hypertension, diabetes mellitus, dyslipidemia
- Mother living, age 57 years; chronic daily "sick" headaches
- No siblings
- Paternal grandparents died at ages 58 and 65 years, both of ischemic stroke
- Maternal grandparents, living, ages 73 and 84; hypertension, osteoarthritis

Social History
- Married
- Employed as an account officer in a local bank
- No tobacco use, "social" alcohol intake (1 to 2 glasses of wine on weekends), drinks 3 to 4 caffeinated beverages per day

Medication Profile
- Advair 250/50 mg, 1 inhalation twice daily
- Albuterol 2 inhalations prn for bronchospasm
- Omeprazole 20 mg PO daily
- Sertraline 150 mg PO daily
- Combination ethinyl estradiol/norgestimate oral contraceptive
- Naproxen sodium 220 mg, 2 PO twice daily prn for headache

Review of Systems
- Headache, severe in intensity
- Sensitivity to light
- No chest pain or palpitations
- No shortness of breath or wheezing
- Nauseated, anorectic
- Dizzy, difficulty concentrating

Physical Exam
VS: Blood pressure 138/82 mm Hg, pulse 88 beats per minute, respiratory rate 16/minute, temperature 37.0°C (98.6°F), oral
HEENT: No papilledema, no neck stiffness
CV: RRR, normal S_1, S_2, no murmur, rub, or gallop
Chest: CTA
Abdomen: Benign, bowel sounds positive
Neurologic: Non-focal

Labs
CBC and chemistry panel within normal limits

- What is your assessment of this patient's condition?
- What medical comorbidities or drug therapies may be contributing to her distress?
- Identify treatment goals for this patient.
- What nonpharmacologic options are needed at present, and what options are appropriate in the long term for this patient?
- What pharmacologic therapy would you recommend for this patient in the acute setting?
- Does this patient require long-term pharmacologic prophylaxis against recurrent headaches?

72 hours. Migraines occurring 15 days per month or for 3 months or longer, without the overuse of analgesic medications, are classified as chronic migraines.[6] Severe and debilitating migraine pain lasting greater than 72 hours is termed status migrainosus.[19] Even in the absence of **neurologic focality**, brain imaging is mandated in patients with frequent, severe, and prolonged attacks or headaches that are atypical for a migraineur's stereotyped presentation.[20]

Tension-Type Headache

Tension-type headache pain differs from migraine pain in that it is usually reported to be mild to moderate, non-pulsating, and bilateral.[6] The pain is described by sufferers as a bandlike tightness or pressure around the head. No transient neurologic deficits are noted, and systemic symptoms are rare.[4] Tension-type headaches infrequently disrupt normal activity. Muscle palpation in the **fronto-temporal** and **parieto-occipital** may identify localized tender points.[4] Neuroimaging and laboratory testing are unrevealing, and they are unnecessary if the presentation and clinical history are classic for TTHs.

Cluster Headache

Pain associated with cluster headache differs from migraine and TTH in that it is severe, intermittent, and short in duration.[6] Headaches typically occur at night, but attacks may occur multiple times per day.[9] The pain is usually unilateral, but unlike migraine it is not described as pulsatile.[6] Aura is not a feature, and pain intensity peaks early after onset and may persist for hours.[6] The headache is described as explosive and excruciating. A constellation of features ascribed to parasympathetic overactivity can be seen, such as ipsilateral conjunctival injection, lacrimation, rhinorrhea, and sweating.[9] Unlike migraineurs, cluster headache disorder patients tend to become excited and restless during attacks, rather than seeking quiet and solitude.[16]



Clinical Presentation and Diagnosis of Migraine without Aura

Patients experiencing migraine without aura display the following headache symptoms and characteristics:

Two or more of the following present:

1. Pain interrupts or worsens with physical activity
2. **Unilateral** pain
3. Pulsating pain
4. Moderate to severe pain intensity

Two or more of the following present during headache:

1. Nausea
2. Vomiting
3. **Photophobia**
4. **Phonophobia**
5. **Osmophobia**

Duration: 4 to 72 hours (treated or not treated)
Criteria for diagnosis: Five or more attacks fulfilling the above criteria are necessary for diagnosis
Laboratory assessments that may be helpful in excluding medical comorbidities: Complete blood cell count (CBC), chemistry panel, thyroid function tests, erythrocyte sedimentation rate (ESR)



Clinical Presentation and Diagnosis of Migraine with Aura

Patients experiencing migraine with aura may display the following headache symptoms and characteristics:

One or more of the following present with no motor weakness:

1. Visual symptoms (positive and/or negative; reversible)
2. Sensory symptoms (positive and/or negative; reversible)
3. Dysphasic speech (reversible)
4. Moderate or severe pain intensity

Two or more of the following present:

1. Homonymous visual symptoms and/or unilateral sensory symptoms
2. One aura symptom develops at least 5 minutes prior and/or a second aura symptom develops 5 minutes or more after headache
3. Duration of each symptom 4 to 60 minutes

Criteria for diagnosis: Two or more attacks fulfilling the above criteria are necessary for diagnosis



Clinical Presentation and Diagnosis of Tension-Type Headache

Patients experiencing tension-type headache may display the following headache symptoms and characteristics:

Two or more of the following present:

1. Bilateral pain
2. Non-pulsating pain
3. Mild or moderate pain intensity

Both of the following present:

1. No nausea or vomiting (anorexia possible)
2. Either photophobia or phonophobia (not both)

Duration: 30 minutes to 7 days
Criteria for diagnosis: Ten or more attacks fulfilling the above criteria occurring on average less than 1 day per month are necessary for diagnosis



Clinical Presentation and Diagnosis of Cluster Headache

Patients experiencing cluster headache may display the following headache symptoms and characteristics:

1. Unilateral pain
2. **Orbital**, **supraorbital**, or temporal pain
3. Sharp and stabbing pain

One or more of the following present:

1. Conjunctival injection and/or lacrimation
2. Nasal congestion and/or **rhinorrhea**
3. Eyelid edema

Duration of pain: 2 seconds to 10 minutes
Frequency of attacks: One or more per day more than half of the time
Criteria for diagnosis: Twenty or more attacks fulfilling the above criteria are necessary for diagnosis

TREATMENT OF HEADACHE DISORDERS

Desired Outcomes

❺ *The primary short-term goal of migraine treatment is to achieve rapid pain relief that allows the patient to resume normal activities.*[21] ❻ *The long-term goal of therapy is prevention of headache recurrence and diminution of headache severity. Similarly, the goal of TTH is to lessen headache pain, while the long-term goal is to avoid analgesic dependence.*[22] *The short-term goal in cluster headache therapy is to achieve rapid pain relief.* Prophylactic therapy may be necessary to obtain the intermediate-term outcome of reducing the frequency and severity of headaches within a periodic cluster series, as well as to achieve the long-term goal of delaying or eliminating recurrent periods.[23]

General Approach to Treatment

The most important goal of acute headache management is pain relief. The primary pharmacologic agents used in the acute setting include analgesics and serotonin receptor agonists (triptans).[24] Despite available pharmacologic therapy, most headache patients are not treated adequately and rely on over-the-counter products for pain relief.[25] ❼ *Pharmacologic treatment of acute headache should be started early to abort the intensification of pain and to improve symptomatic response to therapy.* The long-term management of headache syndromes focuses on lifestyle modification and other nonpharmacologic therapeutic options, but if the headaches are severe and frequent, then prophylactic pharmacologic therapy is needed.[26] Several so-called "red flags" have been identified that, if present, warrant urgent physician referral and further diagnostic evaluation (Table 31–1).

TABLE 31–1. Headache Red Flags That, if Present, Warrant Urgent Further Evaluation

New onset, sudden, and/or severe
Onset after 40 years of age
Stereotyped pattern worsens
Systemic signs (e.g., fever, weight loss, accelerated hypertension)
Focal neurologic symptoms (i.e., other than typical visual or sensory aura)
Papilledema
Cough-, exertion-, or Valsalva-triggered headache
Pregnancy or postpartum
Patients with cancer, human immunodeficiency virus, and other infectious and immunodeficiency disorders
Seizures

Nonpharmacologic Therapy

Patient education is key to the successful management of headache disorders. Recording headache frequency, duration, and severity in a "headache diary" provides useful information for the patient regarding headache precipitants and insight for the clinician in selecting appropriate management strategies.[27] To prevent future occurrences, exposure to headache triggers (Table 31–2) should be limited. In the acute setting, environmental control may be able to abort a migraine attack. Many patients benefit from resting in a dark, quiet area.[28] Behavioral interventions, such as biofeedback, relaxation training, and cognitive-behavioral therapy, are effective and can be recommended for headache prevention.[17] Tension-type headaches may also be managed through stress management training.[17] Acupuncture has yielded inconsistent benefits in clinical trials.[22] Cluster headache patients should be advised to moderate alcohol use and curtail tobacco abuse.[23] Emotional distress may compound headache pain through the outward displacement of inner conflicts into somatization. Psychological interventions are urged in such instances, and they should be considered in all headache sufferers resistant to standard medication treatments.[29] All such non-prescription therapies may be useful in augmenting pharmacologic response.

Pharmacologic Therapy

Migraine

Analgesics such as NSAIDs and opioids are the initial pharmacologic option for the acute management of migraine headache. If these prove to be ineffective, then migraine-specific medications, such as triptans, are administered.[30] Early, abortive treatment should be the rule. If orally administered medications are selected, then appropriate larger doses than otherwise needed to produce pain relief are provided due to the enteric stasis and poor drug absorption accompanying migraine attacks.[20] Intranasal, parenteral, and rectal administration can circumvent this complication.

Clinical trial evidence supports many NSAID medications in the acute treatment of migraines with and without aura.[30] The currently marketed cyclooxygenase-2 (COX-2) selective

TABLE 31–2. Migraine Triggers

Behavioral
Fatigue
Menstruation or menopause
Sleep excess or deficit
Stress
Vigorous physical activity
Environmental
Flickering lights
High altitude
Loud noises
Strong smells
Tobacco smoke
Weather changes
Food
Alcohol
Caffeine intake or withdrawal
Chocolate
Citrus fruits, bananas, figs, raisins
Dairy products
Fermented or pickled products
Food containing:
Monosodium glutamate (Asian food, seasoned salt)
Nitrites (processed meats)
Saccharin or aspartame (diet soda or diet food)
Sulfites (shrimp)
Tyramine (cheese, wine, organ meats)
Yeast (breads)
Medications
Cimetidine
Estrogen or oral contraceptives
Indomethacin
Nifedipine
Nitrates
Reserpine
Theophylline
Withdrawal due to overuse of analgesics, benzodiazepines, decongestants, or ergotamines

drugs are not clearly supported for migraine use, but are likely acceptable. Acetaminophen alone, or in proprietary combinations with aspirin, opioids, caffeine, or the barbiturate butalbital are also effective.[28] Although deemed to have a benign adverse-effect profile on gastric mucosal integrity and renal blood flow, overwhelming clinical experience supports the observation that the overuse of acetaminophen may lead to tolerance or dependence clinically manifested as acute withdrawal headaches.[31] These so-called rebound headaches are the result of poor attention to prevention therapies, and thus chronic use of daily analgesics.[32]

The triptans are considered specific therapies in that they target the pathophysiology underlying migraine.[33] They abort headache through beneficial effects on neuronal imbalances.[11] Triptans inhibit neurotransmission in the trigeminal complex and activate serotonin 1b/1d pathways that modulate nociception in the brain stem. They also decrease the release of vasoactive peptides leading to vascular reactivity and pain.[34] Triptans are a welcome addition to the therapeutic armamentarium in that they are available in intranasal, subcutaneous, and oral dosage forms. The marketed agents differ in their dosing and pharmacokinetic properties, but all are effective treatments to abort or diminish migraine headache pain (Table 31–3).[35] Patient response can be variable. If a patient does not respond to one agent, then another is selected before labeling a patient triptan-unresponsive.[36] The initial severity of pain correlates with response, thus, administration should be prompt. Relief is usually experienced within 2 to 4 hours. Treatment delay may lead to decreased analgesia through the development of refractory central pain sensitization. Efficacy tends to be dose-related, though adverse effects are less so.[37] The most common side effects are a sensation of warmth, dizziness, chest fullness, and nausea. Rarely, ischemic vascular events may be precipitated by the vasoconstrictive nature of these drugs.[34] An initial dose under direct practitioner supervision is indicated for patients presumed at cardiovascular risk. Triptans are avoided in patients experiencing migraine associated with neurologic focality, previous stroke, poorly controlled hypertension, or unstable angina. Triptans are relatively contraindicated for routine use in pregnancy.[30] Triptans should not be used with concurrent ergotamine administration.[34]

Ergotamine derivatives produce salutary effects on serotonin receptors similarly to triptans. They also impact adrenergic and dopaminergic receptors. Ergotamine tartrate and dihydroergotamine are the most commonly employed agents.[20] The latter is not available in an oral dosage form. Analgesic onset is within 4 hours, though additional dosing is required if an acceptable response is not appreciated. When dosed parenterally, these drugs are usually provided with an antiemetic, due to their potential to worsen the nausea associated with migraine. Metoclopramide and chlorpromazine are the drugs of choice. Intranasal dihydroergotamine can be self-administered to abort an attack.[20] The outpatient use of subcutaneous ergotamines is limited by the lack of a prefilled syringe form. The same cautions as those for triptans apply to ergot use in patients at risk for vascular events.

The choice of initial therapy for acute migraine attacks is a subject of debate among specialists.[38] Some believe that nonspecific analgesics should be used first-line, while others believe migraine-specific drugs should be the choice for patients with severe pain or a history of significant disability. A stepped-care approach within attacks from less to more specific drugs is usually recommended.[39] Once a history of headache refractory to common analgesics is established, triptans should be utilized as initial therapy. In patients who present to the hospital with intractable pain, intravenous metoclopramide supplemented with dihydroergotamine may be needed. Oral medications in this setting are not utilized, as nausea and vomiting limit their bioavailability. Migraineurs with frequent and severe attacks are candidates for prophylactic treatment.

Tension-Type Headache

Most individuals who experience episodic TTHs will not seek medical attention.[22] Instead, they will find relief with the use of

TABLE 31–3. Comparison of Serotonin Receptor Agonists (Triptans)[59–65]

Medication (Brand Name)	Dosage Forms	Strength (mg)	Usual Dosage (mg)	May Repeat In	Potential Drug Interactions
Almotriptan (Axert)	Oral tablets	6.25, 12.5	6.25–12.5		Ergot derivatives
Eletriptan (Relpax)	Oral tablets	20, 40	20–40		Substrate: CYP3A4, CYP2D6; ergot derivatives
Frovatriptan (Frova)	Oral tablets	2.5	2–5	2 hours	Substrate: CYP1A2; ergot derivatives
Naratriptan (Amerge)	Oral tablets	1, 2.5	2.5	4 hours	Substrate: CYP450 (various); ergot derivatives
Rizatriptan (Maxalt and Maxalt MLT)	Oral tablets, disintegrating tablets	5, 10	5–10	2 hours	Ergot derivatives; MAO_A inhibitors
Sumatriptan (Imitrex)	Subcutaneous injection	6	6	1 hour	Ergot derivatives; MAO_A inhibitors
	Oral tablets	25, 50, 100	50	2 hours	
	Nasal spray	5, 20	5–20	2 hours	
Zolmitriptan (Zomig and Zomig-ZMT)	Oral tablets, disintegrating tablets	2.5, 5	2.5	2 hours	Substrate: CYP1A2; ergot derivatives; MAO_A inhibitors
	Nasal spray	5	5	2 hours	

CYP, cytochrome P-450 isoenzyme; MAO, monoamine oxidase.
Data from references 59–65.

widely available over-the-counter analgesics. Acetaminophen products and NSAIDs are commonly utilized. An individual patient may benefit from topical analgesics (e.g., ice packs) or physical manipulation (e.g., massage) during an acute attack, but the evidence supporting nonpharmacologic therapies is inconsistent.[6] Relaxation techniques can often reduce headache frequency and severity. When pain is unrelieved, prescription-strength NSAID use is required or the combination of acetaminophen with an opioid analgesic may be necessary. The frequency of use of these more potent analgesics should be limited to prevent dependency. Use for more than 2 days per week suggests the need for prophylactic therapy.[40] In those sufferers who do not seek expedient medical attention, but rely instead on the frequent use of unprescribed analgesics, medication-overuse headache may supervene. This chronic daily headache syndrome requires physician referral to desensitize patient-initiated analgesic tolerance and dependence.[41]

Cluster Headache

Cluster headache responds to many of the same treatment modalities used in acute migraine; however, initial prophylactic therapy is required to limit the frequency of recurrent headaches within a periodic series. A novel therapy specific to cluster headaches is the administration of high-flow-rate oxygen: 100% at 5 to 10 L/minute by non-rebreather facemask for approximately 15 minutes.[42] If pain is not aborted, then retreatment is indicated. No side effects are seen with short-term oxygen use. If oxygen therapy is not wholly effective, then pharmaceuticals are useful as adjunctive therapy. They are also used when supplemental oxygen is not readily available. The triptan class agents are safe and effective. Intranasal or subcutaneous sumitriptan has demonstrated efficacy in decreasing cluster headache pain.[43] Oral triptans are also effective, but their delayed onset of action may limit their applicability in acute cluster headache treatment.[44] Cluster headache pain is rapid in onset, achieves peak intensity quickly, and is of short duration. Oral agents may have utility in limiting the recurrence of cluster attacks. Intranasal, intramuscular, or intravenous ergotamine agents are an alternative to triptan use.[6] Repeated dosing may break a cluster series. For those patients in whom triptans and ergotamine derivatives are contraindicated due to ischemic vascular disease, octreotide may be helpful to relieve pain.[45] Octreotide is a somatostatin analogue that has a shorter half-life, and it is available for subcutaneous administration. Unlike the other abortive agents, it has no vasoconstrictive effects. The most prominent treatment emergent adverse effect with octreotide use is gastrointestinal upset. Glucocorticoids, provided intravenously and later tapered orally, are also an effective option when cluster headache attacks are not satisfactorily controlled.[9]

Pharmacologic Therapy for Headache Prophylaxis

❽ *Prophylaxis for headache disorders is indicated if significant disability occurs or pain-relieving medications are used two or more times per week.*

Migraine Prophylaxis

Migraine headaches that are severe, frequent, or lead to significant disability will require long-term medication therapy. Prophylactic therapy is also recommended for migraines associated with neurologic focality, as it may prevent permanent sequelae. Although multiple medication classes have garnered Food and Drug Administration (FDA)-labeling for migraine prevention, there is no consensus on the best initial therapy (Table 31–4). The choice of pharmacologic agent should be individually tailored to patient tolerability and medical comorbidities.

The β-blockers propranolol and timolol are FDA-approved for migraine prophylaxis, but other drugs in the class are also as effective.[46] Cautious dosage titration is advised for those patients who do not have other indications for β-blocker use. Rizatriptan interacts with propranolol and thus dosages must be titrated downward, or another triptan chosen for abortive therapy.[36] Comorbid reactive airway disease is a relative contraindication to β-blocker prophylaxis, and patients with cardiac conduction disturbances should be closely monitored. Calcium channel antagonists are often used when patients cannot tolerate β-blockers. They are purported to beneficially impact aura as well as pain. The different calcium channel blockers are variably effective, and none carries an FDA indication. Moreover, even in responsive patients, tachyphylaxis may develop. Recently, renin-angiotensin antagonists have been noted to decrease headache frequency and severity in migraine sufferers.[47] Consensus recommendations for hypertension treatment often advocate multidrug regimens to achieve tight blood pressure control[48]; combination therapy with the agents noted above are ideal for migraineurs with comorbid hypertension.

Low-dose amitriptyline or other tricyclic antidepressants (TCAs) are also of proven efficacy in migraine prevention.[27] Due to sedation, these medications are commonly administered at night. The use of later-generation tricyclic medications (e.g., nortriptyline) or heterocyclic compounds (e.g., trazodone) decreases the dose-limiting adverse effects of TCAs, especially those attributable to their anticholinergic properties (e.g., dry mouth, constipation, and urinary retention). Whether the various selective serotonin reuptake inhibitors (SSRIs) can yield consistent efficacy in the majority of migraineurs is questionable.[21] Although they affect serotonin balance in the brain, their utility may derive from their beneficial impact on mood and anxiety, rather than through serotonergic effects on migraine generation. Concurrent TCA and triptan administration may rarely precipitate the serotonin syndrome, which presents clinically with confusion, gastrointestinal upset, symptomatic blood pressure changes, and muscle rigidity.[20]

The antiepileptics valproic acid and topiramate are approved for migraine prophylaxis. Gabapentin and lamotrigine are anecdotally reported to be efficacious as well. In patients whose migraine headaches are believed to be related to trigeminal neuralgia, carbamazepine is employed as prevention for both disorders. The precise mechanism of benefit of these agents is unclear, but enhancement of γ-aminobutyric acid (GABA) neuroinhibition and modulation of the neuroexcitatory amino acid glutamate is likely.[49] Divalproex sodium doses are gradually titrated to 1000 mg per day; topiramate is titrated to a maximum of 100 mg twice per day. At these doses, serum drug level monitoring is infrequently needed. These medications are as effective as propranolol at reducing the frequency and severity of migraines and are preferred for prevention in patients intolerant to β-blockers.[50] Topiramate is especially useful in metabolic syndrome, diabetes, and dyslipidemic patients, as it is unlikely to lead to the weight gain often seen with valproic acid use. Patients prescribed topiramate should be advised to stay well hydrated to prevent **dysgeusia**, disordered taste, and more seriously, hyperthermia.

Methysergide is an ergotamine derivative that impacts central serotonin balance.[51] It is reserved for use in migraineurs refractory to other agents, due to its significant adverse-effect profile. As an ergot compound, it is a vasoconstrictor that may worsen vascular dilatory reserves and precipitate cardiovascular events or ischemic stroke in those with

TABLE 31–4. Medications for Prophylaxis of Migraines[66–68]

Medication (Brand Name)	Usual Dosage (mg per day)	Main Adverse Effects
Antiepileptics		
Gabapentin (Neurontin)	1200–2400	Paresthesias, dizziness, fatigue, nausea
Lamotrigine (Lamictal)	50–200	
[a]Topiramate (Topamax)	50–200	
Valproic acid (Depakene)	500–1500	
[a]Divalproex sodium (Depakote)	500–1500	
β-Blockers		
Atenolol (Tenormin)	50–200	Fatigue, exercise intolerance
Metoprolol (Lopressor)	50–200	
Nadolol (Corgard)	20–160	
[a]Propranolol (Inderal)	80–240	
[a]Timolol (Blocadren)	20–30	
Calcium Channel Blockers		
Amlodipine (Norvasc)	2.5–10	Constipation
Verapamil (Calan)	120–320	
Tricyclic Antidepressants		
Amitriptyline (Elavil)	10–150	Weight gain, dry mouth, sedation
Nortriptyline (Pamelor)	10–150	
Ergot Alkaloids		
Ergotamine tartrate (Cafergot)	1	
Methysergide (Sansert)	2–6	
Others		
Hormones (various)	Varies per agent	
Muscle Relaxants (various)	Varies per agent	
Trazodone (Desyrel)	25–150	

[a]FDA-approved for migraine prophylaxis.
Data from references 66–68.

underlying atherosclerotic disease. Inflammatory fibrosis is a rare, but potentially serious, adverse reaction associated with prolonged use of methysergide. **Retroperitoneal fibrosis**, pulmonary fibrosis, or fibrosis in cardiac tissue can occur. Drug withdrawal usually reverses the condition, so treatment should be interrupted for at least a 3-week interval every 6 months. On occasion, cardiac valvular damage can be irreversible.

Tension-Type Headache Prophylaxis

The prevention of chronic TTHs employs the same pharmacologic strategies as for migraine prophylaxis. Tricyclic antidepressants are a mainstay of chronic therapy. The efficacy of serotonergic agents remains in question. Although there is little need for muscle relaxants (e.g., methocarbamol) in the treatment of acute TTH, they are often provided as a preventive intervention.[6] Combination prophylactic therapies may be needed to wean patients from daily analgesic abuse. Stress reduction techniques augmenting pharmacologic therapies may be particularly effective in this setting. The injection of botulinum toxin into cranial muscles has demonstrated prophylactic efficacy for severe TTHs.[41]

Cluster Headache Prophylaxis

The calcium channel blocker verapamil is the mainstay of cluster attack prevention and chronic prophylaxis.[6] Within an attack period, it is dosed at 240 to 360 mg per day. Higher doses may be necessary to stave off recurrent cluster periods. Beneficial effects may be appreciated after 1 week of treatment, but 4 to 6 weeks is usually needed to fully assess response. Adverse effects include smooth muscle relaxation with the subsequent exacerbation of gastroesophageal reflux and the development of constipation. Caution should be exercised in patients with myocardial disease, as verapamil is an **inotropic** and **chronotropic** cardiac depressant. Pharmacokinetic drug-drug interactions must be considered, as verapamil is a potent inhibitor of oxidative metabolism through cytochrome P-450 (CYP) enzyme 3A4. Eletriptan is a CYP3A4 substrate and should not be concurrently administered.[36] Lithium is another effective therapy to reduce headache frequency in a cluster series and to limit recurrences.[9] The dose administered should be individualized to achieve a low-serum concentration (0.4 to 0.8 mEq/L or mmol/L). Dose adjustments in the setting of renal disease and congestive heart failure are required.[6] Lithium is contraindicated in patients concurrently prescribed thiazide diuretics and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Patient persistence with long-term lithium therapy may be hindered by the emergence of tremor, gastrointestinal distress, and lethargy. Verapamil and lithium doses can be lowered when used in combination with ergotamine. If possible, bedtime dosing of these therapies is recommended, given the nocturnal predilection of cluster headache attacks.[16] Methysergide can shorten the course of cluster attacks, but long-term use should be avoided.



Patient Encounter, Part 3: Creating a Care Plan

Based on the information presented, create a care plan for the acute and chronic management of this patient's headache. Your plan should include: (1) a statement of drug-related needs and/or problems, (2) goals of therapy, (3) a patient-specific detailed therapeutic plan, and (4) a plan for clinical follow-up to determine whether goals have been achieved and adverse effects avoided.

SPECIAL POPULATIONS

Migraine Headache in Children and Adolescents

Migraine headaches are common in children, and their prevalence increases in the adolescent years.[2,3] The diagnosis and evaluation of headaches is especially difficult in children, given their decreased ability to articulate symptoms. Treatment presents another challenge to the practitioner, because medications used for headache management in adults have not been fully evaluated for efficacy and safety in children. Consensus panel recommendations identify ibuprofen as effective and acetaminophen as probably effective in the acute treatment of headache in patients over the age of 6.[26] Aspirin use is avoided due to the risk of precipitating **Reye's syndrome**. Antiemetic therapy can be used alone or in combination with analgesics; promethazine is usually prescribed, as it is less prone to cause **extrapyramidal reactions** than other antiemetics. For adolescents over the age of 12, triptans are effective and are beneficial for abortive migraine therapy.[26] Medication prophylaxis for migraines in children and adolescents is understudied. The data are conflicting, and no consensus recommendation for the use of preventive drug therapy exists.[26] Nonpharmacologic interventions and trigger identification and avoidance are advised.

Pregnancy

Headaches are more common in women than in men. Fluctuation in estrogen levels is believed to account for this gender discrepancy.[52] Hence, headaches are common in pregnancy. Tension-type headaches predominate; migraine attacks may increase in frequency, but more usually decrease in frequency during pregnancy.[53] Recommendations for headache care during pregnancy are based on an insufficient evidence base and are largely anecdotal. As headaches are not associated with fetal harm, reflexive pharmacologic therapy should be avoided and drug treatment choices considered carefully. Standard nonpharmacologic therapies are often sufficient. Acetaminophen is safe for the pregnant woman and her fetus.[54] NSAIDs are avoided late in the third trimester to prevent detrimental prostaglandin

alterations leading to premature **ductus arteriosus** closure. Opioids are second-line agents. They are not to be used chronically, as they can lead to dependence in the mother and acute withdrawal in the baby after birth. Centrally-acting antiemetic agents are safe and may be useful as adjunctive agents. Corticosteroids may be needed for intractable headache relief. Prednisone and methylprednisolone are preferred, as they are metabolized in the placenta and do not expose the fetus. In pregnant women with migraine, vasoconstrictive agents such as triptans are relatively contraindicated, even though maternal registry data reveal little **teratogenicity**.[55] Ergot compounds are strictly avoided, as they may precipitate uterine contractions and consequent ischemia leading to hypoxemia in the fetus. Migraine prophylaxis is considered cautiously, as β-blockers and calcium channel antagonists may lead to maternal hypotension and diminished placental blood flow or fetal bradycardia. Antiepileptic drug use in this setting has not been sufficiently studied to allow definitive recommendations.

Some headache disorders are specific to the pregnant state. These include postprocedure headaches and those associated with preeclampsia. The former are the result of dural puncture with cerebrospinal fluid leakage after spinal anesthesia.[56] Puncture headache generally responds to bed rest in the supine position, though analgesics may be needed as well. The latter are seen in the third trimester accompanied by the clinical triad of hypertension, edema, and proteinuria. Preeclamptic headache pain is believed to result from alterations in cerebral blood flow.[57] Headaches experienced in preeclamptic women herald eclampsia, and urgent delivery is indicated. Antihypertensives are administered to prevent intracranial thrombosis or hemorrhage and prophylactic anticonvulsants are provided to prevent eclamptic seizures.

OUTCOME EVALUATION

- Monitor patients for the relief of headache pain and the lack of headache recurrence. Assure that full patient functionality is restored. Note environmental and behavioral triggers; the onset, character, and duration of pain; and associated symptoms and physical findings.
- Assess frequency and severity of headaches to determine the need for prophylactic therapy.
- Monitor patients for adverse effects of abortive therapies used for headache pain relief:
  - Acetaminophen: Monitor patients for analgesic overuse, which may lead to dependence and the precipitation of withdrawal headaches.
  - NSAIDs: Monitor patients for gastrointestinal distress, signs or symptoms of gastrointestinal bleeding, and hypertension and edema that may reflect renal dysfunction. Monitor CBC and serum creatinine as clinically indicated.
  - Opiates: Monitor patients for sedation and depressed cognition. Address constipation with use of stimulant laxatives.
  - Serotonin receptor agonists (triptans): Monitor patients for flushing, palpitations, chest pain, and shortness of breath. Recommend electrocardiography if symptoms persist.
  - Ergotamine derivatives: Monitor cardiovascular complications as for serotonergic agents.
- If prophylactic medications are required, monitor patients for short- and long-term adverse effects:
  - Antiepileptics: Monitor patients for dizziness, fatigue, nausea, and paresthesias. Assess changes in weight at quarterly intervals.
  - β-Blockers: Monitor patients for bradycardia (heart rate less than 60 bpm), symptomatic hypotension (blood pressure less than 90/60 mm Hg), and easy fatigability.
  - Calcium channel blockers: Monitor for cardiovascular effects similarly to β-blockers. If dihydropyridine calcium channel blockers are employed, assess for dependent edema. Consider withdrawal if GERD or constipation responds poorly to therapy.
  - Tricyclic antidepressants: Monitor for change in vision, sedation, dry mouth, gastrointestinal upset, and orthostatic dizziness.



Patient Care and Monitoring

❾ *Regimens for headache disorders should be individualized based on headache type, pattern of occurrence, response to therapy, medication tolerability, and comorbid medical conditions.*

1. Assess the patient complaint to yield a detailed description of headache: precipitating factors; presence or absence of prodromal symptoms; location, intensity, and duration of pain; changes in sensory acuity; and neurologic alterations.
2. Determine if immediate referral for emergency or specialist care is necessary.
3. Obtain a thorough history of non-prescription and prescription drug use and complementary and alternative therapies utilized, as well as identifying medication allergies.
4. Identify the presence of drug-drug interactions that may guide therapeutic decision making in regard to selecting acute and prophylactic headache treatments.
5. Obtain a complete medical and social history, identifying any potential drug-disease interactions or social factors that may influence treatment choices.
6. Obtain a family medical history, focusing on headache or mental health disorders in first-degree relatives.
7. Complete a review of systems and physical examination to identify causes or complications of headache.

(*Continued*)

8. Determine the type of headache disorder and rule out acute complications.
9. Recommend appropriate pharmacologic therapy to abort headache based on type, patient characteristics, current medication profile, and comorbid conditions.
10. Educate the patient on administration, maximum dosage, and anticipated adverse effects of the prescribed medication.
11. Recommend appropriate nonpharmacologic therapy to abort headache and to prevent future headaches.
12. Determine if the patient is a candidate for prophylactic pharmacologic therapy.
13. Recommend appropriate pharmacologic treatment for prevention of future headaches.
14. Assess response to therapy indicated by the absence of pain and a return to normal activities. Assess response to prophylactic therapy by improvements in headache frequency and severity.
15. Instruct the patient to keep a headache diary to identify potential causes of headaches and responses to therapy.
16. Provide the patient specific information regarding actions to take if therapy is ineffective or adverse effects develop.
17. Educate the patient on the importance of adherence to the individualized pharmacologic regimen to prevent headache and to diminish pain upon recurrence.
18. Educate the patient on the warning symptoms and signs of headache complications, and when to seek emergency medical attention.

ABBREVIATIONS

CBC: complete blood cell count
CGRP: calcitonin gene-related peptide
COX-2: cyclooxygenase-2
CTA: clear to auscultation
CYP: cytochrome P-450 isoenzyme system
ESR: erythrocyte sedimentation rate
FDA: Food and Drug Administration
GABA: γ-aminobutyric acid
GERD: gastroesophageal reflux disease
ICHD: International Classification of Headache Disorders
IHS: International Headache Society
MAO_A: Monoamine oxidase type A
NSAID: non-steroidal anti-inflammatory drug
SSRI: selective serotonin reuptake inhibitors
TCA: tricyclic antidepressant
TTH: tension-type headache

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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32 Alzheimer's Disease

Gary M. Levin, Toya M. Bowles, and Megan J. Ehret



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Describe the epidemiology of Alzheimer's disease and its effects on society.
2. Describe the pathophysiology including genetic and environmental factors that may be associated with the disease.
3. Detail the clinical presentation of the typical patient with Alzheimer's disease.
4. Describe the clinical course of the disease and typical patient outcomes.
5. Describe how nonpharmacologic therapy is combined with pharmacologic therapy for patients with Alzheimer's disease.
6. Recognize and recommend treatment options for disease-specific symptoms as well as behavioral/non-cognitive symptoms associated with the disease.
7. Develop an alternative treatment plan for patients with Alzheimer's disease.
8. Educate patients and/or caregivers about the expected outcomes for patients with Alzheimer's disease, and provide contact information for support/advocacy agencies.

Key Concepts

❶ Alzheimer's disease is characterized by progressive cognitive decline including memory loss, disorientation, and impaired judgment and learning.

❷ Pathologic hallmarks of the disease in the brain include **neurofibrillary tangles** and **neuritic plaques** (**senile plaques**) made up of various proteins, which result in a shortage of the neurotransmitter acetylcholine.

❸ A diagnosis can be made only at autopsy; therefore the diagnosis is established following an extensive history and physical examination, and by ruling out other potential causes of dementia.

❹ Treatment is focused on delaying disease progression and preservation of functioning as long as possible.

❺ The current gold standard of treatment for cognitive symptoms includes pharmacologic management with a cholinesterase inhibitor and/or an *N*-methyl-D-aspartate (NMDA) antagonist.

❻ The general approach to treatment of cognitive symptoms includes both pharmacologic and nonpharmacologic management.

❼ Treatment of behavioral symptoms should begin with nonpharmacologic treatments, but may also include antipsychotic agents and/or antidepressants.

❽ Delaying disease progression through pharmacotherapy can reduce the total cost of treating AD and delay nursing home placement.

❶ *Alzheimer's disease (AD) is a non-reversible, progressive dementia manifested by gradual deterioration in cognition and behavioral disturbances.* AD is primarily diagnosed by exclusion of other dementias. There is no single symptom unique to AD; therefore diagnosis relies on a thorough patient history. The exact pathophysiologic mechanism underlying AD is not entirely known, although certain genetic and environmental factors may be associated with the disease. There is currently no cure for AD; however, drug treatment can slow symptom progression over time.

Family members of AD patients are also profoundly affected by the increased dependence of their loved one as the disease progresses. Early education and social support of both the patient and family is also important treatment. The Alzheimer's

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TABLE 32–1. Ten Warning Signs of Alzheimer's Disease

1. Memory loss: more than typical forgetfulness without remembering later
2. Difficulty performing familiar everyday tasks (e.g., preparing a meal and grooming)
3. Problems with language: forgetting simple words or substituting unusual words
4. Disorientation to time and place: may forget where they are and/or how they got there
5. Poor or decreased judgment: dress without regard to weather or falling prey to scam artists
6. Problems with abstract thinking: not just difficulty balancing a checkbook, but forgetting what the numbers represent
7. Misplacing things in unusual places: such as placing an iron in a freezer
8. Changes in mood or behavior: rapid mood swings with no apparent reason why
9. Changes in personality: extreme confusion, suspicion, or fearfulness
10. Loss of initiative: passivity and loss of interest in usual activities

Data from reference 1 with permission.

Association has developed a checklist of common symptoms (Table 32–1).[1]

EPIDEMIOLOGY AND ETIOLOGY

AD is the most common type of dementia, affecting approximately 4.5 million Americans in the year 2000.[2] Table 32–2 lists the different classifications of dementia.[3] This chapter will address only dementia of the Alzheimer's type.

The prevalence of AD increases with age and it is most prevalent in persons age 65 years and older. In the year 2000, it was estimated that there were 4.5 million people in the United States with AD. Of those affected, 7% were 65 to 74 years of age, 53% were between 75 and 84 years of age, and 40% were persons over 85 years of age.[2] It is projected that by the year 2050 there will be a three-fold increase in prevalence yielding potentially 13.4 million AD patients due to a population increase in persons over 65 years of age. Additionally, the cost to society due to rising Medicare spending for AD is projected to increase from $62 billion in 2000 to over $1 trillion in 2050. Furthermore, the costs associated with nursing home care alone are projected to increase from $19 billion in 2000 to $118 billion in 2050 (Fig. 32–1).[4,5] The severity of AD also correlates with increasing age and is classified



Patient Encounter, Part 1

A woman arrives at the clinic with her 80-year-old mother, LB, complaining that her mother is becoming increasingly forgetful and confused with old age. The woman complains that her mother sometimes takes her diabetes and hypertension medications at a frequency greater than that prescribed. This has become more frequent in the last 6 months and the mother has been getting very agitated when her daughter confronts her. The woman asks you for a pill organizer and if any of the over-the-counter drugs claiming to help with memory would help her mother.

- What information is suggestive of AD?
- Does the mother have any risk factors for AD?
- How would you approach and address the daughter's question?

TABLE 32–2. Classification of Dementia

Dementia of the Alzheimer's type (early- or late-onset)
With or without behavioral symptoms
Vascular dementia
Uncomplicated, with delirium, with delusions, and with depressed mood
Dementia due to HIV disease
Dementia due to head trauma
Dementia due to Parkinson's disease
Dementia due to Huntington's disease
Dementia due to Pick's disease
Dementia due to Creutzfeldt-Jakob disease
Dementia due to a specific general medical condition (specify)
Dementia that is substance-induced
Dementia due to multiple etiologies
Dementia not otherwise specified

HIV, human immunodeficiency virus.
Data from reference 3 with permission.

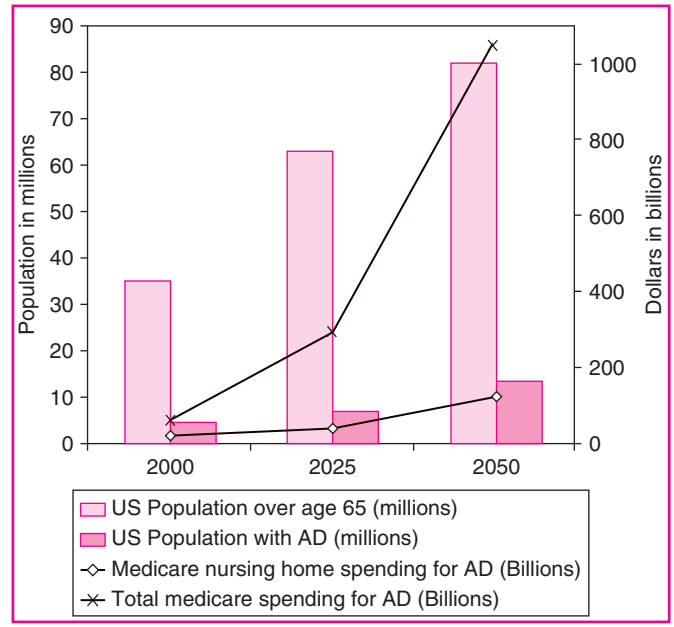


FIGURE 32–1. Projected increases in the population of patients with Alzheimer's disease, Medicare nursing home spending, and total Medicare spending. (Based on data from references 4 and 5.)

as mild, moderate, or severe. Other risk factors associated with AD besides age include family history, female gender, vascular risk factors such as diabetes, hypertension, heart disease, and current smoking.[6,7] However, it is unknown how other factors such as environment contribute and interact with the genetic predisposition for AD.

The mean survival time of persons with AD is reported to be approximately 6 years from the onset of symptoms until death. However, age at diagnosis, severity of AD, and other medical conditions affect survival time.[8] Although AD does not directly cause death, it is associated with an increase in various risk factors which often contribute to death such as senility, sepsis, stroke, pneumonia, dehydration, and decubitus ulcers.

The exact etiology of AD is unknown; however, it has been suggested that genetic factors may contribute to errors in protein synthesis resulting in formation of abnormal proteins involved in the pathogenesis of AD.[9] Early onset, which is defined as AD prior to age 60, accounts for approximately 1% of all AD. This type is usually familial and follows an autosomal dominant pattern in approximately 50% of cases of early-onset AD. Mutations in three genes, presenilin 1 on chromosome 21, **amyloid** precursor protein (APP) on chromosome 21, and presenilin 2 on chromosome 1, lead to an increase in β-A4 peptide fragments of APP which forms neuritic plaques that are the pathologic hallmark of AD.[10]

The genetic basis for the more common late-onset AD appears more complex. Genetic susceptibility is more sporadic and it may be more dependent on environmental factors.[9] The apolipoprotein E (apo E) gene on chromosome 19 has been identified as a strong risk factor for late-onset AD. There are three variants of apo E; however, carriers of two or more of the apo E4 allele have an earlier onset of AD (approximately 6 years earlier) compared with non-carriers.[9] Only 50% of AD patients have the apo E4 allele, thus indicating it is only a susceptibility marker.

PATHOPHYSIOLOGY

❷ *The pathologic hallmarks of the disease in the brain include neurofibrillary tangles and neuritic plaques made up of various proteins, which result in a shortage of the neurotransmitter acetylcholine.* These are primarily located in brain regions involved in learning, memory, and emotional behaviors such as the cerebral cortex, hippocampus, basal forebrain, and amygdala.[11]

Tangles

Neurofibrillary tangles are intracellular and consist of abnormally phosphorylated tau protein which is involved in microtubule assembly. Tangles interfere with neuronal function resulting in cell damage, and their presence has been correlated with the severity of **dementia**.[12] Unfortunately, these tangles are insoluble even after the cell dies, and they cannot be removed once established. The neurons that provide most of the cholinergic innervation to the cortex are most prominently affected.[13] Therefore, prevention is the key to targeted therapy of these tangles.

Plaques

Neuritic or senile plaques are extracellular protein deposits of fibrils and amorphous aggregates of β-amyloid protein.[11] This formed protein is central to the pathogenesis of AD. The β-amyloid protein is present in a non-toxic, soluble form in human brains. In AD, conformational changes occur that render it insoluble and cause it to deposit into amorphous diffuse plaques associated with dystrophic neuritis.[14] Over time, these deposits become compacted into plaques and the β-amyloid protein becomes fibrillar and neurotoxic. Inflammation occurs secondary to clusters of astrocytes and microglia surrounding these plaques.

Acetylcholine

The neurotransmitter acetylcholine (Ach) is responsible for transmitting messages between certain nerve cells in the brain. In AD, the plaques and tangles damage these pathways, leading to a shortage of Ach, resulting in learning and memory impairment.[15] The loss of Ach activity correlates with the severity of AD. The basis of pharmacologic treatment of AD has been to improve cholinergic neurotransmission in the brain. **Acetylcholinesterase** is the enzyme that degrades Ach in the synaptic cleft. Blocking this enzyme leads to an increased level of Ach with a goal of stabilizing neurotransmission.[16] In the United States, the four cholinesterase inhibitors approved for the treatment of AD are tacrine, donepezil, rivastigmine, and galantamine.

Glutamate

Glutamate is the primary excitatory neurotransmitter in the central nervous system (CNS) involved in memory, learning, and neuronal plasticity. It acts by providing information from one brain area to another and affects cognition through facilitation of connections with cholinergic neurons in the cerebral cortex and basal forebrain.[17] In AD, one type of glutamate receptor, *N*-methyl-D-aspartate (NMDA), is less prevalent than normal. There also appears to be overactivation of unregulated glutamate signaling. This results in a rise in calcium ions that induces secondary cascades which lead to neuronal death and an increased production of APP.[16] The increased production of APP is associated with higher rates of plaque development and hyperphosphorylation of tau protein.[18] The drug memantine is a non-competitive NMDA

antagonist which targets this pathophysiologic mechanism.[19] Memantine is presently the only agent in this class that is approved for the treatment of AD.

Cholesterol

Increased cholesterol concentrations have been associated with AD. The cholesterol increases β-amyloid protein synthesis which can lead to plaque formation.[16] Also, the apo E4 allele is thought to be involved in cholesterol metabolism and is associated with higher cholesterol levels.[16]

Estrogen

Estrogen appears to have properties that protect against memory loss associated with normal aging. It has been suggested that estrogen may block β-amyloid protein production and even trigger nerve growth in cholinergic nerve terminals.[20,21] Estrogen is also an antioxidant and helps prevent oxidative cell damage.[20] It is important to note, however, that the Women's Health Initiative Memory Study reported that hormone replacement with either estrogen alone or estrogen plus medroxyprogesterone resulted in negative effects on memory.[22]



Clinical Presentation of Alzheimer's Disease

General

The diagnosis of AD relies on thorough mental status testing and neuropsychological tests, medical and psychiatric history, neurologic exam, interview of caregivers and family members, and laboratory and imaging data to support the diagnosis and exclude other causes.

Signs and Symptoms

- Cognitive: memory loss, problems with language, disorientation to time and place, poor or decreased judgment, problems with learning and abstract thinking, misplacing things
- Non-cognitive: changes in mood or behavior, changes in personality, or loss of initiative
- Functional: difficulty performing familiar tasks

Laboratory Tests

- Magnetic resonance imaging (MRI) or computed tomography (CT) is used to measure changes in brain size and volume and rule out stroke, brain tumor, or a cerebral edema.
- Tests to exclude possible causes of dementia include a depression screen, vitamin B_{12} deficiency, thyroid function tests [thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine], complete blood cell count, and chemistry panel.[21]
- Other diagnostic tests to consider for differential diagnosis: erythrocyte sedimentation rate, urinalysis, toxicology, chest x-ray, heavy metal screen, HIV testing, cerebrospinal fluid (CSF) examination, electroencephalography, and neuropsychological tests such as the Folstein Mini Mental Status Exam.

CLINICAL PRESENTATION AND DIAGNOSIS

❸ *Diagnosing AD relies on a thorough medical and psychological history, mental status testing, and laboratory data to exclude other possible causes. There are no biological markers other than those pathophysiologic changes found at autopsy that can confirm AD.* The American Academy of Neurology has adopted practice guidelines for the diagnosis and management of AD.[23] The diagnostic criteria are based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (Table 32–3)[24] or the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). These diagnostic criteria are 85% to 90% accurate in diagnosing AD.[24]

AD is a progressive disease, which over time affects multiple areas of cognition. The symptoms of AD can be divided into cognitive symptoms, non-cognitive symptoms (i.e., behavioral), and functional symptoms for assessment and treatment purposes. Table 32–4 describes the stages of cognitive decline.[25,26]

TABLE 32–3. Diagnostic Criteria for Alzheimer's Disease Based on DSM-IV-TR

Dementia of the Alzheimer's type
A. The development of multiple cognitive deficits manifested by both
  (1) memory impairment (impaired ability to learn new information or to recall previously learned information)
  (2) one or more of the following cognitive disturbances:
    (a) aphasia (language disturbance)
    (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
    (c) agnosia (failure to recognize or identify objects despite intact sensory function)
    (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)
B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
C. The course is characterized by gradual onset and continuing cognitive decline.
D. The cognitive deficits in criteria A1 and A2 are not due to any of the following:
  (1) other central nervous system conditions that cause progressive deficits in memory and cognition
  (2) systemic conditions that are known to cause dementia
  (3) substance-induced conditions
E. The deficits do not occur exclusively during the course of delirium.
F. The disturbance is not better accounted for by another **Axis I** disorder.

Data from American Psychiatric Association with permission.[3]

TABLE 32–4. Stages of Cognitive Decline

Stage	Clinical Attribute	Pathology and Clinical Picture
Stage 1	No cognitive impairment	No memory problems and no impairment is evident to a health care professional.
Stage 2	Very mild decline	Lapses of memory; forgetting familiar names or locations of personal objects (e.g., keys or glasses); problems not evident to friends, family, coworkers, or health care professionals.
Stage 3	Mild cognitive decline	Friends, family, and coworkers begin to notice deficiencies; problems with names or words become evident; performance issues become evident; retention of reading material declines; losing valuable objects; decline in planning and organizational abilities.
Stage 4	Moderate cognitive decline (mild or early-stage AD)	Medical interview detects clear-cut deficiencies; decreased knowledge of current events; impaired ability to perform difficult mathematical problems (e.g., serial 7's); decreased ability to perform complex tasks (managing finances); decreased recall of personal history; individuals may become withdrawn and subdued.
Stage 5	Moderately severe cognitive decline (moderate AD)	Major gaps in memory appear and assistance with day-to-day activities is necessary; inability to recall details such as current address and telephone number may begin; difficulty with orientation to place and time; less challenging mathematical problems may become difficult (e.g., serial 4's or 2's); can still recall their own name and those of spouse and children.
Stage 6	Severe cognitive decline (moderately severe AD)	Significant personality and behavioral symptoms may emerge (delusions, suspiciousness, hallucinations, compulsions) and extensive help with ADLs become necessary (e.g., toileting); loss of awareness of recent experiences and surroundings; may still recall their own name, but recall of other personal history is decreasing; need help in getting dressed properly; disruptions of sleep/wake cycle occur; increase in urinary and fecal incontinence; wandering and getting lost becomes common.
Stage 7	Very severe cognitive decline (severe AD)	Final stage of illness; loss of ability to respond to surroundings; inability to speak and control movement; help is required for eating, walking, and toileting; movements become abnormal and rigid and swallowing is impaired.

AD, Alzheimer's disease; ADLs, activities of daily living.
Data from Alzheimer's Association[25] and Reisberg B with permission.[26]

TREATMENT

Desired and Expected Outcomes

Although there are currently five agents approved for the treatment of Alzheimer's disease, none of these agents are curative or are known to directly reverse the disease process. ❹ *Consequently, the primary outcome of treatment of Alzheimer's disease is to symptomatically treat the cognitive symptoms of the patient and preserve the patient's functioning for as long as possible.* Secondary goals include treating psychiatric and behavioral symptoms that may occur during the course of the disease.

General Approach to Treatment

❺ *The current gold standard of treatment for cognitive symptoms includes pharmacologic management with a cholinesterase (ChE) inhibitor and/or an NMDA antagonist.* There are currently four ChE inhibitors available on the United States market: tacrine, rivastigmine, galantamine, and donepezil. The use of tacrine is limited due to its propensity for hepatotoxicity and difficult titration schedule. Psychiatric and behavioral symptoms that occur during the course of the disease should be treated as they occur.

Essential elements in the treatment of AD include education, communication, and planning with the family/caregiver of the patient. Treatment options, legal and financial decisions, and course of the illness need to be discussed with the patient and family members. In this regard, the clinician's emphasis should be on helping to maintain a therapeutic living environment while minimizing the burden of care resulting from the disease.

Nonpharmacologic Treatment

Treatment of Alzheimer's disease involves both pharmacologic and nonpharmacologic methods, because this disease can be devastating to both the patient and the family. Upon the initial diagnosis, the patient and family should be counseled on the course of the illness, prognosis, available treatments, legal decisions, and quality-of-life issues. The life of a patient with Alzheimer's disease must become progressively more simple and structured as the disease progresses, and the caregiver must learn to keep requests and demands on the patient simple. The family of the patient will need to be prepared to face changes in life that will occur as the disease becomes worse. Basic principles in the treatment of patients with AD include:

- Using a gentle, calm approach to the patient
- Giving reassurance when needed
- Empathizing with the patient's concerns
- Using distraction and redirection



Patient Encounter, Part 2: The Medical History, Physical Exam, and Diagnostic Tests

HPI
LB has seen a neurologist to address her cognitive decline and behavioral issues and is at the clinic for follow-up after obtaining her assessments and labs.

PMH
- Diabetes mellitus since age 55; it was well controlled until last year when it worsened because of increased confusion of when to take her medication
- Hypertension treated for 20 years and well controlled; has been hypotensive on a few occasions recently during physicals
- Insomnia which is getting worse

FH
Father died of myocardial infarction at age 76; mother died of breast cancer at age 79

SH
Lives alone; denies drinking alcohol or smoking

Meds
- Hydrochlorothiazide 25 mg PO once daily
- Losartan 50 mg PO twice daily
- Metformin 1000 mg PO twice daily
- Lorazepam 1 mg PO at bedtime

ROS
(+)weight loss of 12 lb (5.5 kg); (–) N/V/D, change in appetite, heartburn, chest pain, or shortness of breath

PE
VS: blood pressure 128/62 mm Hg supine, pulse 77 beats per minute, respiratory rate 15/minutes, temperature 37°C (98.6°F)
Gen: Poorly-groomed, thin woman looks stated age
Neuro: Folstein Mini Mental Status Exam score 16/30; disoriented to month, date, and day of week, clinic name and floor; poor registration with impaired attention and short-term memory; recalled 0 out of 3 items; good language skills but problems with commands
CT Scan: Mild to moderate generalized cerebral atrophy

- Based on the new information, what is your assessment of the patient?
- What nonpharmacologic and pharmacologic interventions could be recommended?
- What are the short-term and long-term treatment goals?

- Maintaining daily routines
- Providing a safe environment
- Providing daytime activities
- Avoiding overstimulation
- Using familiar decorative items in the living area
- Bringing abrupt declines in function and the appearance of new symptoms to professional attention

Preparation in the early stages of the illness will lessen caregiver stress as the disease progresses.

Conventional Pharmacologic Treatment for Cognitive Symptoms

Cholinesterase Inhibitors (Donepezil, Rivastigmine, and Galantamine)

❺ *The ChE inhibitors all have the indication for the treatment of mild to moderate dementia of the Alzheimer's type.* Guidelines for the treatment of AD were written before the approval of memantine and recommend the use of ChE inhibitors as a valuable treatment for AD.[27–29] None of the ChE inhibitors have been compared in head-to-head studies, so the decision to use one over another is based on differences in mechanisms of action, adverse reactions, and titration schedules.

Treatment should begin as early as possible in patients with a diagnosis of AD.[30] Figure 32–2 provides a recommended treatment algorithm for AD.[31] Patients should be switched to another ChE inhibitor from their initial ChE inhibitor if they show an initial lack of efficacy; initially respond to treatment, but lose clinical benefit; or experience safety/tolerability issues. This switch should not be attempted until the patient has been on a maximally tolerated dose for a period of 3 to 6 months. The switch should also be based on realistic expectations of the patient and/or caregiver.[32] ChE inhibitor therapy should be discontinued in patients who experience poor tolerance or compliance, who show a lack of clinical improvement after 3 to 6 months at optimal dosing, who continue to deteriorate at the pretreatment rate, or who demonstrate dramatic clinical deterioration following initiation of treatment.[33]

Donepezil

❺ *Donepezil is a piperidine cholinesterase inhibitor, which reversibly and non-competitively inhibits centrally active acetylcholinesterase.*[34] This specificity is claimed to result in fewer peripheral side effects as compared to the other ChE inhibitors.

Donepezil is approved for the treatment of mild to moderate dementia of the Alzheimer's type at a dose of 5 mg/day. This dose should be increased to 10 mg/day if needed after 4 to 6 weeks. Table 32–5 describes the dosing strategies for all of the approved agents for Alzheimer's disease.[34–38]

Adverse reactions with donepezil include nausea, vomiting, and diarrhea. These are typical cholinergic side effects to expect with all of the cholinesterase inhibitors. Table 32–6 compares the major side effects for all of the approved agents for Alzheimer's disease.[34–38]

Only a small number of drug interactions have been reported with donepezil. In vitro studies show a low rate of binding of donepezil to cytochrome P-450 (CYP)3A4 or 2D6. Whether or not donepezil has the potential for enzyme induction is not known. No interactions with theophylline, cimetidine, warfarin, digoxin, or ketoconazole have been documented. In vitro studies show that inhibitors of CYP3A4 and 2D6 have the potential to inhibit the metabolism of donepezil. The clinical relevance of this is unknown. However, monitoring for possible increased peripheral side effects is advised

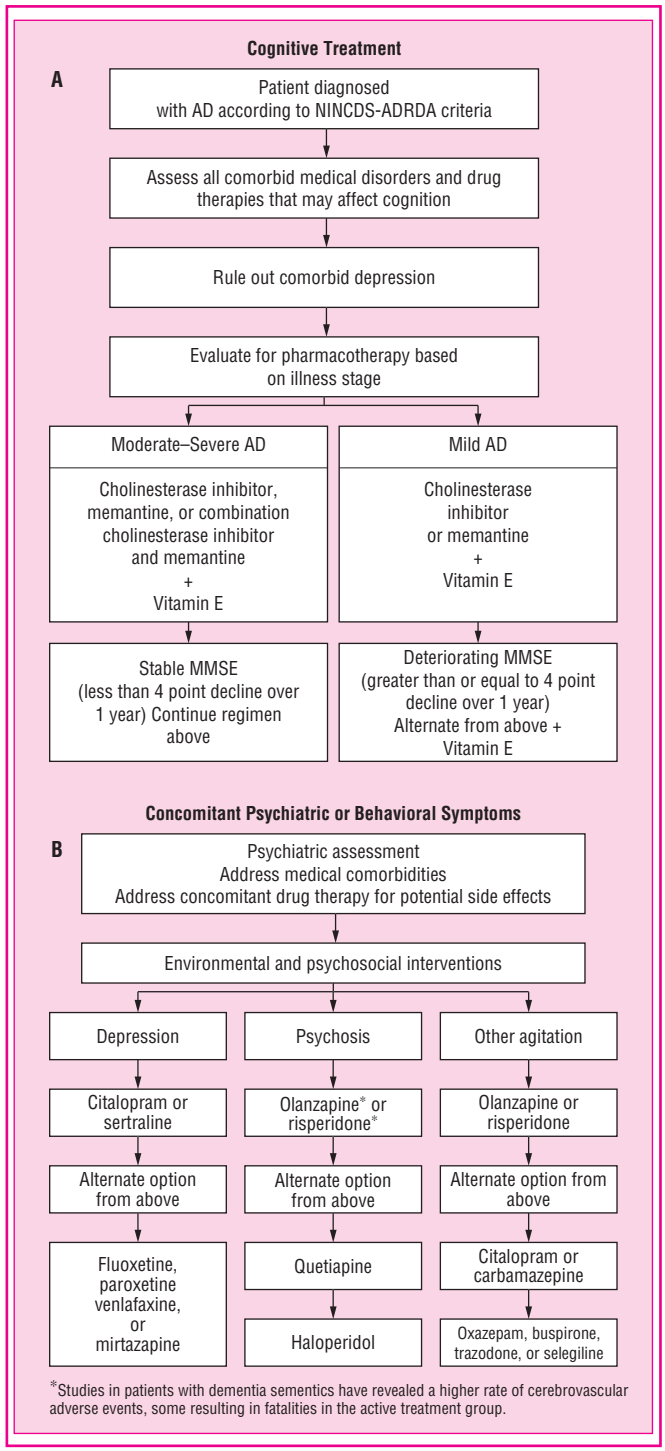


FIGURE 32–2. Treatment algorithm for Alzheimer's disease. *A.* Cognitive treatment. *B.* Treatment of psychiatric or behavioral symptoms. AD, Alzheimer's disease; MMSE, Mini Mental Status Examination; NINCDS-ADRDA National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association. (From Faulkner JD, Bartlett J, Hicks P. Alzheimer's disease. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1164, with permission.)

when adding a CYP2D6 or 3A3/4 inhibitor to donepezil treatment. Also, inducers of CYP2D6 and 3A4 could increase the rate of elimination of donepezil.[34]

Rivastigmine

❺ *Rivastigmine has central activity for both the acetylcholinesterase and butyrylcholinesterase enzymes.*[36] Acetylcholinesterase is found in two forms: globular 4 and globular 1. In postmortem studies, globular 4 is significantly depleted, while globular 1 is still abundant. Thus, blocking metabolism of globular 1 may lead to higher concentrations of acetylcholine. Rivastigmine has higher activity at globular 1 than at globular 4. Theoretically this may be advantageous, as rivastigmine prevents the degradation of acetylcholine via the acetylcholinesterase globular 1 over the course of the disease as compared to the other ChE inhibitors.

The dual inhibition of acetylcholinesterase and butyrylcholinesterase may lead to broader efficacy. As acetylcholinesterase activity decreases with disease progression, the acetylcholinesterase-selective agents may lose their effect, while the dual inhibitors may still be effective due to the added inhibition of butyrylcholinesterase. However, this has not been demonstrated clinically.

Rivastigmine is approved for the treatment of mild to moderate dementia of AD at an initial dose of 1.5 mg twice daily; if this dose is tolerated for at least 2 weeks, then the dose can be increased to 3 mg twice daily. Increases to 4.5 mg twice daily and 6 mg twice daily should be attempted only after at least 2 weeks at the previous dose. Tolerability and absorption are improved when the dose is given with food.

Cholinergic side effects (nausea, vomiting, and diarrhea) are common with rivastigmine, but are usually well tolerated if the recommended dosing schedule is followed. If side effects cause intolerance, several doses can be held, then dosing can be restarted at the same or next lower dose. There are no pharmacokinetic drug interactions with drugs metabolized via CYP1A2, 2D6, 3A4/5, 2E1, 2C9, 2C8, or 2C19 expected. Drugs that induce or inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine.[36]

Galantamine

❺ *Galantamine is a ChE inhibitor, which elevates acetylcholine in the cerebral cortex by slowing the degradation of acetylcholine.*[37] It also modulates the nicotinic acetylcholine receptors to increase acetylcholine from surviving presynaptic nerve terminals. In addition, it may increase glutamate and serotonin levels. The clinical benefit of action of these additional neurotransmitters is unknown.

Galantamine is approved for the treatment of mild to moderate dementia of Alzheimer's disease. It can be dosed once or twice daily (if using the immediate-release tablet or extended-release capsule). The initial dose is 8 mg daily (or 4 mg twice daily) for 4 weeks. If tolerated the dose can be increased if needed to 16 mg daily (or 8 mg twice daily) for at

TABLE 32–5. Dosing Strategies for Cognitive Agents

	Tacrine	Donepezil	Rivastigmine	Galantamine	Memantine
Starting dose	10 mg four times daily	5 mg daily	1.5 mg twice daily	4 mg twice daily or 8 mg daily	5 mg daily
Maintenance dose	20–40 mg four times daily	5–10 mg daily	3–6 mg twice daily	8–12 mg twice daily or 16–24 mg daily	10 mg twice daily
Time between dose adjustments	4–6 weeks	4–6 weeks	2 weeks	4 weeks	1 week

Data from product Information for tacrine, donepezil, rivastigmine, galantamine, and memantine.[34–38]

least 4 weeks. Again, if this dose is tolerated, the dose can be increased if needed to 24 mg daily (or 12 mg twice daily).

The adverse reactions associated with galantamine are similar to that observed with the ChE inhibitors (e.g., nausea, vomiting, and diarrhea).

CYP3A4 and 2D6 are the major enzymes involved in the metabolism of galantamine. Pharmacokinetic studies with inhibitors of this system have resulted in increased galantamine concentrations or reductions in clearance. Similarly to donepezil, if inhibitors are given concurrently with galantamine, monitoring for increased cholinergic side effects should be done. Studies with inducers of these enzymes have not been completed.[37]

NMDA Receptor Antagonist

Memantine

❺ *Memantine is a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) type of glutamate receptors, which are located ubiquitously throughout the brain.* It regulates activity throughout the brain by controlling the amount of calcium that enters the nerve cell, a process essential for establishing an environment required for information storage. Overstimulation of the NMDA receptor by excessive glutamate allows too much calcium into the cell, disrupting information processing. Blocking NMDA receptors with memantine may protect neurons from the effects of excessive glutamate without disrupting normal neurotransmission.[38]

Memantine is indicated for the treatment of moderate-to-severe dementia of the Alzheimer's type. The initial dose is 5 mg/day with increases to 20 mg/day if needed, with a minimum of 1 week between dosage increases. Doses greater than 5 mg/day should be given in two divided doses. A suggested titration is: 5 mg/day for at least 1 week; 5 mg twice daily for at least 1 week; 15 mg/day (5 mg in the morning and 10 mg in the evening) for at least 1 week; then 10 mg twice daily. If the patient has a creatinine clearance of 5 to 29 mL/minute, then the target dose should be 5 mg twice daily. It is likely to be given as monotherapy, but can be given in combination with ChE inhibitors.

TABLE 32–6. Comparative Common Adverse Effects of AD Medications from Clinical Trial Data[a]

Adverse Event	Tacrine (n = 634)	Donepezil (n = 747)	Rivastigmine (n = 1189)	Galantamine (n = 1040)	Memantine (n = 940)
Elevated liver function tests	29%	NR	NR	NR	NR
Nausea or vomiting	28%	NR	NR	NR	NR
Nausea	NR	11%	47%	24%	NR
Vomiting	NR	5%	31%	13%	3%
Diarrhea	16%	10%	19%	9%	NR
Headache	11%	10%	17%	8%	6%
Dizziness	12%	8%	21%	9%	7%
Muscle cramps	9%	6%	NR	NR	NR
Insomnia	6%	9%	9%	5%	NR
Fatigue	4%	5%	9%	5%	2%
Anorexia	9%	4%	17%	9%	NR
Depression	4%	3%	6%	7%	NR
Abnormal dreams	NR	3%	NR	NR	NR
Weight decrease	3%	3%	3%	7%	NR
Abdominal pain	8%	NR	13%	5%	NR
Agitation	7%	NR	NR	NR	NR
Rhinitis	8%	NR	4%	4%	NR

[a]Caution is urged in making comparisons between drugs based on these data, as different clinical trials often collect adverse event data using different methodologies.
NR, not reported.
Data from Product Information tacrine, donepezil, galantamine, memantine, and rivastigmine.[34–38]

Adverse reactions associated with memantine include: constipation, confusion, dizziness, headache, coughing, and hypertension. These adverse effects are similar to those experienced with ChE inhibitors. Extra monitoring should be done if memantine is given concurrently with a ChE inhibitor.

In vitro studies have shown that memantine produces minimal inhibition of CYP450 enzymes CYP1A2, 2A6, 2C9, 2D6, 2E1, and 3A4. These data indicate that no pharmacokinetic interactions with drugs metabolized by these enzymes should be expected.[38]

Non-conventional Pharmacologic Treatment

❻ *Many other non-conventional treatments have been used as adjunctive treatments during the course of Alzheimer's disease.* Vitamin E has often been recommended for use as an adjunctive treatment because of its antioxidant properties.[39] It has potential effectiveness, a favorable side-effect profile, and low cost. The maintenance dose of vitamin E should be titrated to 1000 International Units twice daily. However, a recent meta-analysis suggests that high doses (greater than 400 International Units per day) of vitamin E should be avoided due to an increased all-cause mortality.[40] Estrogen has been investigated for use in AD, but as mentioned previously, was associated with an increased risk of dementia. Non-steroidal anti-inflammatory drugs (NSAIDs) have also been investigated for their place in the therapy of Alzheimer's disease. There is a lack of convincing data and significant adverse effects (gastritis and gastrointestinal bleeds) associated with their use, so they are not recommended for general use in the treatment or prevention of AD at this time.[41] Statins (3-hydroxy-3-methylglutaryl-CoA reductase inhibitors) should be reserved for those patients who have other indications for their use.[42] Ginkgo biloba has also been studied for its potential use in AD. Until this product has more standardized manufacturing and long-term use is investigated, it should be recommended with caution.[43]

Treatment for Behavioral Symptoms

❼ *Treatment of behavioral symptoms should begin with nonpharmacologic treatments, but may also include antipsychotic agents and/or antidepressants.* Nonpharmacologic recommendations for treatment include:[44]

- Music
- Videotapes of family members
- Audio tapes of the voices of caregivers
- Walking and light exercise
- Sensory stimulation and relaxation

The atypical antipsychotics are the preferred agents for the treatment of psychosis (hallucinations, delusions, and suspiciousness) and the disruptive behaviors (agitation and aggression) of Alzheimer's disease. Double-blind, controlled trials support the efficacy of risperidone and olanzapine in reducing the rate of psychosis and agitation.[45–47] Risperidone should be initiated at 0.25 mg/day and titrated in 0.25 to 0.5 mg/day increments to 1 mg/day, with a maximum dose of 2 mg/day.[45,46,48] Olanzapine has been studied with modest results at doses of 5 to 10 mg/day, and 15 mg/day has not shown to be any better than placebo.[47]

In April 2005, the Food and Drug Administration (FDA) issued a statement requesting black-box warnings on all atypical antipsychotics stating that elderly people with dementia-related psychosis treated with an atypical antipsychotic are at an increased risk of death compared to those treated with placebo. Of a total of 17 placebo-controlled trials investigating olanzapine, aripiprazole, quetiapine, and risperidone in elderly demented patients with behavioral disorders, 15 showed a numerical increase in mortality in the drug-treated group compared to the placebo-treated groups (1.6 to 1.7 times increased risk of death). Specific causes for these deaths were heart-related events (heart failure and sudden death) and infections (mostly pneumonia). The atypical antipsychotics are not currently approved for the treatment of elderly patients with dementia-related psychosis.

Differentiating between depression and dementia can be difficult, so symptoms of depression should be documented for several weeks prior to initiating therapy for the treatment of depression with AD. Citalopram and sertraline are recommended as first-line agents because of their efficacy in placebo-controlled trials.[49] Indications for the use of antidepressants include depression characterized by poor appetite, insomnia, hopelessness, anhedonia, withdrawal, suicidal thoughts, and agitation.

Other miscellaneous therapies for AD include benzodiazepines for anxiety, agitation, and aggression. However, their routine use is not advised.[28] Additionally, benzodiazepines have been associated with an increase in falls leading to the potential for hip fractures in the elderly.[50] Buspirone has shown benefit in treating agitation and aggression in a limited number of patients with minimal adverse effects.[51,52] In open-label and controlled studies, selegiline decreased anxiety, depression, and agitation.[53,54] Finally, trazodone has been shown to decrease insomnia, agitation, and dysphoria, and has been used to treat sundowning in Alzheimer's patients. Figure 32–2 also provides a treatment algorithm for the behavioral symptoms of Alzheimer's disease.[31]

PHARMACOECONOMIC CONSIDERATIONS

❽ *Delaying disease progression through pharmacotherapy can reduce the total cost of treating AD and delay nursing home placement.* Studies with donepezil, rivastigmine, and galantamine have predicted decreases in total costs of AD therapy and delayed nursing home placement.[55–58] A placebo-controlled trial with memantine also reported cost savings and a lower

incidence of institutionalization than in the placebo group.[59] Although these studies show a reduced cost of treating AD, the true cost-effectiveness of these therapies has yet to be established. Further prospective pharmacoeconomic trials of longer duration and more comprehensive cost analysis are needed to determine the position of pharmacotherapy in the treatment of Alzheimer's disease.

OUTCOME EVALUATION

- The success of therapy is measured by the degree to which the care plan decreases the pretreatment deterioration rate, preserves the patients' functioning, and treats psychiatric and behavioral symptoms. The primary outcome measure is thus subjective information from the patient and the caregiver, although the MMSE can be a helpful tool for monitoring changes in the severity of illness. There are no physical examination or laboratory parameters that are used to evaluate the success of therapy.
- Once a tolerated agent is found, continue that therapy until poor tolerance or compliance occurs, no clinical improvement is seen with 3 to 6 months of optimal dosing, or the pretreatment deterioration rate continues. Inform the patient and the caregiver that the treatments available for Alzheimer's disease are not curative, but may slow the deterioration rate of the patient.
- Treat behavioral and psychiatric issues as they arise. Consider the patient's choices of nonpharmacologic and pharmacologic options before recommending a treatment. Discontinue the pharmacologic treatments periodically to re-evaluate the need for continued treatment.
- Develop a plan to assess the effectiveness of the cholinesterase inhibitor in slowing the deterioration of the patient after an appropriate interval (3 to 6 months). Assess improvement in quality-of-life measures such as ability to function independently and for slowing of memory deterioration. Evaluate the patient for the presence of adverse drug reactions, drug allergies, and drug interactions at appropriate intervals. Continue to be a resource for the patient and caregiver throughout the long course of the disease.

SUMMARY

Alzheimer's disease is a progressive deterioration of cognitive abilities, and patients are likely to have behavioral disturbances and personality changes in the later stages of the disease. Additionally, the disease can be extremely taxing on the patient and caregiver and be very costly to both the family members and society. In an effort to help prepare patients and their caregivers for the inevitable, the Alzheimer's Association has developed ten quick tips on "Living with Alzheimer's disease" (Table 32–7).[60] Although there are many resources available for patients, caregivers affected by AD, and health care professionals, the Alzheimer's Association stands out as the organization that can provide many resources as well as facilitate contacts with other organizations. Contact the association at:

Alzheimer's Association
Contact Center: 1.800.272.3900
TDD Access: 1.312.335.8882
Web site: www.alz.org
E-mail: info@alz.org
National Office: 225 N. Michigan Ave., Fl. 17
Chicago, IL 60601–7633



Patient Care and Monitoring

1. Assess the frequency and duration of the patient's cognitive and non-cognitive symptoms. Could the patient be depressed?
2. Review any available diagnostic data from the medical and psychiatric history including interviews from family, neuropsychological testing, and other labs.
3. Obtain a thorough history of prescription, non-prescription, and natural drug product use. Is the patient taking any medications that could contribute to cognitive changes in the elderly?
4. Educate both the patient and caregivers about lifestyle modification and refer them to support when needed.
5. Monitor pharmacotherapy initiation. Is it titrated correctly?
6. Develop a plan to monitor cognitive response to treatment over time.
7. Routinely assess medication compliance.
8. Educate patient and caregivers on what to expect from pharmacotherapy.
9. Regularly evaluate the patient for the presence of adverse drug reactions, drug allergies, and drug-drug and drug-disease interactions.
10. Be a resource and give continuous support to the patient and caregivers throughout the long course of the disease.

TABLE 32–7. Living with Alzheimer's Disease: Ten Quick Tips

1. Carry with you a book of important notes and photos.
2. Enroll in Alzheimer's Association Safe Return®.
3. Be open to accepting help from others.
4. Keep doing the things you most enjoy.
5. Talk to others who have Alzheimer's.
6. Find ways to laugh as often as you can.
7. Maintain your physical health.
8. Take steps to make your home safe.
9. Extend the time you can live safely in your home with help from your family and friends.
10. Put plans in place now for your future.

Data from the Alzheimer's Association with permission.[60]

ABBREVIATIONS

Ach:	acetylcholine
AD:	Alzheimer's disease
Apo E:	apolipoprotein E
APP:	amyloid precursor protein
ChE:	cholinesterase
CNS:	Central Nervous System
CSF:	cerebrospinal fluid
CT:	computed tomography
CYP:	cytochrome P-450
DSM-IV-TR:	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
FDA:	Food and Drug Administration
HIV:	human immunodeficiency virus
MMSE:	Mini Mental Status Examination
MRI:	magnetic resonance imaging
NINCDS-ADRDA:	National Institute of Neurological and Communicative Disorders and Stroke/ Alzheimer's Disease and Related Disorders Association
NMDA:	*N*-methyl-D-aspartate
NSAID:	non-steroidal anti-inflammatory drug
TSH:	thyroid-stimulating hormone

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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33 Substance-Related Disorders

Sally K. Guthrie, Kirk J. Brower, and Maher Karam-Hage



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Identify the extent of abuse of and dependence on commonly used drugs in different segments of the United States population.
2. Explain the commonalities of action of abused substances on the reward system in the brain.
3. Identify the typical signs and symptoms of intoxication associated with the use of alcohol, opioids, cocaine/amphetamines, and cannabis, and determine the appropriate treatment measures to produce a desired outcome following episodes of intoxication.
4. Determine when a patient meets criteria for substance dependence.
5. Describe the different approaches to treating drug withdrawal, and identify the circumstances in which each of these different approaches would be most appropriate.
6. Recognize when long-term maintenance therapy is indicated for an opioid addict, and describe how to choose and initiate a maintenance regimen.
7. Determine which nonpharmacologic therapies should be used, either alone or in combination with pharmacologic treatments, to foster a recovery from addiction.
8. Recommend a comprehensive treatment and monitoring program to establish lifestyle changes that help maintain sobriety and prevent relapse.

Key Concepts

❶ Virtually all abused substances appear to activate the same brain reward pathway.

❷ While activation of the reward pathways explains the pleasurable sensations associated with acute substance use, chronic use of abused substances resulting in both addiction and withdrawal may be related to neuroadaptive effects occurring within the brain.

❸ Individuals with a pattern of chronic use of commonly abused substances should be assessed to determine if they meet Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for substance dependence (addiction).

❹ The treatment goals for acute intoxication of ethanol, cocaine/amphetamines, and opioids include (1) management of psychological manifestations of intoxication, such as aggression, hostility, or psychosis, and (2) management of medical manifestations of intoxication such as respiratory depression, hyperthermia, hypertension, cardiac arrhythmias, or stroke.

❺ The treatment goals for withdrawal from ethanol, cocaine/amphetamines, and opioids include: (1) a determination if pharmacologic treatment of withdrawal symptoms is necessary, (2) management of medical manifestations of withdrawal such as hypertension, seizures, arthralgias, and nausea, and (3) referral to the appropriate program for substance abuse treatment.

❻ To facilitate recovery from addiction it is necessary to utilize a comprehensive biopsychosocial assessment that includes the motivation for change. Pharmacologic treatments are always adjunctive to psychosocial therapy.

❼ While pharmacologic agents may help prevent relapse, psychotherapy should be the core therapeutic intervention. Motivational enhancement therapy (MET), cognitive-behavioral therapy (CBT), 12-step facilitation (TSF), behavioral couples therapy (BCT), community reinforcement approaches, and contingency management are the best-studied forms of psychotherapy in this group of patients.

❽ Certain pharmacologic agents have been helpful in the treatment of withdrawal and in drug maintenance programs.

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⑨ A major component of successful treatment of addiction is to continue monitoring the use of medications such as disulfiram, naltrexone, or acamprosate, which are designed to decrease craving or to block the hedonic effects of abused substances. Also, it is important to identify a mechanism for long-term support of sobriety that might be appropriate for a specific individual such as Alcoholics Anonymous, a spiritual group, or professional recovery programs for professionals such as doctors, nurses, and police officers.

Substance abuse and dependence are highly prevalent problems in the United States and in the world. In the United States the use of all substances of abuse has undergone a series of periodic cycles of societal tolerance or condemnation. As an example, cocaine was first isolated from coca leaves in 1860 by a chemistry graduate student in Germany. Its use was advocated by many in the medical establishment until around the mid-1890s when it became evident that chronic use of cocaine might be addictive in some individuals and could be associated with deleterious physiologic effects. Its use decreased following restriction of prescribing and dispensing of cocaine in the early twentieth century. Cocaine continued to be abused by a small segment of the population, but by and large, much of the medical community seemed to forget the earlier cocaine epidemic. By the late 1970s, at least one pharmacology textbook indicated that cocaine was not addictive. Unfortunately, in the 1980s a smokeable formulation of cocaine (crack) became available, and cocaine use again became an epidemic. The cyclic nature of substance abuse is common to many drugs, including heroin and marijuana, in addition to cocaine.

The abused substances covered in this chapter include: nicotine, alcohol, cocaine, amphetamines, cannabis, and opioids. While many more substances can be and have been abused, these drugs are among the most popular.

EPIDEMIOLOGY

In the United States the federal government annually conducts the National Survey on Drug Use and Health, using a sample of persons who are 12 years of age or older to determine the prevalence of licit and illicit drug use.[1] In 2004, 7.9% of the American population (12 years of age and older) had used an illicit drug within the previous month. Fifty percent of the population currently used alcohol, and 6.9% were heavy users. Tobacco use has declined in recent years from a high of 42% in 1965 to a rate of 29.2% in 2004. Unfortunately, use in the younger age groups remains high. In 2004 39.5% of Americans in the 18- to 25-year-old range reported using cigarettes within the previous month. The trends in prevalence of use for eighth, tenth, and twelfth graders are shown in Fig. 33–1. The use of any illicit drug and of marijuana have both decreased since 1999, and this decrease seems to be correlated with an increase in the perceived risk for using marijuana, cigarettes, heroin, and alcohol among 8th graders.[2]

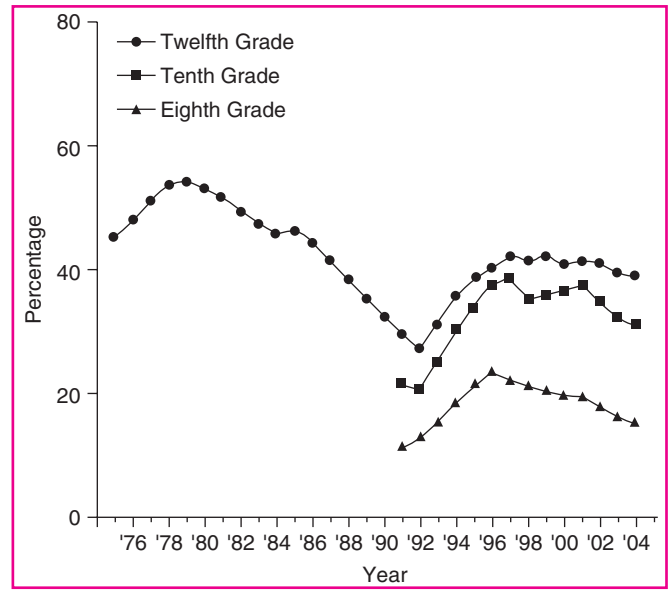


FIGURE 33–1. Trends in illicit drug use in eighth, tenth, and twelfth graders from the Monitoring the Future Survey. Data from reference 2.

While initiation of the use of substances is often in middle and high school, chronic use may be established in young adulthood. The National Alcohol Epidemiologic Survey reported that 16.2% of its 18- to 29-year-old sample met criteria for alcohol abuse or dependence.[3]

The association of substance abuse with emergency department (ED) visits in 21 different metropolitan areas in the United States is reported by the Drug Abuse Warning Network (DAWN). This survey tracks ED visits that are due to a condition induced by or related to drug use. Included in the data are ED visits associated with alcohol, alone and in combination with other substances of abuse, including cocaine, heroin, marijuana, and major stimulants. Figure 33–2 indicates the number of ED visits that are associated with illicit

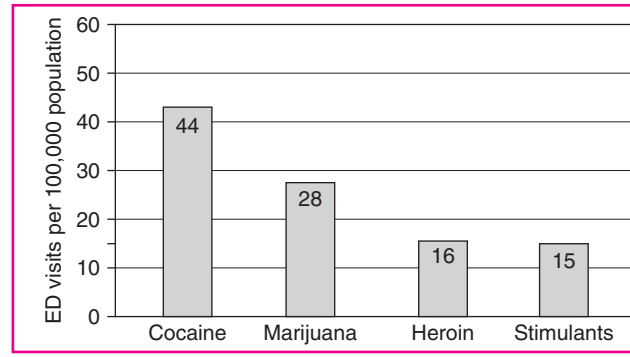


FIGURE 33–2. Emergency department visits associated with illicit drugs for the third and fourth quarters of 2003. Data from reference 4.

drugs per 100,000 people in the population. Abuse of alcohol in combination with other substances ranged from 69 to 75 per 100,000 in each 4-year age subpopulation range from the ages of 18 to 44. The rate dropped to 59 per 100,000 for the 45- to 54-year-old group, and down to 15 for those 55 to 64, and further to 3 per 100,000 population for the 65 and over age group.[4]

The results of these surveys indicate that substance abuse is wide ranging, begins early, and is associated with a considerable number of medical emergencies.

PATHOPHYSIOLOGY

Reward Pathway

Abused drugs generally produce pleasant effects that are desired by the user. However, while most individuals will experience these pleasant effects, not everyone abuses these drugs, and not everyone who abuses them becomes dependent on them. Why some persons abuse drugs while most people do not is a complex area of research. It appears that genetic, environmental, and cultural factors may all interact to predispose some individuals to substance abuse and subsequent dependence. The initial hedonic experiences secondary to use of drugs appear to be primarily due to their ability to activate the primary reward circuits in the brain. These same reward circuits operate under normal circumstances to reinforce certain activities that promote survival, such as food, social affiliation, or sexual activity.

❶ *Virtually all abused substances appear to activate the same brain reward pathway.* Key components of the reward pathway are the dopamine (DA) mesocorticolimbic system that projects from the ventral tegmental area (VTA) and the nucleus accumbens (NA) to the prefrontal cortex, the amygdala, and the olfactory tubercle (Figs. 33–3 and 33–4).[5] Animal studies indicate that ablation of DA neurons in the NA results in decreases in cocaine self-administration. Although many other neurotransmitters can be involved in activation of the reward system, DA appears to be the final common neurotransmitter of this pathway.[6]

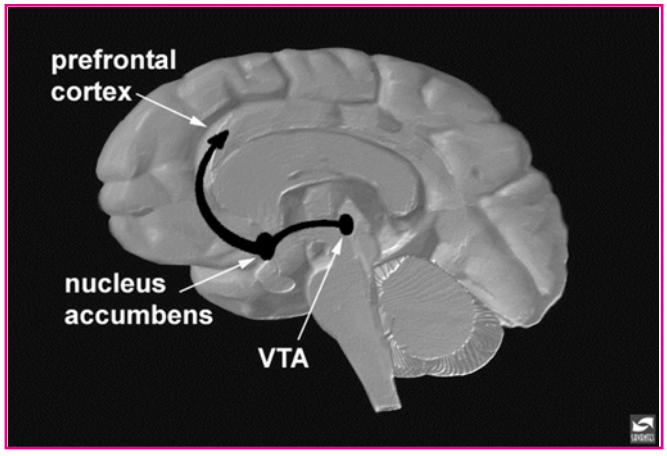


FIGURE 33–3. Location of the dopamine neural tracts associated with the reward system in the brain. Data from reference 5. (From http://www.drugabuse.gov/pubs/Teaching/)

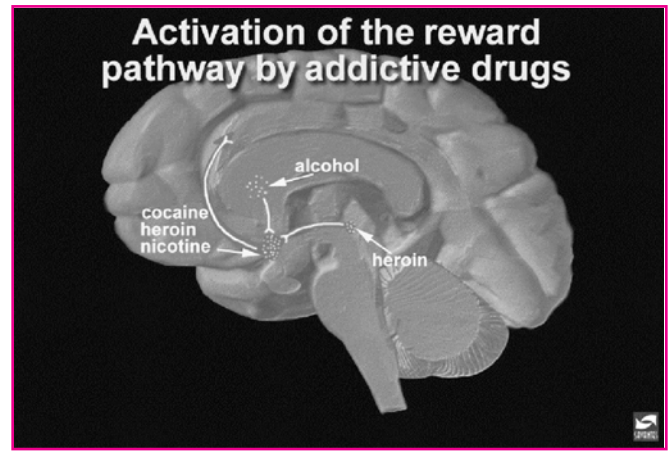


FIGURE 33–4. Where different abused substances interact with the reward system in the brain. Data from reference 5. (From: http://www.drugabuse.gov/pubs/Teaching/)

Cocaine and stimulants, such as amphetamines, probably cause euphoria by blocking the DA reuptake transporter. Additionally, amphetamines also cause the reverse transport of DA into the extracellular space.[6] Although opioids eventually utilize the same circuitry as stimulants, initially they activate μ opioid receptors, in the NA or VTA, which ultimately results in an increase of DA release in the NA. However, reinforcement of opioid use may derive from two mechanisms because in animal studies, when the DA fibers are destroyed, the reinforcing effects of opioids remain.[6] Ethanol probably produces its effects through multiple neurotransmitter pathways. Antagonists of γ-aminobutyric acid (GABA) reverse some of the behavioral effects of ethanol, suggesting that there may be cross-reactivity between benzodiazepines and alcohol, and that alcohol may somehow modulate GABA receptors. Ethanol may activate the DA system indirectly by facilitating the activity of GABA neurons in the pars reticulata, ultimately disinhibiting the VTA DA neurons, resulting in an increase in DA in the NA.[6] There also may be an interaction between serotonin (5-HT) and the reinforcing effects of ethanol, because both 5-HT reuptake inhibitors and 5-HT_{2C} receptor antagonists decrease ethanol intake in animals. However, studies of these drugs that have been conducted in alcohol-dependent humans have not been very promising. Animal studies have indicated that when opioid antagonists are administered to the central nucleus of the amygdala that oral ethanol self-administration will decrease. Studies in humans have noted a modest decrease in alcohol consumption in alcoholics who took a long-acting opioid antagonist (naltrexone) following detoxification. Finally, small doses of ethanol inhibit *N*-methyl-D-aspartate (NMDA) glutamate receptors, and animals

will substitute glutamate receptor antagonists for ethanol, suggesting that they find the effects of the two drugs to be similar. Nicotine also affects the reward pathways by more than one mechanism. In animal studies, either DA antagonists or destruction of DA neurons in the NA decrease nicotine self-administration. Nicotine also interacts with the opioid pathway, because opioid antagonists can precipitate nicotine withdrawal in animals. Finally, marijuana's main active component, tetrahydrocannabinol (THC), binds to cannabinoid-1 (CB_1) receptors resulting in activation of DA neurons in the mesocorticolimbic system. THC also increases the release of DA into the shell of the NA.[6]

Neuronal Adaptation

❷ *While activation of the reward pathways explains the pleasurable sensations associated with acute substance use, chronic use of abused substances resulting in both addiction and withdrawal may be related to neuroadaptive effects occurring within the brain.* Chronic use of drugs of abuse appears to cause a generalized decrease in DA neurotransmission, probably in response to the intermittent increases in DA induced by the frequent use of these drugs. Additionally, with chronic drug use, release of corticotropin-releasing factor (CRF) is increased, indicating an activation of central stress pathways. In vivo microdialysis studies in rats withdrawing from ethanol, cocaine, or THC all showed an increase in extracellular CRF. Also, microinjections of a CRF antagonist into the amygdala reversed some of the anxiogenic behaviors seen during withdrawal.[7]

Two neuroadaptive models have been used to explain how changes in reward function are associated with the development of substance dependence: sensitization and counteradaptation.[7] Sensitization refers to the increased response following repeated intermittent administration of a drug. This is in contrast to the tolerance to drug effects that occurs secondary to continuous exposure to the drug. Sensitization may be akin to the increase in craving a drug after repeated intermittent use of the drug and would facilitate transition from occasional use to compulsive use. Counteradaptation postulates that the initial positive rewarding feelings are followed by the opposing development of tolerance. Since tolerance takes longer to dissipate than the positive rewarding effects, a cycle of escalating drug use ensues. Ultimately, chronic activation of the reward system may result in a depletion of neurotransmitter systems that are overactivated in an effort to maintain response to drugs of abuse. During withdrawal, microdialysis experiments have documented decreases in dopaminergic and serotonergic transmission in the NA. Also seen during alcohol withdrawal are an increase in opioid receptor sensitivity combined with decreased GABAergic and increased NMDA glutamatergic transmission in the accumbens-amygdala pathway. The increase in CRF and concomitant decrease in neuropeptide Y during withdrawal are associated with increases in anxiety and an activation of norepinephrine (NE) pathways, which in turn also activates more CRF release, possibly resulting in an amplification of arousal and stress and maybe even neurotoxic effects if these effects are long-lasting.[7]

With regard to relapse, multiple factors are associated with an increased risk including the availability of the abused drug, an increase in psychological stressors, and a triggering of conditioning factors (cues) such as seeing a white powder or going to a location where drugs were often previously used or obtained. These factors may be acting to trigger residual adaptational changes that occurred in the brain during the period of drug addiction.

OVERALL THEORY OF USE OF PHARMACOLOGIC AGENTS TO TREAT SUBSTANCE ABUSE

Unfortunately, unlike some medical diseases, substance dependence cannot be cured with medications alone. However, we can sometimes alleviate the effects of drug intoxication, attenuate the adverse effects of withdrawal, or use agents that may somewhat decrease craving for, and relapse to, abused substances.

The intoxicating effects of opioids appear to be due to their action as agonists on mu (μ) receptors of the opioid neurotransmitter system. Competitive μ opioid antagonists such as naloxone and naltrexone acutely reverse many of the adverse effects of opioids. To date we do not have specific antagonists for most other abused substances, so rapid pharmacologic reversal of intoxication is usually not possible.

Similarly, reversal of withdrawal syndromes caused by abused substances is not always possible. One pharmacologic solution for reversing a drug withdrawal syndrome, most commonly employed by dependent individuals, is to re-administer the drug that caused the physiologic dependence. The more commonly used clinical method is to administer a medication that has some cross-dependence with the abused drug, but also has fewer of the reinforcing effects and a more predictable pharmacokinetic profile. A good example is the use of benzodiazepines for the withdrawal of ethanol. While benzodiazepines can cause dependence, they are rated as less desirable than ethanol by substance abusers, they cause fewer of the long-term adverse health effects of ethanol, and they are easier to manage medically.

In the case of heroin addiction, maintaining the addict on a regimen of medically managed, orally administered opioids may be preferred over rapidly detoxifying the patient who has a high likelihood of returning to heroin use when extensive strategies for rehabilitation have not been put in place. In order to allow time for psychosocial strategies to help the addicted individual change his or her overall lifestyle, a period of opioid agonist treatment may be indicated. This strategy has been used to maintain addicts on either orally administered μ opioid agonists such as methadone, or partial agonists such as buprenorphine.

No matter which method has been used to facilitate detoxification from the abused substance, addicts have a high risk for reusing substances and manifesting their dependence again. In the long term, the most effective mechanisms for maintaining sobriety are psychosocial strategies rather than pharmacologic ones.



Patient Encounter 1

BB, a 48-year-old man with a history of hypertension, presents to your clinic for follow-up evaluation of his hypertension. You notice that he admits to drinking from one-half to one pint (237–473 mL) of whiskey daily. He says he drinks more on the weekends, but he drinks every day. When you question him about his drinking he says that he doesn't think that it's a problem but admits that his wife has told him he needs to "cut down." He doesn't believe that he is alcohol dependent because on workdays he never drinks before 5 P.M. He admits to having had occasional blackouts.

- What information would suggest that this gentleman might be alcohol dependent?
- What additional information would you need to determine if he meets the criteria for alcohol dependence?

CLINICAL PRESENTATION AND DIAGNOSIS

❸ *Individuals with a pattern of chronic use of commonly abused substances should be assessed to determine if they meet the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for substance dependence (addiction).*[8] Criteria are not defined for each separate abused substance; rather, a pattern of behavior common to the abuse or dependence of all drugs of abuse is established.

The criteria for abuse indicate an established pattern of using a substance that has resulted in undesirable family, job, or legal consequences, such as recurrent instances of neglecting school, work, or family responsibilities, or being arrested for driving under the influence. However, abuse becomes dependence when tolerance to the drug, withdrawal from the drug, or an inability to discontinue use of the drug is apparent or there is a loss of control over its use or the use has become compulsive. The criteria for substance dependence from the DSM-IV-TR are listed below.

Criteria for Diagnosis of Substance Dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

(1) tolerance, as defined by either of the following:
  (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect
  (b) markedly diminished effect with continued use of the same amount of the substance
(2) withdrawal, as manifested by either of the following:
  (a) the characteristic withdrawal syndrome for the substance
  (b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms
(3) the substance is often taken in larger amounts or over a longer period than was intended
(4) there is a persistent desire or unsuccessful efforts to cut down or control substance use
(5) a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use of the substance (e.g., chain-smoking), or recover from its effects
(6) important social, occupational, or recreational activities are given up or reduced because of substance use
(7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

specify if:
With Physiological Dependence: evidence of tolerance or withdrawal (i.e., either item 1 or 2 is present); or
Without Physiological Dependence: no evidence of tolerance or withdrawal (i.e., neither item 1 nor 2 is present)
(Reprinted from the Diagnostic and Statistical Manual of Mental Disorders, Copyright 2000, American Psychiatric Association, with permission.)

Intoxication Signs and Symptoms

Euphoria is the one symptom that most drugs of abuse (with the exception of tobacco) have in common. Other signs and symptoms are specific to the particular drug or class of drugs involved. Table 33–1 lists the psychological/behavioral and



Patient Encounter 2

KI, a 27-year-old woman, was admitted to the cardiology unit from the emergency department after she called 911 claiming that she had severe chest pain. Upon arrival in the ED it was noted that her blood pressure was slightly elevated at 143/92 mm Hg, and that she was diaphoretic. She was in otherwise good physical condition, with no previous cardiac history. After a urine toxicology screen was positive for cocaine she admitted that she had smoked several rocks of crack an hour prior to having the chest pain. She said she almost never uses crack, but she's currently really depressed because she has lost her job.

- What are the possible physical signs and symptoms of cocaine use?
- What are the possible psychiatric symptoms associated with cocaine use?

TABLE 33–1. Signs and Symptoms of Drug Intoxication

Drug	Behavioral Effects	Physiologic Effects
Ethanol	Mood lability, inappropriate aggressive or sexual behavior, giddiness or verbally loud, impaired judgment; possibly progressing to somnolence and coma as the blood level increases	*At blood levels of 0.02 g%–0.09 g% (4.34 to 19.5 mmol/L)*: may see some prolonged reaction time and muscular incoordination *At blood levels from 0.1 g%–0.2g% (21.7 to 43.4 mmol/L)*: may see obvious prolonged reaction time, obvious incoordination and ataxia, and mental impairment *At blood levels from 0.2 g% to 0.3g% (43.4 to 65.1 mmol/L)*: marked ataxia, some dysarthria, and possible nausea and vomiting *At blood levels from 0.3 g% to 0.4g% (61.5 to 86.8 mmol/L)*: severe dysarthria, amnesia, and hypothermia *At blood levels from 0.4g%–0.6g% (86.8 to 130.2 mmol/L)*: alcoholic coma often occurs, accompanied by decreased respiration, blood pressure, and body temperature *Blood levels between 0.6 g% and 0.8 g% (130.2 to 173.6 mmol/L)*: are often fatal resulting from respiratory arrest, aspiration of gastric contents, or airway obstruction due to flaccid tongue
Cocaine/ stimulants	Initially, most prominent effect is elated mood, although depression may occur; hypervigilance and anxiety that may progress to panic; with high doses or chronic use, may see impairment of judgment, violence to others or self, paranoia or psychosis with delusions and hallucinations (hallucinations are generally tactile or auditory, rarely visual); an increase in motor activity is common; compulsive or stereotyped behavior (e.g., skin picking) may be seen; severe intoxication may result in a self-limited delirium	*Neurologic*: papillary dilation, headache, tremor, hyperreflexia, muscle twitching, flushing, hyperthermia or cold sweats, seizures, coma, possible cerebral hemorrhage *Cardiovascular*: increased pulse and blood pressure, peripheral vasoconstriction, arrhythmias, myocardial infarction *Gastrointestinal*: nausea and vomiting *Renal*: possible incontinence or renal failure *Neuromuscular*: **rhabdomyolysis**, possibly resulting in renal failure
Opioids	Euphoria and sedation are the most prominent effects; analgesia is also prominent; slurred speech, and impaired memory and attention can be seen along with psychomotor retardation	Nausea and vomiting; respiratory depression that is dose-related and may progress to coma; constipation is very common in chronic users, itching, miosis (pinpoint pupils)
Cannabis	Euphoria or giddiness and increase in appetite may occur; depending on the social setting and the amount ingested, may see panic, paranoia, hallucinations, depersonalization or delirium	*Ocular* effects include conjunctival reddening, a slight miosis, and decreased intraocular pressure *Cardiovascular*: tachycardia and vasodilation combined with orthostatic hypotension in high doses *Neuromuscular*: decreased muscular coordination may be seen; *Gastrointestinal/genitourinary*: dry mouth is common and urinary retention may occur in some persons

Data from references 9, 10, and 11.

physiologic effects of intoxication with ethanol, cocaine and amphetamines, opioids, and cannabis.[9–11]

Withdrawal Signs and Symptoms

Though most abused drugs can cause some degree of physiologic dependence, the severity of withdrawal varies considerably among these drugs. Table 33–2 lists the common withdrawal symptoms seen upon abstinence from drug use.[9–12]

TREATMENT OF INTOXICATION SYNDROMES

❹ *The treatment goals for acute intoxication due to ethanol, cocaine/amphetamines, and opioids include: (1) management of*

TABLE 33–2. Signs and Symptoms of Drug Withdrawal

Drug	Duration	Symptoms
Ethanol	As ethanol level decreases	Vivid dreams, insomnia
	Within 6–24 hours	Tremor, nausea and vomiting, tachycardia (greater than 110 bpm), hypertension (greater than 140/90 mm Hg)
	6–48 hours	Convulsions (usually 1–2 grand mal–type, but they can be more numerous and possibly fatal)
	Days 3–5	Delirium tremens
	Onset at any time	Hallucinations, usually visual
Cocaine/ amphetamine	Immediately following binge	Stimulant craving, accompanied by intense dysphoria, depression, anxiety, agitation
	Within 1–4 hours	Desire for sleep, dysphoria continues
	Days 3–4	Hypersomnia, increased appetite, craving may dissipate slightly, but returns strongly later
Opioids	For shorter-acting opioids (e.g., heroin, morphine, hydrocodone, oxycodone) withdrawal may begin within 6–24 hours following the last dose and last for about 1 week; with longer-action opioids (e.g., methadone) it may take up to 2–4 days for withdrawal to emerge, and it will last longer	*Gastrointestinal*: nausea and vomiting, diarrhea, and dehydration *Neurologic/psychologic*: irritability, restlessness, yawning, tremulousness, and twitching *Cardiovascular*: increase in heart rate, blood pressure *Musculoskeletal*: chills, increased body temperature, piloerection, rhinorrhea *Ocular*: lacrimation and dilated pupils
Nicotine	Within 24 hours of cessation of use	The severity of symptoms reflects the degree and duration of nicotine use; symptoms include anxiety, irritability, frustration, anger, craving, difficulty concentrating, decreased heart rate, and increased appetite
Cannabis	Withdrawal is not usually noticeable, except in heavy, chronic marijuana users; withdrawal occurs within 24 hours, peaks in 2–4 days and resolves in 1–2 weeks	Symptoms are generally mild and reflect the degree and duration of dependence; symptoms include irritability, insomnia, restlessness, anorexia, diaphoresis, diarrhea, and muscle twitches; mild increases in heart rate and blood pressure may also occur

Data from references 9, 10, 11, and 12.

psychological manifestations of intoxication, such as aggression, hostility, or psychosis, and (2) management of medical manifestations of intoxication such as respiratory depression, hyperthermia, hypertension, cardiac arrhythmias, or stroke. In all cases of intoxication associated with a substance use disorder (abuse or dependence), referral to and participation in substance abuse treatment following acute treatment for intoxication is desirable.

Alcohol Intoxication

Most cases of mild to moderate intoxication with alcohol, as well as cases in which blood alcohol levels (BALs) are at the lower limits of legal intoxication (80 to 100 mg%, 0.08 to 0.1% or 17.4 to 21.7 mmol/L), do not require formal treatment. Such intoxications are characterized by mood lability, loud or inappropriate behavior, slurred speech, incoordination, or unsteady gait.

Providing a safe environment and supportive reassurance until the effects of alcohol have worn off is sufficient in most cases. At more severe levels of intoxication, confusion, stupor, coma, and death may be observed. In nontolerant individuals, confusion, depressed consciousness, and vomiting are observed at BALs of 200 to 300 mg% (0.2 to 0.3%, or 43.4 to 65.1 mmol/L); stupor and coma are seen with BALs exceeding 300 to 400 mg% (0.3 to 0.4%, or 65.1 to 86.8 mmol/L). Death may occur at levels of 400 mg% (0.4% or 86.8 mmol/L) or higher from cardiac arrhythmias or respiratory depression. Thus, the most important physiologic goal of treating high levels of intoxication is maintaining cardiopulmonary functioning, including the prevention of aspiration. Accordingly, vital signs must be monitored regularly. Serial BALs at least hourly are strongly recommended, and patients should not be allowed to leave the treatment setting on their own while legally intoxicated (greater than or equal to 80 mg% [0.8% or 17.4 mmol/L]). Initially, BALs may continue to rise if gastrointestinal absorption is still occurring. Otherwise, the BAL generally decreases at a rate of 15 to 20 mg% (0.015 to 0.02% or 3.3 to 4.34 mmol/L) per hour. Although more tolerant individuals may not show the same level of symptoms for a given BAL as non-tolerant individuals, behavioral tolerance and tolerance for vital physiologic functions may differ. Thus, alcoholic patients who are awake and alert at a BAL greater than or equal to 400 mg% (0.4% or 86.8 mmol/L) may still be at risk for cardiopulmonary instability and collapse.

Other causes of confusion, stupor, or coma must be ruled out, because alcohol-intoxicated individuals commonly combine alcohol with other substances, sustain head and other injuries, and have vitamin deficiencies and electrolyte abnormalities. If consciousness is impaired, then thiamine should be given intravenously or intramuscularly at 100 mg daily for at least 3 days. Patients may also develop adverse interactions between alcohol and medications that have been prescribed, including disulfiram. See Table 33–3 for a listing of drug-drug interactions.[13–15] If hypoglycemia is suspected, then thiamine administration should precede administration of glucose-containing fluids to prevent precipitation of an acute Wernicke's syndrome.

Behaviorally, patients may insist on driving, become physically aggressive and agitated, or otherwise become a danger to self or others. Indeed, most suicidal behaviors among alcohol-dependent individuals occur while intoxicated. In such cases, the desired outcomes are appropriate management of medical problems, prevention of harmful behaviors, and stabilization of mood. Less commonly, agitation may require treatment with haloperidol such as 5 to 10 mg by mouth every 2 to 4 hours, or 5 mg either intravenously (IV) or intramuscularly (IM) every 1 to 2 hours. Antipsychotics, however, may lower the seizure threshold and are best avoided. Sedation with benzodiazepines has been used in some cases, but the risk of respiratory depression when mixed with the alcohol already in the patient's system can be dangerous if not fatal.

There are no available medications that can fully reverse the effects of alcohol intoxication. Caffeine and other stimulants can induce arousal and alertness, but they are less effective at reversing the poor judgment and motor incoordination that are vital for complex tasks such as driving. Thus, stimulants are neither indicated nor a viable option to make driving safe. Flumazenil (Romazicon®) reverses the effects of benzodiazepine agonists at GABA receptors, which mediate some of alcohol's effects, but alcohol also acts on many other neurotransmitter systems making flumazenil generally ineffective in reversing alcohol intoxication.

Stimulant Intoxication (Cocaine and Amphetamines)

The desired outcomes of the treatment of stimulant intoxication are appropriate management of medical and psychiatric problems. Medical problems include hyperthermia, hypertension, cardiac arrhythmias, stroke, and seizures. Some medical problems are related to route of administration such as nosebleeds with intranasal administration and infections with intravenous administration. Psychiatric effects include anxiety, irritability, aggression, and psychosis. Psychosis may take the form of tactile hallucinations (such as the sensation of bugs crawling under one's skin, aka formication), visual hallucinations (usually simple geometric shapes), and most commonly auditory hallucinations, as well as paranoia or delusions of grandeur. Cocaine is short-acting, and a single dose of a benzodiazepine sedative-hypnotic may be sufficient treatment for anxiety reactions. Depending on the half-life of the benzodiazepine, one or more sequential doses may be required for amphetamine intoxication. Because stimulants are commonly used in combination with alcohol or opioids, benzodiazepines could increase their sedative and respiratory depressant effects, so a comprehensive drug history and urine drug screen should be obtained. In a small percentage of patients, benzodiazepines can cause paradoxical activation and aggression. Thus, antipsychotics may be needed. Antipsychotics are definitely indicated when psychosis is present, and the psychosis usually responds quite rapidly in the absence of other co-occurring psychiatric disorders.

Opioid Intoxication

The word opioid is used to refer to the overall class including the semi- and fully-synthetic agents, but the word "opiate" only refers to the naturally occurring opioids such as heroin, opium, and morphine.

Patients who are acutely intoxicated with an opioid usually present with **miosis**, euphoria, slow breathing and slow heart rate, low blood pressure, and constipation. Seizures may occur with certain agents such as meperidine (Demerol®). It is critically important to monitor patients carefully to avoid cardiac/respiratory depression and death from an excessive dose of opioids. One strategy is to reverse the intoxication by utilizing naloxone (Narcan®) 0.4 to 2 mg IV every 2 to 3 minutes up to 10 mg. Alternatively, the IM/SC route may be used if IV access is not available. Because naloxone is shorter-acting than most abused opioids, it may need to be readministered at periodic intervals; otherwise the patient could lapse into cardiopulmonary arrest after a symptom-free interval of reversed

TABLE 33–3. Drug Interactions with Abused Drugs or Drugs Used to Treat Drug Abuse

Drug	Interacting Drug	Type of Interaction and Appropriate Action
Amphetamine	Monoamine oxidase inhibitors (phenelzine, tranylcypromine, *possibly linezolid*)	Pharmacodynamic interaction resulting in an increase in blood pressure; possibly resulting in a hypertensive emergency or stroke; avoid this combination.
	Sodium bicarbonate	Sodium bicarbonate increases renal tubular reabsorption of amphetamine, resulting in a prolonged amphetamine elimination half-life; be aware of this combination.
Buprenorphine	There are currently no reported drug interactions with buprenorphine; however, buprenorphine is metabolized primarily by CYP3A4	*Theoretically* buprenorphine metabolism could be inhibited by itraconazole, ketoconazole, grapefruit juice, and erythromycin or any other CYP3A4 inhibitor; the effects may be greater than expected for the dose of buprenorphine being given; may need to decrease buprenorphine dose. Conversely buprenorphine metabolism could by increased by carbamazepine, phenytoin, St. John's wort, efavirenz, and nevirapine, or any other CYP3A4 inducer; the effects may be less than expected; may need to increase buprenorphine dose.
Cigarette smoking	Clozapine	Cigarette smoking induces CYP1A2; increasing the metabolism of clozapine; may need to increase usual clozapine dose when a patient begins to smoke, or decrease clozapine dose if smoking is stopped or nicotine replacement is used instead of smoking.
	Olanzapine	Similar interactions as clozapine; may need to increase the usual olanzapine dose when a patient begins to smoke, or decrease olanzapine dose if smoking is stopped or nicotine replacement is used instead of smoking.
	Theophylline	Theophylline is also a CYP1A2 substrate; may need to increase the usual theophylline dose when a patient begins to smoke, or decrease the theophylline dose if smoking is stopped or nicotine replacement is used instead of smoking.
Clonidine	Amitriptyline, imipramine, desipramine (also likely with nortriptyline, doxepin, protriptyline, and trimipramine)	Pharmacodynamic interaction; clonidine acts as an agonist at α_2-receptors, and these TCAs block this receptor to varying degrees; the result is an increase in blood pressure; either avoid this interaction by choosing another antidepressant or increase the dose of clonidine.
	Cyclosporine	Clonidine may increase cyclosporine blood levels; although only a single case report supports this, it would be prudent to monitor cyclosporine blood levels in a patient receiving clonidine.
	Mirtazapine	This interaction is the same as the one when clonidine is combined with TCAs; however, mirtazapine is a more potent α_2-receptor blocker than the TCAs; avoid this interaction and choose an alternative antidepressant without α_2-blocking effects.
Disulfiram	Benzodiazepines (including alprazolam, chlordiazepoxide, diazepam, flurazepam, halzepam, prazepam, triazolam)	Disulfiram inhibits CYP enzymes 1A2, 2C9, and 3A4; many benzodiazepines are metabolized via these pathways; lorazepam, temazepam, and oxazepam are NOT metabolized via the CYP450 system and are reasonable alternatives. Otherwise, if benzodiazepines are combined with disulfiram the pharmacologic effect may be greater than expected, and the dose of benzodiazepine may need to be lowered.
	Cocaine	Disulfiram decreases the clearance of cocaine from the body; may see increased or prolonged cocaine effects with this combination.
	Isoniazid	The addition of disulfiram to isoniazid therapy has resulted in changes in affect and behavior and decreased coordination; avoid the combination if possible; if they must be given concomitantly, monitor closely.

(*Continued*)

TABLE 33–3. Drug Interactions with Abused Drugs or Drugs Used to Treat Drug Abuse (*Continued*)

Drug	Interacting Drug	Type of Interaction and Appropriate Action
	Phenytoin	Disulfiram decreases the metabolism of phenytoin, resulting in higher phenytoin levels; the dose of phenytoin will need to be reduced; since phenytoin undergoes nonlinear metabolism it is difficult to predict the magnitude of increase in blood levels that could be seen; it is best to avoid this interaction if possible; otherwise, closely monitor phenytoin blood levels.
	Theophylline	Disulfiram inhibits CYP1A2, resulting in an increase in theophylline blood levels; monitor theophylline blood concentration; may need to decrease theophylline dose.
	Warfarin	Disulfiram inhibits several of the enzymes responsible for warfarin metabolism; increased PT/INR have been noted; if disulfiram is added to warfarin therapy, carefully monitor PT/INR; the warfarin dose will probably have to be decreased.
Ethanol	Acetaminophen	Chronic ethanol use increases the risk of hepatotoxicity when acetaminophen is used in high doses; however, acute ingestion of alcohol along with an acetaminophen overdose decreases the toxicity of acetaminophen.
	Cefamandole, cefoperazone, cefotetan, and moxalactam, metronidazole	A disulfiram-type reaction may occur when these anti-infectives are combined with alcohol; the reaction includes flushing, diaphoresis, tachycardia, headache, and increases in blood pressure; avoid alcohol if these drugs are used.
	Isoniazid	Hepatotoxicity is a higher risk when isoniazid is given to those who chronically drink large amounts of alcohol; avoid isoniazid in this group if possible, otherwise monitor LFTs.
	Methotrexate	Hepatotoxicity is a higher risk when methotrexate is given to those who chronically drink large amounts of alcohol; avoid methotrexate in this group if possible; otherwise monitor LFTs.
	Monoamine oxidase inhibitors	Ethanol DOES NOT interact with MAOIs; however, tyramine may be a component of some aged alcoholic drinks, such as red wines or tap beers; if a reaction occurs, hypertension and a pounding headache are the most likely symptoms; usually white wine is fine (in moderation) and most widely available domestic canned beers do not contain significant amounts of tyramine.
Methadone	Carbamazepine	Carbamazepine is an inducer of CYP3A4 and methadone is primarily metabolized via CYP3A4; if carbamazepine is added to a drug regimen containing methadone, the methadone dose will probably need to be adjusted upward to avoid withdrawal.
	Efavirenz	This HIV drug is a CYP3A4 inducer; efavirenz decreases methadone blood levels and has precipitated withdrawal in opioid-dependent individuals; may need to increase methadone dose.
	Fluconazole	Fluconazole is an antifungal agent that moderately inhibits CYP3A4; when added to a drug regimen containing methadone, higher blood levels have been noted; adjustment of methadone dose should be based on clinical judgment, but a decrease of dose may be necessary. *NOTE: Both itraconazole and ketoconazole are more potent inhibitors of CYP3A4, although interactions have not yet been reported, theoretically, they are very likely to occur, resulting in elevated methadone concentrations.*
	Nevirapine	Nervirapine is an HIV drug that is a CYP3A4 inducer; in a small sample, nevirapine caused a 50% reduction in methadone blood levels, resulting in complaints of methadone withdrawal symptoms in patients receiving methadone maintenance; may need to increase methadone dose in patients who have nevirapine added to their drug regimen.
	Phenobarbital	An inducer of many CYP450 enzymes; may result in complaints of withdrawal symptoms in methadone maintenance patients when added to their drug regimen; may need to increase methadone dose.

TABLE 33–3. Drug Interactions with Abused Drugs or Drugs Used to Treat Drug Abuse (*Continued*)

Drug	Interacting Drug	Type of Interaction and Appropriate Action
	Phenytoin	Similar to phenobarbital; may need to increase methadone dose when phenytoin is added to a methadone maintenance drug regimen to avoid withdrawal symptoms.
	St. John's wort	This herbal remedy may induce CYP3A4; the certainty of an interaction probably rests on the specific preparation being used, but caution would dictate that this herbal product should be avoided in those receiving methadone treatment; withdrawal symptoms have been noted in patients taking methadone maintenance who have added St. John's wort to their drug regimen.

CYP. cytochrome P450 isoenzyme; HIV, human immunodeficiency virus; INR, International Normalized Ratio; LFTs, liver function tests; MAOI, monoamine oxidase inhibitor; PT, prothrombin time; TCA, tricyclic antidepressant.
Data from references 13, 14, and 15.

intoxication. In addition, naloxone can induce withdrawal symptoms in opioid-dependent patients, so patients may awaken feeling quite distressed and agitated. It is also critical to secure the airway and ensure breathing. In some cases intubation and manual/ mechanical ventilation may be required. This is a necessary measure to avoid oxygen desaturation leading to brain **hypoxia** or anoxia that may cause brain damage or death.

Overall, intoxication with any of the substances discussed above is evidence of substance abuse and is strongly suggestive of substance dependence. In all cases it is important to strongly emphasize to the patient that this is an issue that needs to be addressed, and that entry into a treatment program could be very beneficial.

TREATMENT OF WITHDRAWAL SYNDROMES

❺ *The treatment goals for withdrawal from ethanol, cocaine/amphetamines, and opioids include: (1) a determination if pharmacologic treatment of withdrawal symptoms is necessary, (2) management of medical manifestations of withdrawal such as hypertension, seizures, arthralgias, and nausea, and (3) referral to the appropriate program for substance abuse treatment.* The desired outcomes in the treatment of withdrawal syndromes are to ensure patient safety, comfort, and successful transition from treatment of withdrawal to treatment of dependence. Referral to specialized treatment for substance dependence is strongly recommended following treatment for withdrawal syndromes, because treatment of withdrawal is not sufficient to prevent relapse to problematic substance use. Achieving a drug-free state by detoxification and then rehabilitation with a focus on total abstinence is the ideal outcome.

Alcohol Withdrawal

There are four different alcohol withdrawal syndromes, which differ in terms of their pharmacologic treatment and need for hospitalization.

Uncomplicated Alcohol Withdrawal

This is the most commonly observed syndrome, and as the name denotes, is not complicated by seizures, delirium tremens (DTs), or hallucinosis. Symptoms are typically rated using a validated scale such as the Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar; Table 33–4).[16] The recommended CIWA-Ar threshold score for treating uncomplicated alcohol withdrawal with medications on an outpatient basis is between 8 and 10. For patients that score greater than or equal to 15, inpatient treatment should be strongly considered. Patients who score 20 or higher on the CIWA-Ar should always be treated with medications. The risks of not treating high-scoring patients with medications are seizures and DTs, and those with a prior history of seizures or DTs have an increased risk for subsequent episodes. Therefore, when a history of seizures or DTs is positive, the lower threshold of 8 is recommended, and hospitalization is safer than outpatient detoxification. There is some evidence for "kindling" during successive episodes of alcohol withdrawal, such that symptom severity and complications increase with additional withdrawal episodes. Thus, some authors recommend routinely using medications when the CIWA-Ar score is in the 8 to 10 range.

Benzodiazepines are the evidence-based treatment of choice for uncomplicated alcohol withdrawal.[17] Barbiturates are not recommended because of their low therapeutic index due to respiratory depression. Some of the anticonvulsants have also been used to treat uncomplicated withdrawal (particularly carbamazepine and sodium valproate). Although anticonvulsants provide an alternative to benzodiazepines, they are not as well studied and are less commonly used. The most commonly employed benzodiazepines are chlordiazepoxide, diazepam, lorazepam, and oxazepam. They differ in three major ways: (1) their pharmacokinetic properties, (2) the available routes for their administration, and (3) the rapidity of their onset of action due to the rate of gastrointestinal absorption and rate of crossing the blood–brain barrier.

Benzodiazepines can be administered using a symptom-triggered approach when withdrawal signs and symptoms are already present.[18] In this approach, medication is administered every hour when the CIWA-Ar is greater than or equal to 8. For the shorter-acting agents, oxazepam (15 to 60 mg orally) or lorazepam (1 to 4 mg orally) is given, and the CIWA-Ar is repeated hourly after each administration during the first 24 hours until the patient is comfortably sedated. Because of

TABLE 33–4. Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar)

Patient Name _____

Date: _____ Time: _____

Pulse: _____ BP: _____

NAUSEA & VOMITING: Ask "Do you feel sick to your stomach? Have you vomited?" Observation.

0 No nausea and no vomiting
1 Mild nausea with no vomiting
2
3
4 Intermittent nausea with dry heaves
5
6
7 Constant nausea, frequent dry heaves and vomiting

TREMOR: Arms extended and fingers spread apart. Observation.

0 No tremor
1 Not visible, but can be felt fingertip to fingertip
2
3
4 Moderate, with patient's arms extended
5
6
7 Severe, even with arms not extended

PAROXYSMAL SWEATS: Observation.

0 No sweat visible
1 Barely perceptible sweating, palms moist
2
3
4 Beads of sweat obvious on forehead
5
6
7 Drenching sweats

ANXIETY: Ask, "Do you feel nervous?" Observation.

0 No anxiety, at ease
1 Mildly anxious
2
3
4 Moderately anxious or guarded, so anxiety is inferred.
5
6
7 Equivalent to acute panic states, as seen in severe delirium or acute schizophrenic reactions

AGITATION: Observation.

0 Normal activity
1 Somewhat more than normal activity
2
3
4 Moderately fidgety and restless
5
6
7 Paces back and forth during most of the interview, or constantly thrashes about

TACTILE DISTURBANCES: Ask "Have you any itching, pins & needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?" Observation.

0 None
1 Very mild itching, pins & needles, burning or numbness
2 Mild itching, pins & needles, burning or numbness
3 Moderate itching, pins & needles, burning or numbness
4 Moderately severe hallucinations
5 Severe hallucinations
6 Extremely severe hallucinations
7 Continuous hallucinations

AUDITORY DISTURBANCES: Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?" Observation.

0 Not present
1 Very mild harshness or ability to frighten
2 Mild harshness or ability to frighten
3 Moderate harshness or ability to frighten
4 Moderately severe hallucinations
5 Severe hallucinations
6 Extremely severe hallucinations
7 Continuous hallucinations

VISUAL DISTURBANCES: Ask, "Does the light appear to be too bright? Is the color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?" Observation.

0 Not present
1 Very mild sensitivity
2 Mild sensitivity
3 Moderate sensitivity
4 Moderately severe hallucinations
5 Severe hallucinations
6 Extremely severe hallucinations
7 Continuous hallucinations

HEADACHE, FULLNESS IN HEAD: Ask "Does your head feel different? Does it feel like there is a band around your head?" Do not rate dizziness or lightheadedness. Otherwise, rate severity.

0 Not present
1 Very mild
2 Mild
3 Moderate
4 Moderately severe
5 Severe
6 Very severe
7 Extremely severe

ORIENTATION AND CLOUDING OF SENSORIUM: Ask, "What day is this? Where are you? Who am I?" Observation.

0 Oriented and can do serial additions
1 Cannot do serial additions or is uncertain about date
2 Disoriented for date by no more than 2 calendar days
3 Disoriented for date by more than 2 calendar days
4 Disoriented for place and/or person

Total Score: _____

Rater: _____

Maximum Possible Score: 67

Data from reference 16.

their short half-life, dosing on subsequent days may be needed, and the risk of seizures may possibly (although not definitively proven) be higher. For the longer-acting agents, chlordiazepoxide and diazepam, the symptom-triggered approach is used in combination with another technique known as loading. With the loading technique, chlordiazepoxide at doses of 50 to 100 mg or diazepam (10 to 20 mg) is administered orally at 1-hour intervals during the first 24 hours until the patient is comfortably sedated and the CIWA-Ar score is lower than 4. Due to differences in disposition and metabolism, the absolute amount of benzodiazepine required in the first 24 hours will vary, but the majority of patients will respond to about 400 mg of chlordiazepoxide or 60 mg of diazepam. Some may require higher dosages, but it is important to monitor closely for respiratory depression or excessive sedation. Then loading is stopped, and for the next 24 hours the benzodiazepine is used as needed only if the CIWA-Ar score is greater than or equal to 8, although the long half-lives of these drugs and their active metabolites usually provides a natural taper without further drug administration. The loading technique is especially useful in the hospital, where patients can be medically monitored throughout the day. If vital signs are elevated in the absence of high CIWA-Ar scores, then anti-adrenergic drugs like clonidine or propanolol may be used if there are no contraindications (see Chapter 2, Hypertension).

In contrast to chlordiazepoxide and diazepam, lorazepam and oxazepam are not metabolized into active compounds in the liver. Instead, they are excreted by the kidneys following glucuronidation. This is important because many alcohol-dependent patients have compromised liver function. Therefore, when treatment is initiated before the results of blood tests for liver function are known, as is often the case in outpatient clinics, lorazepam and oxazepam may be preferred. Patients with liver disease may still be treated with diazepam and chlordiazepoxide, but at lower doses. This can be accommodated with the loading technique, although hourly dosing with 5 mg of diazepam or 25 mg of chlordiazepoxide may be sufficient.

Oxazepam is available in oral form only, so it is useful only for uncomplicated withdrawal. Other benzodiazepines are available in injectable form and will be further described below. Diazepam and lorazepam are more lipophilic than chlordiazepoxide and oxazepam, resulting in quicker gastrointestinal absorption and passage across the blood–brain barrier, which makes them valuable in an inpatient setting, especially to treat or prevent seizures. However, their faster onset of action may be associated with feeling high, which can be a disadvantage of their use.

Alcohol Withdrawal Seizures

Alcohol withdrawal seizures (AWS) are a medical emergency and should be treated in an inpatient setting. Withdrawal seizures are usually few in number and generalized. The occurrence of focal seizures or status epilepticus may suggest another etiology. Management consists of keeping the airway open and preventing self-injury during convulsions. Benzodiazepines are the treatment of choice. Intravenous (IV) diazepam 5 to 10 mg is preferred to terminate a seizure in progress if IV access is available. The dose may be repeated in 5 minutes if seizures persist. Alternatively, lorazepam 4 mg may be given IM, followed by insertion of an IV line when convulsive movements have subsided. In the event of a recurrent seizure, lorazepam 2 mg IV may be administered if the patient already received IM lorazepam. Intramuscular use of diazepam or chlordiazepoxide should be avoided because of erratic absorption that complicates the timing of subsequent doses and can result in delayed oversedation. IV benzodiazepines may depress respiration, so they should be administered only when and where advanced cardiopulmonary support is readily available. When the patient becomes conscious enough to take medication orally, then treatment may continue using the loading procedure for diazepam or the symptom-triggered technique for lorazepam as described above. Electrolyte imbalances can contribute to seizures and should be corrected if they exist. IV magnesium sulfate should be given in addition to benzodiazepine treatment. Hypomagnesemia can be corrected with magnesium sulfate 1 g every 6 hours IV for the first day of withdrawal, assuming renal function is intact. Oral replenishment of magnesium may be difficult to accomplish due to resultant diarrhea. As with alcohol intoxication, thiamine should be given IV or IM at 100 mg daily for at least 3 days to prevent precipitation of an acute Wernicke's encephalopathy, although some guidelines recommend higher doses (250 mg daily parenterally for 3 to 5 days) for patients with signs of malnutrition or a history of not eating properly.[19] Still higher doses of thiamine (500 mg three times daily parenterally for at least 2 days followed by 250 mg IM or IV daily for 5 days) have been recommended to treat suspected or diagnosed cases of Wernicke's encephalopathy and to prevent the development of Korsakoff's syndrome.[19] In addition, thiamine administration should always precede administration of any dextrose-containing IV fluids.

Alcohol Withdrawal Delirium (Delirium Tremens or DTs)

Deterium tremens is another medical emergency that requires hospitalization in order to prevent mortality. Parenterally administered benzodiazepines are the treatment of choice.[20] A sample regimen consists of diazepam 5 mg IV (at 2.5 mg/minute) every 5 to 10 minutes until "light somnolence" is achieved, referring to a tendency to fall asleep without stimulation or a light stage of sleep from which the patient is easily awakened. If the first two doses of diazepam are not effective, then 10 mg IV every 5 to 10 minutes can be administered for the third and fourth doses. If still not effective, then up to 20 mg IV may be used thereafter. Once a state of light somnolence is induced, then it should be maintained with diazepam 5 to 20 mg IV every 1 hour as needed. Similarly, lorazepam 1 to 4 mg IV every 5 to 10 minutes or lorazepam 1 to 4 mg IM every 30 to 60 minutes may be given to achieve light somnolence, which is then maintained by similar doses every hour as needed. The antipsychotic haloperidol is given only for severe agitation that is

unresponsive to benzodiazepine therapy. The evidence does not support the use of an antipsychotic as a single agent.[20] Haloperidol may be given as 0.5 to 5 mg IV or IM every 30 to 60 minutes as needed or 0.5 to 5 mg orally every 4 hours as needed. The newer-generation antipsychotic agents have not been studied yet for the treatment of DTs. Thiamine should be given according to the same guidelines described above for AWS.

Alcohol Hallucinosis

Alcohol hallucinosis refers to auditory hallucinations that occur during a clear sensorium, which distinguishes it from DTs, during which hallucinations are associated with a reduced clarity of awareness of the environment. Alcohol hallucinosis is generally treated with oral antipsychotics at usual therapeutic dosages for psychosis.

Stimulant Withdrawal (Cocaine Withdrawal and Amphetamine Withdrawal)

Cocaine and amphetamine withdrawal are grouped together because their symptom profiles as described in DSM-IV-TR[8] are identical, and the physiologic basis of their withdrawal syndromes involves the DA neurotransmitter system. Stimulants of this group also include methylphenidate, but not nicotine and caffeine, which have different neurophysiologic mechanisms of action. Although neurophysiologic alterations underlie the syndrome of stimulant withdrawal, its symptoms are manifested psychologically for the most part as a depressed or dysphoric mood. Consequently, the major adverse complication of stimulant withdrawal is profound depression with suicidal thoughts, and the major goal of treatment is to prevent suicide. Other symptoms that are commonly associated with the mood disturbance include fatigue, sleep disturbance, increased appetite, psychomotor retardation or agitation, and/or vivid dreaming, although these symptoms are neither life-threatening nor require pharmacologic treatment. Therefore, unless suicidality warrants hospitalization, stimulant withdrawal can be treated on an outpatient basis with psychological support and reassurance.

A number of medications have been studied to alleviate symptoms of stimulant withdrawal and the intense craving that may accompany it, but inconsistent results across controlled trials preclude any recommendations for their routine use. Patients with stimulant use disorders should be referred to substance abuse treatment because of the high risk for continued use either during or immediately following stimulant withdrawal.

Opioid Withdrawal

Almost no one dies from opioid withdrawal per se; however, underlying medical complications (e.g., hypertension or recent myocardial infarction) increase the risk of death. Therefore, it is important to manage and stabilize any medical issues (i.e., uncontrolled blood pressure or diabetes, among others), and then determine if hospitalization is appropriate. Patients with underlying medical problems should be evaluated for possible triage to an inpatient detoxification program, to be followed up with substance abuse treatment on either the inpatient or outpatient level. Rapid referral to substance abuse treatment will help "seize the moment" and introduce patients to the concept of recovery while they still vividly remember the negative consequences from abusing substances. Withdrawal from opioids is commonly described by patients as resembling "a bad case of the flu" and symptoms include nausea, vomiting, diarrhea, anxiety, headaches, **mydriasis**, **rhinorrhea**, lacrimation, muscle/bone/joint pain, piloerection, yawning, fever, increased heart rate, and hypertension. The use of clinical withdrawal scales such as Clinical Opiate Withdrawal Scale (COWS),[21] provides high interrater reliability and clinical utility since it is an objective measurement of withdrawal severity. See Table 33–5 for a copy of the COWS instrument. The baseline score helps to make the decision to treat pharmacologically or to observe. A score of less than or equal to 5 is considered very mild, and these patients usually do not require pharmacologic intervention, although they benefit from supportive environment and observation. A score of 5 to 12 is considered mild and 13 to 24 is moderate. Patients with scores in these ranges should be managed with a symptom-based approach (Table 33–6) or initiation of buprenorphine induction/detoxification. A score of 25 to 36 is moderately severe, and greater than 36 is considered severe withdrawal. In severe withdrawal either buprenorphine or a full μ agonist is recommended for detoxification. Methadone is the most commonly used full μ agonist, but under current United States law, methadone detoxification requires referral to a federally approved methadone detoxification program. The two possible options for the treatment of opioid withdrawal in regular clinical settings are symptomatic treatment and μ opioid agonists.

Symptomatic treatment focuses on minimizing the withdrawal symptoms to help patients be as comfortable as possible (Tables 33–6 through 33–8). This is combined with the use of methadone or buprenorphine (Suboxone® or Subutex®) to suppress the withdrawal symptoms by providing a μ opioid full or partial agonist in a tapering dose schedule within a controlled environment.

Treatment with a μ opioid agonist is accomplished with either buprenorphine or methadone. Buprenorphine is a partial agonist at the μ opioid receptors that can be used sublingually. It is available in three formulations, two of which are indicated for the treatment of addiction. Buprenorphine plus naloxone (Suboxone®) in ratio of 4:1 (2 mg/0.5 mg or 8 mg:2 mg) is the recommended formulation unless the patient is pregnant or hypersensitive to naloxone, in which case buprenorphine without naloxone (Subutex®) is recommended. Naloxone was added to the Suboxone® formulation to secure Food and Drug Administration (FDA) approval in the United States. Since naloxone is poorly absorbed when used sublingually but blocks opioid receptors if injected, this combination is designed to minimize diversion of the drug to the street for intravenous use. Only 10% of buprenorphine is bioavailable if it is swallowed, but

TABLE 33–5. Clinical Opiate Withdrawal Scale (COWS)

Patient's Name:_____ Date and Time __/__/____:____
Reason for assessment:_____

Resting Pulse Rate: _____beats/minute
Measured after patient is sitting or lying for one minute
0 pulse rate 80 or below
1 pulse rate 81–100
2 pulse rate 101–120
4 pulse rate greater than 120

Sweating: *over past_hour not accounted for by room temperature or patient activity*
0 no report of chills or flushing
1 subjective report of chills or flushing
2 flushed or observable moistness on face
3 beads of sweat on brow or face
4 sweat streaming off face

Restlessness: *observation during assessment*
0 able to sit still
1 reports difficulty sitting still, but is able to do so
3 frequent shifting or extraneous movements of legs/arms
5 unable to sit still for more than a few seconds

Pupil size
0 pupils pinned or normal size for room light
1 pupils possibly larger than normal for room light
2 pupils moderately dilated
5 pupils so dilated that only the rim of the iris is visible

Bone or joint aches: *if patient was having pain. Previously, only the additional component attributed to opiates withdrawal is scored*
0 not present
1 mild diffuse discomfort
2 patient reports severe diffuse aching of joints/muscles
4 patient is rubbing joints or muscles and is unable to sit still because of discomfort

Runny nose or tearing *Not accounted for by cold symptoms or allergies*
0 not present
1 nasal stuffiness or unusually moist eyes
2 nose running or tearing
4 nose constantly running or tears streaming down cheeks

GI Upset: *over last _hour*
0 no GI symptoms
1 stomach cramps
2 nausea or loose stool
3 vomiting or diarrhea
5 multiple episodes of diarrhea or vomiting

Tremor: *observation of outstretched hands*
0 no tremor
1 tremor can be felt, but not observed
2 slight tremor observable
4 gross tremor or muscle twitching

Yawning: *observation during assessment*
0 no yawning
1 yawning once or twice during assessment
2 yawning three or more times during assessment
4 yawning several times/minute

Anxiety or irritability
0 none
1 patient reports increasing irritability or anxiousness
2 patient obviously irritable or anxious
4 patient so irritable or anxious that participation in the assessment is difficult

Gooseflesh skin
0 skin is smooth
3 piloerection of skin can be felt or hairs standing up on arms
5 prominent piloerection

Total Score:_____
The total score is the sum of all 11 items

Initials of person
completing assessment: _____

Data from reference 21.

50% is bioavailable via the sublingual route. An IM/IV preparation of buprenorphine is available in the United States (Buprenex®), and its bioavailability reaches 80% if used IM and100% if used IV. The Buprenex® formulation is indicated only for anesthesia and operative pain use, but not detoxification or maintenance of opioid dependence, due to the high risk for abuse and diversion.

To initiate a buprenorphine induction, a patient has to be suffering moderate or severe withdrawal, and the last opioid use should be at least 12 to 24 hours earlier, depending on the half-life of the particular opioid (the longer the half-life, the longer a clinician should wait before initiating buprenorphine induction). The score on the COWS should be greater than or equal to 5, otherwise buprenorphine likely will induce withdrawal since it has high affinity for μ receptors and it will displace any other μ opioid agonist that is present. Also, buprenorphine should not be used in those taking greater than 60 to 80 mg/day of methadone because buprenorphine would have low efficacy; the methadone dose should be decreased below this amount prior to induction of buprenorphine detoxification. Once

TABLE 33–6. A "Symptoms-Based" Treatment Approach for Opioid Withdrawal

This approach includes the use of any single or a combination of two or more of the following agents, depending on the symptoms reported:

a) Clonidine (Catapres®) 0.1–0.2 mg every 6–8 hours blocks the peripheral response and reduces anxiety (shaking, sweating, and piloerection). Patients may be given as-needed doses, maximum dosage not to exceed 1.2 mg in 24 hours. BP should be monitored prior to each clonidine dose in the clinic. Hold if systolic blood pressure is below 85 or diastolic is below 55 mm Hg.

Advantages and Limitations: Clonidine is a non-narcotic agent that effectively reduces opioid withdrawal. However, lethargy, craving, insomnia, and muscle pains are not as well treated as other withdrawal symptoms, and supplemental medications are often necessary. Patients with low blood pressure may require inpatient treatment. Avoid in pregnant patients; they can be treated with buprenorphine (Subutex®, NOT Suboxone®) or methadone in a government-licensed program.

b) Dicyclomine (Bentyl®) at 20 mg orally every 8–12 hours up to 80 mg per 24 hours as needed for abdominal cramps.

c) Loperamide (Imodium®) 2-mg capsules; use 2 capsules by mouth initially, then 1 capsule by mouth as needed for diarrhea (max dose 4 capsules/day).

d) Trimethobenzamide (Tigan®) suppository 200 mg; one per rectum daily as needed for nausea or vomiting to help with stomach contractions and cramping.

e) Non-steroidal anti-inflammatory or analgesic medications (acetaminophen 500 mg—1 g by mouth every 6 hours or ibuprofen 600 mg by mouth every 8 hours or naproxen 600 mg by mouth) for general pain.

f) Benzodiazepines such as lorazepam (Ativan®) by mouth 1 mg every 6–8 hours or oxazepam (Serax®) 15–30 mg every 6–8 hours to help with anxiety and sleep.

Developed by K. Brower and M. Karam-Hage.

withdrawal is established, buprenorphine can be started at 2 to 4 mg every 2 hours with a maximum recommended dose of 8 mg the first day (Table 33–9). The next day, if the patient is still in withdrawal, the first buprenorphine dose should be the total amount required in the previous 24-hour period. Then the dose can be increased gradually every 2 hours up to a maximum of 16 mg. By the third day the dose can be increased up to 32 mg per day to achieve maximum relief of withdrawal symptoms (see Table 33–9 for a typical induction regimen). Then the dose

TABLE 33–7. Sample Regimen of Clonidine for Withdrawal from All Opioids Except Methadone and Fentanyl (Duragesic®) Patches

Day	Clonidine Oral Dosage
1	0.1 mg four times daily
2	0.1 mg four times daily to 0.2 mg three times daily
3–5	Maintain day 2 dose as tolerated
6+	Decrease dose by 0.1–0.2 mg/day; reduce nighttime dose last

Developed by K. Brower and M. Karam-Hage.

TABLE 33–8. Sample Regimen of Clonidine for Withdrawal from Methadone (Up to 20–30 mg/day) or Equivalent Fentanyl (Duragesic®) Patches

Day	Clonidine Oral Dosage
1	0.1 mg four times daily
2	0.1 mg four times daily to 0.2 mg three times daily
3	0.1 mg four times daily to 0.2 mg four times daily
4–10	Maintain on day 3 dose
11+	Decrease by 0.2 mg/day; reduce nighttime dose last

Developed by K. Brower and M. Karam-Hage.

is tapered down gradually to zero within 1 to 2 weeks (a 25% reduction per day is a general rule of thumb). Methadone, can also be used for opioid detoxification; however, in the United States this can be done only at a federally approved methadone clinic. Methadone detoxification regimens will not be covered here. The reader is referred to the literature for additional information.[22]

General Patient Guidelines for Outpatient Opioid Detoxification

When treating opioid withdrawal with pharmacologic agents, patient safety is the highest priority. The first step is to educate patients about the course of withdrawal. Symptoms peak at around 5 to 7 days and may last up to 2 weeks. Patients also need to be advised regarding the side effects of the drugs used to treat detoxification. For instance, clonidine causes dizziness from low blood pressure, sedation (which may impair driving or operating heavy machinery), and dry mouth. There is also an overdose potential if clonidine is mixed with opioids or other central nervous system (CNS) sedatives or antihypertensives. The risk of these adverse events needs to be balanced with potential benefits. The side effects of buprenorphine include constipation (most commonly), sedation, and headaches. It should also be noted that there is a potential for serious overdose when buprenorphine is mixed with benzodiazepines or other sedative-hypnotics. The risk of

TABLE 33–9. Sample Regimen[a] for Buprenorphine Induction Treatment of Opioid Withdrawal

Day	Buprenorphine Oral Dosage
1	2 mg every 2 hours (max 8 mg on first day)
2	Start by total dose of day 1, with additional 2 mg every 2 hours (max 16 mg)
3	Start by total dose of day 2, with additional 4 mg every 2 hours (max 32 mg)
4–5	Maintain on dose required to alleviate withdrawal symptoms
6+	Decrease dose by 25% each day (or less if patient does not tolerate 25%)

[a]For withdrawal from any opioid including fentanyl (Duragesic®) patches. Data from reference 21.

developing physiologic tolerance to buprenorphine is high if it is used for prolonged periods. In this case buprenorphine should be slowly tapered to discontinuation. However, withdrawal from buprenorphine is easier and less severe than withdrawal from a pure agonist such as methadone.

Successful transition from treatment of withdrawal to treatment of opioid dependence in a rehabilitation setting is the most important challenge for a clinician. Patients often think that all they need is detoxification, but this is not the case because a successful outcome is tied to successful rehabilitation and acquiring recovery skills after detoxification. This goal can be accomplished by either achieving detoxification on site during rehabilitation or by quick and seamless transition of the patient from detoxification to a rehabilitation program. The more time that elapses between the two, the greater the likelihood of failure and return to drug use. This transition is especially important for patients who have engaged in ultra-rapid opioid detoxification using naltrexone or naloxone under conscious sedation. These opioid detoxification regimens are experimental and controversial and they are currently considered to be risky procedures due to several reported deaths mainly due to pulmonary edema.[23]

Nicotine Withdrawal

Smoking cessation counseling should be provided to all smokers, and those interested should be directed and assisted to achieve cessation. Furthermore, it is now a standard of practice for clinicians to screen for smoking and provide all smokers with brief advice and assistance with appropriate medications to quit or provide referral to specialized services when needed.[24]

Symptomatic detoxification from nicotine is achieved with any of the currently available nicotine replacement therapies (NRTs) or a combination thereof.[25] Several CNS neurotransmitters are affected by nicotine including DA, NE, 5-HT, glutamate, GABA, and endogenous opioid peptides. In the brain, nicotine activates nicotinic acetylcholine (nAch) receptors, which are part of the neurotransmitter-gated ion channel family and have crucial neuromodulatory roles in the CNS.[26] Nicotine dependence is assessed using the Fagerström Test for Nicotine Dependence, and a score of greater than or equal to 4 is indicative of physical dependence on nicotine.[27] Nicotine withdrawal can be measured using any of the available scales (e.g., the Wisconsin Scale for Nicotine Withdrawal). In the United States, the FDA does not have the authority to regulate tobacco products; however, it does regulate all NRT formulations. Some of the NRTs are prescription only (Rx), and some are available over the counter (OTC); others are available in both forms. The FDA has approved the following NRTs: polacrilex gum (OTC); patches (16- or 24-hour) (Rx and OTC); nasal spray (Rx); buccal inhaler (puffer) (Rx); flavored gum (OTC); and lozenges (OTC). Table 33–10 shows NRT and other smoking cessation products. Non-nicotine medications that are thought to be helpful for craving and maybe even withdrawal from nicotine include sustained-release bupropion (Zyban® or Wellbutrin-SR®), nortriptyline (Pamelor®), clonidine (Catapres®). The sustained-release form of the antidepressant bupropion was approved by the FDA with a new name (Zyban®) for the treatment of tobacco dependence. It is started 1 to 2 weeks before the quit date. It is begun at 150 mg per day for 3 to 7 days and then increased to 300 mg/day (150 mg twice daily). Bupropion blocks reuptake of DA and NE. Additionally, it acts as a noncompetitive antagonist on a high-affinity nAch receptor. It reduces nicotine reinforcement, withdrawal, and craving.[28] Doubling up the NRTs (i.e., double patch or adding NRTs to each other) is a more effective strategy for certain refractory smokers than either strategy used alone.[29] Studies have also

TABLE 33–10. Pharmacotherapies for Smoking Cessation

Medication	Dose Range and Use
Nicotine patch *Transdermal*	7–22 mg/day (started at 21 mg per day × 2 weeks then 14 mg per day × 2 weeks then 7 mg/day)
Nicotine gum *Buccal*	20–40 mg/day; 2 or 4 mg/piece; one piece every 2 hours up to 10 times/day
Nicotine lozenge *Buccal*	20–40 mg/day; 2–4 mg/lozenge; one lozenge every 2 hours, up to 10 times/day
Nicotine nasal spray *Intranasal*	16–32 mg/day; 1–2 mg/spray, one in each nostril up to 16 times/day
Nicotine vapor inhaler *Buccal*	6–16 mg/day; continuous puffing up to 10 puffs per cartridge maximum of 12 cartridges daily (approx. 120 puffs)
Bupropion *Oral tablets*	Begin at 150 mg/day × 3–7 days then 300 mg/day in twice-per-day dosing
Clonidine *Oral tablets*	0.6–1.2 mg/day, 2–3 times/day
Tricyclic antidepressants Nortriptyline Doxepin	Given by mouth once daily or in two divided doses 75–150 mg/day 150–250 mg/day

Data from reference 25.

suggested that NRTs are safe in certain high-risk patients such as those with cardiac diseases (i.e., post–myocardial infarction) and pregnant smokers, as long as the risk/benefit ratio is favorable.

Second-line pharmacotherapies include nortriptyline and clonidine. Clonidine exhibits modest efficacy in smoking cessation trials, and two meta-analyses that included a total of 13 placebo-controlled clinical trials indicate that it is superior to placebo, with odds ratios of 2.4 (1.7 to 32.8) and 2.0 (1.3 to 3.0).[30] Several tricyclic antidepressants (TCAs), that inhibit the reuptake of NE and 5-HT, such as nortriptyline, might facilitate smoking cessation, either alone or in combination with behavioral treatment. However, TCAs have significant disadvantages, including a significant anticholinergic burden, cardiac side effects, and possible lethality in overdose.[31]

Nonpharmacologic Treatments for Tobacco Cessation

Behavioral treatment delivered by a variety of clinicians (e.g., physician, psychologist, nurse, pharmacist, and dentist) increases abstinence rates. The five A's should be applied by all clinicians:[24]

- Ask if they smoke
- Advise to quit
- Assess motivation for change
- Assist if willing to change
- Arrange for follow-up

The Department of Health and Human Services, in concert with other public health and federal government agencies, has provided general guidelines for smoking cessation[24] (Table 33–11).

There are in excess of 100 studies validating the use of multimodal behavioral therapies for smoking cessation, either alone or in combination with pharmacologic therapies. Multimodal behavioral therapies without pharmacologic agents achieve double the quit rates compared with controls, and the 6-month efficacy ranges between 20% and 25%. Not every smoker requires the same amount of intervention.

One of the possible future directions in smoking cessation is the controversial notion of substituting smokeless tobacco for cigarettes. The idea is based on the premise that the exposure to most carcinogens in tobacco is a result of formation by pyrolysis during the combustion of tobacco. This approach has not been embraced widely by public health and anti-tobacco advocates because certain diseases are more prevalent in users of smokeless tobacco such as gum disease (i.e., gingivitis), and oral (mouth and lip) cancers. Among the different types of smokeless tobacco some products may be safer than others, such as the Swedish Snus® (widely available in Sweden and available OTC in some states in the United States). These contain air dried and processed tobacco that eliminates most nitrosamines that are produced by bacterial fermentation of tobacco and constitute a major group of carcinogenic substances present in tobacco. Other potentially promising developments in different phases of testing[25] include:

- Cannabinoid receptor CB_1-blockers, such as rimonabant (under FDA review)
- A combination of the nicotine antagonist mecamylamine and bupropion (Quitpack®)
- A nicotine partial agonist (Chantix® by Pfizer)
- Nicotine vaccine

TABLE 33–11. General Guidelines on How To Assist if a Patient Wants to Quit Smoking

Start bupropion-SR (Zyban® or Wellbutrin SR®) 1–2 weeks before quit date.
Help patient set a quit date (one of the most important strategies).
Remove all tobacco products the night before the quit date.
Follow-up with patient on the quit date or next day to support self-efficacy.
Provide nicotine replacement: patch, nasal spray or mouth inhaler, gum, or lozenge.
Identify and help educate a support person (best if ex-smoker).
Educate about the high risk for relapse and how to cope with it: "don't quit quitting."

Data from reference 24.

GENERAL APPROACH TO THE TREATMENT OF SUBSTANCE DEPENDENCE

The overall goals in recovery from addiction are the same for all substances and they consist of:

- Developing coping skills: establish a balanced lifestyle between stressors and positive healthy rewards
- Developing a sober social network: this can be through 12-step programs or other mutual self-help resources
- Relapse prevention skills and strategies: the recovering addict should develop a menu of options, a toolbox of coping skills
- Addressing and beginning to process prior histories of interpersonal problems, conflicts, and abuse
- Searching for a spiritual meaning for one's life

All of the above correlate with better long-term outcomes.

❻ *To facilitate recovery from addiction it is necessary to utilize a comprehensive biopsychosocial assessment that includes the motivation for change. Pharmacologic treatments are always adjunctive to psychosocial therapy.* It is important to remember that mere treatment of withdrawal is not sufficient treatment of DSM-IV-TR dependence (addiction), and that medications are always adjunctive to psychosocial therapy. Comorbid psychiatric

conditions such as anxiety, depression, insomnia, pain, and continued smoking should be addressed. All of these conditions increase the risk of relapse to use of drugs. Special precautions are needed when treating dual diagnosis and chronic pain patients with controlled substances.

Nonpharmacologic Therapy

❼ *While pharmacologic agents may help prevent relapse, psychotherapy should be the core therapeutic intervention. Motivational enhancement therapy, cognitive-behavioral therapy, 12-step facilitation, and contingency management are the best-studied forms of psychotherapy in this group of patients.*

Individual Therapy

Traditional psychodynamic therapy in the treatment of addiction often fails; however, the principles of psychodynamic therapy are still valuable and important for a clinician in order to understand the patient and help him or her work through his or her mechanisms of defense, attachment difficulties, processing grief, and coping with internal and external drives.[32] Among the validated and thoroughly studied approaches are the following:

- Enhancing motivation, known as motivational interviewing or *motivational enhancement therapy*, is designed to engage patients with basic principles like expressing empathy, highlighting the discrepancy between patients' ideals and their current behavior, and working within the framework of a specific patient's defenses.
- The development of *coping skills* is designed to help patients cope with life events, daily stressors, and managing painful affects.
- *Cognitive-behavioral therapy* (CBT) has the specific goal of learning relapse prevention techniques such as having a ready "toolbox" to deal with cravings and avoidance of triggers that have led to relapses in the past.
- *Contingency management* consists of providing positive rewards for desirable behavior and setting limits and consequences for undesirable behavior.
- *Improving interpersonal functioning* and enhancing social supports can be accomplished through 12-step facilitation (TSF), or any other mechanism for developing a sober social network.
- Finally, *engaging the spouse or significant other*, as well as the nuclear family, is a very important aspect in the initial stages, as well as in consolidating recovery.

Group Therapy

Group therapy for substance abuse/dependence includes more than three people (ideally 8 to 10) who interact in the same room for 90 to 120 minutes. Group therapy provides patients with the opportunity to bond with others; and the advantages of this can be mutual identification; dealing with shame and guilt; minimizing isolation; and providing peer acceptance and role modeling, realistic feedback, and optimism and hope for the future. The disadvantages are a lack of focus on a particular person's problem, the discussion is not always pertinent to every member, and scheduling times are inflexible. It is also less successful in small communities where people might know each other prior to formation of the group, and/or for people with certain personality disorders such as borderline, schizoid, avoidant, or paranoid.[32]

Pharmacologic Therapy

Maintenance Treatment

❽ *Certain pharmacologic agents have been helpful in the treatment of withdrawal and in drug maintenance programs.* Remaining sober following the treatment of withdrawal is extremely difficult. This is probably related to a complex interaction of biological factors (craving), social factors (lack of employment or lack of a sober social network), and psychological factors (lack of the ability to cope with negative emotions without resorting to drug use). Long-term use of medications to help achieve a reduction in drug craving or to maintain a steady state of legally supervised and predictable drug use may have a better long-term outcome than immediate abstinence. The ultimate goal is always abstinence, but these strategies may allow time to develop new behavioral strategies and a social network within which the patient will be more likely to achieve long-term sobriety.

Alcohol Dependence

Currently the three FDA-approved medications that are indicated to treat alcohol dependence are disulfiram, naltrexone, and acamprosate. Both disulfiram and acamprosate are indicated in patients who have already achieved initial abstinence. Only naltrexone may be initiated without regard to abstinence status.

Disulfiram

Disulfiram works by irreversibly blocking the enzyme aldehyde dehydrogenase, a step in the metabolism of alcohol, resulting in increased blood levels of the toxic metabolite acetaldehyde. As levels of acetaldehyde increase, the patient experiences decreased blood pressure, increased heart rate, chest pain, palpitations, dizziness, flushing, sweating, weakness, nausea and vomiting, headache, shortness of breath, blurred vision, and syncope. These effects are commonly referred to as the disulfiram-ethanol reaction. Their severity increases with the amount of alcohol that is consumed, and they may warrant emergency treatment. Disulfiram is contraindicated in patients who have cardiovascular or cerebrovascular disease, because the hypotensive effects of the disulfiram-alcohol reaction could be fatal in such patients or in combination with antihypertensive medications. Disulfiram is relatively contraindicated in patients with diabetes, hypothyroidism, epilepsy, liver disease, and kidney disease as well as impulsively suicidal patients.

Psychologically, disulfiram works through negative reinforcement, and drinking is avoided to prevent the aversive disulfiram-ethanol reaction. The classic study by Fuller and colleagues demonstrated that the efficacy of disulfiram was compromised by non-compliance.[33] Although that randomized controlled trial is widely cited as a negative study, because no difference between the three groups (disulfiram 250 mg daily, disulfiram 1 mg daily, and a no disulfiram condition) was found for continuous abstinence rates over a 1-year follow-up period, the 250-mg group drank on significantly fewer days (49 days) during that 1-year period than the other groups (75.4 and 86.5 days for the 1-mg disulfiram and no disulfiram groups, respectively). Other controlled trials have demonstrated that disulfiram can be highly effective when procedures for enhancing compliance are employed, such as supervised administration.[34] This may be particularly true when supervised administration is coupled with receiving incentives, such as described above for contingency management techniques, behavioral couples therapy (BCT), and the community reinforcement approach.

The usual starting dose of disulfiram is 250 mg orally per day, and the range is 125 to 500 mg daily. Compared to 250 mg daily, the larger dose is recommended in the absence of a disulfiram-ethanol reaction, and the smaller dose is given when intolerable side effects are experienced. Dosing begins only after the BAL is zero (usually 12 to 24 hours after the last drink) and after the patient understands the consequences of the disulfiram-ethanol reaction. The most common side effects are rash, drowsiness, metallic or garliclike taste, and headache. If drowsiness occurs, the dose may be lowered or given at night. Other adverse effects include optic neuritis and peripheral neuropathy. Because of potential hepatotoxicity with disulfiram including rare cases of fulminant liver failure, estimated at 1 in 25,000 treated patients,[34] baseline liver function tests (LFTs) and periodic monitoring are recommended. If serum levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) are greater than three times normal values, then disulfiram should be withheld and the tests repeated every 1 to 2 weeks until they are normal. Once LFTs are within prescribing range, they may be repeated every 1 to 6 months. Although elevated LFTs may signal disulfiram-induced hepatotoxicity, the more likely cause in clinical practice is non-compliance and ethanol-induced hepatotoxicity. Alcohol-dependent patients are also at high risk for viral hepatitis. Another uncommon side effect of disulfiram is psychosis, which has been reported in doses exceeding 500 mg daily, especially in predisposed patients. Nevertheless, alcohol-dependent patients with schizophrenia and other co-occurring mental disorders have received disulfiram at usual therapeutic doses without difficulties.[35]

The disulfiram-ethanol interaction is described above. Depending on the dose of disulfiram, sensitivity to disulfiram, amount of alcohol consumed, and metabolism, patients may be at risk to have an adverse interaction with alcohol for 2 to 14 days after stopping disulfiram (5 days on average) and should be warned accordingly. See Table 33–3 for additional drug-drug interactions with disulfiram.

Naltrexone

Naltrexone is a competitive opioid antagonist, especially at μ opioid receptors, that decreases alcohol intake in both animals and humans. There is evidence that it works by decreasing both craving for alcohol and alcohol-induced euphoria. The large majority of over 15 double-blind randomized controlled trials of naltrexone versus placebo demonstrate its moderate efficacy for decreasing relapse to heavy drinking,[36] but not for increasing rates of total continuous abstinence. The usual therapeutic dose of naltrexone is 50 mg orally per day, with a range from 25 to 100 mg. The 25-mg dose is commonly given initially as a test dose to minimize side effects, especially nausea, and then increased to 50 mg daily as tolerated. An alternative dosing regimen is 100 mg on Mondays, 100 mg on Wednesdays, and 150 mg on Fridays, which is most conducive for patients taking naltrexone under conditions of supervised observation.

Because naltrexone can precipitate withdrawal in patients dependent on opioids, the first dose should be withheld for 7 to 10 days following the last use of opioids and only when the urine drug screen for opioids is negative. Also, naltrexone can be hepatotoxic, albeit not typically at doses less than 250 mg daily. Nevertheless, the same guidelines for monitoring liver function tests as with disulfiram (described above) are recommended. The most common side effects are nausea, headache, fatigue, and nervousness. It is important for patients to carry a pocket warning card or wear a warning bracelet in the event that emergency treatment is needed, because they will be insensitive to opioid analgesia unless toxic doses are administered. Patients need to be warned of the potential for an opioid overdose under two different conditions. First, dosing with opioids to reverse opioid insensitivity (i.e., naltrexone's competitive blockade of opioid receptors) requires very high doses of opioids that can cause respiratory depression and death. Second, chronic antagonist therapy with naltrexone may cause patients to become hypersensitive to opioid drugs after stopping naltrexone, thereby facilitating respiratory depression and death when opioids are used.

Reported predictors of naltrexone efficacy include a family history of alcoholism, early age at onset of drinking problems, high levels of the active metabolite β-naltrexol, and medication adherence.[37] Combining naltrexone with disulfiram had no advantage over either medication alone in one study of alcohol-dependent patients with comorbid psychiatric disorders.[35] Combining naltrexone with acamprosate is discussed below in the section on acamprosate. Combining naltrexone with CBT possibly may have an advantage over combining naltrexone with other psychotherapies.[38] Long-acting intramuscular forms of naltrexone designed for once-monthly administration have been efficacious on some measures of drinking in randomized controlled trials.[39]

Naltrexone can theoretically increase the risk of hepatotoxicity if combined with disulfiram, although in practice this

was not demonstrated.[35] As mentioned above, it can reverse the effects of opioid receptor agonists, rendering them therapeutically ineffective. Finally, somnolence and lethargy have been reported in combination with the antipsychotic thioridazine.

Acamprosate

Acamprosate is an NMDA receptor antagonist that was approved by the FDA in 2004, but it has been available in Europe for nearly 20 years. Alcohol use acutely inhibits NMDA receptors and chronically causes upregulation of NMDA receptors. During alcohol withdrawal and post–acute alcohol withdrawal, increased activity of the NMDA system is caused by upregulation of receptors and the absence of alcohol-related inhibition. Acamprosate is believed to modulate and normalize the NMDA receptor system, although it is ineffective in diminishing acute withdrawal symptoms. It may also have some GABA-enhancing activity.

The efficacy of acamprosate has been extensively reviewed.[40] In contrast to both disulfiram and naltrexone, acamprosate increases continuous abstinence rates in alcohol-dependent patients for periods of 3 to 12 months.[40] Preliminary evidence suggests that combining acamprosate and naltrexone may be more effective than using either one alone, and a large-scale randomized controlled trial to confirm the efficacy of the combination was recently completed and will be published soon.[41] Project COMBINE also compared medical management alone to medical management in combination with a "combined behavior intervention" (consisting of elements from CBT, MET, and TSF). Combining acamprosate with disulfiram may also increase its efficacy.[42]

The therapeutic dose of acamprosate is 666 mg orally three times daily, and it is supplied as a 333 mg tablet. It can be started at the full dose in most patients without titration. It differs from disulfiram and naltrexone in that it is excreted by the kidneys without liver metabolism. Consequently, it is contraindicated in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/minute), and dose reduction is necessary when the creatinine clearance is between 30 and 50 mL/minute. The most common side effects are gastrointestinal and include nausea and diarrhea. Rates of suicidal thoughts were also increased in patients treated for 1 year with acamprosate (2.4%) versus placebo (0.8%). If necessary the total daily dose may be decreased by 1 to 3 tablets (333–999 mg) per day to alleviate side effects.

Naltrexone can increase blood levels of acamprosate by increasing its absorption, but the clinical significance of this is not known.

Other Agents

Anticonvulsants, especially topiramate, and serotonergic drugs, especially ondansetron, show promise in initial, but well-designed, randomized controlled trials.[43] Further studies are needed. Buspirone is well studied, but results are inconsistent. Finally, a recent meta-analysis of antidepressants to treat alcohol dependence with or without comorbid depression concluded that any beneficial effects were modest at best.[44]

Stimulant Dependence

There are no proven pharmacotherapies for treatment of cocaine or amphetamine dependence. Disulfiram, however, shows some promise in randomized controlled trials for treating cocaine dependence at doses of 250 mg daily, especially in combination with CBT.[45] Its mechanism of action for treating cocaine dependence is not known, but may be due to its inhibition of the dopamine β-hydroxylase enzyme that converts DA to NE in the brain. The resulting increase in DA levels may counter the DA-deficient state that is believed to underlie cocaine withdrawal and craving.

Opioid Dependence

In certain patients who have failed one or more abstinence-based treatments for opioid dependence, maintenance treatment might be the best possible option.

After the conclusion of withdrawal, some patients still don't feel their usual selves for a long time and may relapse to using drugs again, just to "feel normal." Long-term use of opioids results in changes in the brain and the brain might not readily return to its prior homeostasis. Since the goal of treatment is to encourage stability, both in the body and in the patient's life, if an individual is not successful in tapering off of opioids because of a re-emergence of severe withdrawal or a return to opioid use, then maintenance treatment should be considered.

Opioid Agonists

The time-honored opioid agonist treatment for opioid dependence is methadone maintenance, which is beyond the scope of this chapter. In the United States methadone maintenance cannot be provided except in officially designated and approved methadone clinics. The more recent development of the Office-Based Opioid Treatment (OBOT) exclusively utilizes buprenorphine, a partial μ agonist.[21] The effective maintenance dose of buprenorphine (Suboxone®) is usually between 8 and 16 mg per day, with maximum reported efficacy at 64 mg per day. Patients receiving buprenorphine maintenance should sign a treatment contract requiring full compliance, financial responsibility for treatment, adherence to office policies, respectful behavior to staff, agreement to provide random urine samples for drug screens, and patients should bring their bottles for pill counts at every visit. In the event of failure of OBOT, the alternative to buprenorphine maintenance is a referral to an approved methadone clinic where methadone is used at minimal effective doses of 80 mg per day or higher. Under the provisions of the OBOT law physicians may prescribe buprenorphine (Suboxone® or Subutex®) in their office if they meet requirements of expertise in the area of substance abuse or if they receive 8 hours of approved training.[21] In either case a registration with the Drug



Patient Encounter 3

PC, a 19-year-old man, has undergone detoxification of his 3-bags-per-day addiction to heroin. The detoxification regimen began when he had been heroin-free for 24 hours and was undergoing some mild withdrawal symptoms. He was begun on 8 mg daily of sublingual buprenorphine, and the dose of buprenorphine was slowly tapered off during the next 4 weeks. He had begun snorting heroin at about 15 years of age and eventually had progressed to injecting his daily heroin. He dropped out of high school at 17 years of age, prior to graduation, and has never worked, except once in a fast food restaurant for a 2-week period. Since achieving abstinence he has come to realize that he has no legal means of earning a living and he is reluctant to return home to his parents since they have recently divorced. He feels he is worthless and has wasted his life up to now.

- What are the most immediate concerns regarding this young man's newly achieved abstinence?
- How can he be helped to maintain abstinence?
- What are the long-term treatment goals for this young man?

Enforcement Administration (DEA) to obtain a specially designated DEA number is needed after receiving a "waiver."

Opioid Antagonists

Naloxone, naltrexone, and nalmefene (not available yet in the United States for clinical use) can be used to reinforce abstinence. The long-acting naltrexone is especially ideal for health professionals or others who are highly motivated or face major consequences if they do not maintain their abstinence. It is important not to initiate an antagonist until the withdrawal period is over and after 7 to 12 days from the last use of opioid agonists. This is necessary to avoid precipitating more severe withdrawal due to hypersensitive or up-regulated opioid receptors as a result of prior long-term or heavy use of opioid agonists. Naloxone can be used 0.2 to 0.4 mg subcutaneously (naloxone challenge) to test if an individual is indeed abstinent and to make sure it does not induce withdrawal before giving the longer-acting oral naltrexone, although this technique is rarely used in actual practice. Most opioid-dependent patients will be honest about how recently they have used when (1) they understand that severe withdrawal is a consequence of premature naltrexone administration, and (2) a urine test is obtained.

OUTCOME EVALUATION

- To determine immediate treatment outcomes for intoxication and withdrawal syndromes at the individual patient level, evaluate parameters such as blood pressure, heart rate, respirations, and body temperature as well as mental state. Choose from a number of validated and standardized rating scales to monitor the responsiveness of withdrawal syndromes to medical treatment. To determine the overall effectiveness of your health system for the treatment of substance abuse and dependence, you could monitor outcomes using sentinel events such as the rates of cardiopulmonary arrest, seizures, discharges against medical advice, patient violence, and use of physical restraints. The ultimate goal should be to enable the transition of patients to formal substance abuse treatment when indicated, because this is the optimal outcome of treatment for substance-induced intoxications and withdrawals.
- ❾ *A major component of successful treatment of addiction is to continue monitoring the use of medications such as disulfiram, naltrexone, or acamprosate designed to decrease craving or to block the hedonic effects of abused substances. Also, it is important to identify a mechanism for long-term support of sobriety that might be appropriate for a specific individual such as Alcoholics Anonymous, a spiritual group, or professional recovery programs for professionals such as doctors, nurses, and police officers.*
- Important outcome indicators to evaluate postintoxication and/or postwithdrawal treatment of substance abuse and dependence can be divided into three major groups: decreased consumption of substances, decreased problems associated with substance use, and increased psychosocial functioning. Although it is less commonly employed, a quality-of-life scale can help determine how substance abuse/dependence treatment has affected your patients' lives. If you are involved in the cost-justification of services, a cost-benefit analysis could also become important, although this is more often used at the administrative level, rather than the patient care level. In the cases in whom complete abstinence has not been achieved, quantify the consumption of substances using: quantity-frequency measures; rates of abstinence; and time to first relapse as determined by interviews and self-report, and by biological markers such as urine and blood tests. One example of an instrument to measure alcohol-related problems is The Drinker Inventory of Consequences.[46] Another scale that you could use to determine the severity of alcohol-related problems is the Addiction Severity Index, which measures problems associated with any type of substance dependence across a variety of dimensions, including legal, family, psychiatric, medical, and social.[47] If you are concerned about the effects of substance abuse or dependence on cognitive abilities in an older adult, the Mini-Mental State Exam is a commonly used scale. Scores of 26 and higher are generally considered to indicate acceptable cognitive ability with regard to everyday functioning.[48] Quantify overall psychosocial functioning using the Global Assessment of Functioning Scale which is readily accessible in DSM-IV-TR.[8]



Patient Care and Monitoring

1. By evaluating the patient's history and symptoms, determine if substance intoxication or withdrawal are likely.
2. If drug intoxication is a likely scenario:
   - Conduct a physical exam and measure blood pressure, pulse, respiratory rate, and body temperature.
   - In most cases, management of intoxication is supportive. The most important goal is to maintain cardiopulmonary function. If consciousness is impaired, obtain blood chemistries and administer intravenous glucose and thiamine (100 to 250 mg).
   - Cocaine or stimulant intoxication may require administration of a small dose of a short-acting benzodiazepine (e.g., lorazepam 1 to 2 mg) for agitation or severe anxiety. Antipsychotics (e.g., haloperidol 2 to 5 mg) should be used only if psychosis is present. If hyperthermia is present, initiate cooling measures.
   - Observe the patient until the intoxication has resolved [if alcohol, the BAL should be less than 80 mg% (0.08% or 17.4 mmol/L)]. Encourage the patient to consider treatment for substance abuse, especially if this is not the first episode of intoxication.
3. If substance withdrawal is the likely scenario:
   - Determine from which substance or substances the patient is withdrawing.
   - Conduct a physical exam to determine if medical problems are present.
   - If withdrawal is from alcohol, administer the CIWA-Ar to determine withdrawal severity. A score of 8 to 10 denotes relatively mild withdrawal, and the patient can be treated as an outpatient with supportive care only. A score from 11 to 14 can be treated on either an outpatient or inpatient basis, with either supportive care or with benzodiazepines, depending on the presence of underlying medical problems and the prior history of the severity of withdrawal. A score greater than or equal to 15 merits strong consideration of inpatient treatment combined with medications. Those with a score of 20 or greater should always be treated in an inpatient setting with medications.
   - Always treat AWS or DTs in the inpatient setting. The drug of choice for both is a benzodiazepine.
   - Withdrawal from opioids is uncomfortable but unlikely to be fatal unless the patient has underlying medical problems. Administer the COWS to determine the severity of withdrawal. Those with a score of 5 or less require no pharmacologic intervention, while those with scores from 6 to 24 are likely to benefit from either a symptoms-based approach or the initiation of buprenorphine. Those with scores greater than 25 should receive either buprenorphine or an alternative full μ agonist.
4. Withdrawal from nicotine is treated in the outpatient setting. Symptomatic detoxification from nicotine is achieved with any single or combination of NRTs. Additional nonnicotine medications such as bupropion, nortriptyline, and clonidine may be helpful to reduce craving and various other withdrawal symptoms. Including a behavioral therapy component increases abstinence rates when combined with pharmacologic treatment.
5. The overall goals in recovery from addiction are the same for all substances and include improved coping skills and relapse prevention. Methods for accomplishing long-term sobriety include both nonpharmacologic and pharmacologic means.
   - Consider initiation of buprenorphine or methadone maintenance treatment for opioid dependence. In the United States buprenorphine is easier to arrange since physicians can be approved to prescribe buprenorphine following a short course of federally-approved training.
   - Disulfiram (250 mg per day) can be used to promote abstinence from alcohol. Acamprosate and naltrexone can be used to decrease craving for alcohol, but they are not likely to result in complete abstinence from alcohol use.

ABBREVIATIONS

ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
AWS:	alcohol withdrawal seizures
BAL:	blood alcohol level
BCT:	behavioral couples therapy
CB_1:	cannabinoid-1 receptor
CBT:	cognitive-behavioral therapy
CIWA-Ar:	Clinical Institute Withdrawal Assessment for Alcohol-Revised
CNS:	central nervous system
COWS:	Clinical Opiate Withdrawal Scale
CRF:	corticotropin-releasing factor
DA:	dopamine
DAWN:	Drug Abuse Warning Network
DEA:	Drug Enforcement Administration
DSM-IV-TR:	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
DTs:	delirium tremens
ED:	emergency department
FDA:	Food and Drug Administration
GABA:	γ-aminobutyric acid
5-HT:	serotonin
IM:	intramuscular
IV:	intravenous
LFT:	liver function test
MET:	motivational enhancement therapy
NA:	nucleus accumbens
nAch:	nicotinic acetylcholine receptor
NE:	norepinephrine
NMDA:	*N*-methyl-D-aspartate

NRT:	nicotine replacement therapy
OBOT:	Office-Based Opioid Treatment
OTC:	over the counter
Rx:	prescription medication
SC:	subcutaneous
TCA:	tricyclic antidepressant
THC:	tetrahydrocannabinol
TSF:	12-step facilitation
VTA:	ventral tegmental area

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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34 SCHIZOPHRENIA

Deanna L. Kelly and Elaine Weiner



LEARNING OBJECTIVES

UPON COMPLETION OF THE CHAPTER, THE READER WILL BE ABLE TO:

1. Explain the pathophysiologic mechanisms that are thought to underlie schizophrenia.
2. Recognize the signs and symptoms of schizophrenia and be able to distinguish among positive, negative, and cognitive symptoms of the illness.
3. Identify the treatment goals for a patient with schizophrenia.
4. Recommend appropriate antipsychotic medications based on patient-specific data.
5. Compare the side-effect profiles of individual antipsychotics.
6. Describe the components of a monitoring plan to assess the effectiveness and safety of antipsychotic medications.
7. Educate patients and families about schizophrenia, treatments, and the importance of adherence to antipsychotic treatment.

KEY CONCEPTS

❶ Patients presenting with odd behaviors, illogical thought processes, bizarre beliefs, and hallucinations should be assessed for schizophrenia.

❷ A diagnosis of schizophrenia is made clinically, as there are no psychological assessments, brain imaging, or laboratory examinations that confirm the diagnosis.

❸ The goals of treatment are to reduce symptomatology, decrease psychotic relapses, and improve patient functioning and social outcomes.

❹ The cornerstone of treatment is antipsychotic medications. Because most patients with schizophrenia relapse when not medicated, long-term treatment is usually necessary.

❺ Psychosocial support is needed to help improve functional outcomes.

❻ Compared to the older antipsychotics (first-generation antipsychotics), the more recently developed second-generation antipsychotics are associated with a lower risk of motor side effects (tremor, stiffness, restlessness, and dyskinesia); may offer greater benefits for affective, negative, and cognitive symptoms; and may prolong the time to psychotic relapse.

❼ Second-generation antipsychotics as a class are heterogeneous with regard to side-effect profiles. Many second-generation antipsychotics carry an increased risk for weight gain and for the development of glucose and lipid abnormalities; therefore careful monitoring is essential.

❽ Education of the patient and family regarding the benefits and risks of antipsychotic medications and the importance of adherence to their therapeutic regimens must be integrated into pharmacologic management.

In most cases schizophrenia is a chronically debilitating disorder and is likely one of the most devastating of chronic medical illnesses. Conceptually, schizophrenia might better be thought of as a clinical syndrome, comprising several disease entities that manifest with psychotic symptoms, including hallucinations, delusions, and disordered thinking. Commonly, these more flagrant symptoms are accompanied by more insidious ones, including cognitive impairment (abnormalities in thinking, reasoning, attention, memory, and perception), impaired insight and judgment, loss of motivation (avolition), loss of emotional range (restricted affect), and a decrease in spontaneous speech (poverty of speech). The later three symptoms are termed negative symptoms, and when taken together, are frequently called the deficit syndrome. Cognitive impairments and negative symptoms account for much of the poor social and functional outcomes observed in schizophrenia. Schizophrenia is the fourth leading cause of disability among adults and is associated with substantially lower rates of employment, marriage, and

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Patient Encounter, Part 1

AG is a 28-year-old single African-American male with an approximately 3-year history of paranoia, increasing use of marijuana and cocaine, and poor work performance. His symptoms seemed to intensify around his being caught taking money from his girlfriend's bank account to buy cocaine. Since then he has become suspicious that the police were watching his movements and that people on the street knew personal information about him. He has left several jobs one after another due to his belief that other employees were sabotaging him and that people were talking behind his back. He occasionally hears his father speaking to him but has not seen him in 10 years. He is sad and hopeless about the state of his life and very guilty about his substance abuse and stealing from his girlfriend. Though supportive of him, the patient's girlfriend is feeling somewhat frustrated by the patient's withdrawal from her and reluctance to socialize to the extent that they had in the past.

- What diagnoses are suggested by this presentation?
- What additional information would help to clarify the diagnosis?

independent living compared to population norms. Approximately 10% of people with schizophrenia die by suicide.[1] However, earlier diagnosis and treatment, as well as advances in research and newer treatment developments, have led to better outcomes for people who suffer from this complex and challenging illness.

EPIDEMIOLOGY AND ETIOLOGY

One percent of the world's population suffers from schizophrenia and symptoms usually first present in late adolescence or early adulthood.[1] While equally prevalent between genders, symptoms generally appear earlier in males, and males have a younger age at first hospitalization (15 to 24 years) compared to females (25 to 34 years). This earlier age of onset leads to a greater disruption in the successful completion of developmental milestones, which may account for the poorer functional outcomes seen in males compared to females. Men are more likely to be treated in the hospital settings and generally account for 60% to 70% of the total inpatient population with this illness. There does not appear to be significant differences in the incidence or prevalence across cultures or among racial or ethnic groups.

The etiology of schizophrenia remains largely unknown, though the evidence strongly supports a genetic basis for the disorder. First-degree relatives of patients with schizophrenia carry a 10% risk of developing the disorder. When both parents have the diagnosis, the risk to their offspring is 40%. For monozygotic twins, the likelihood of one twin developing the illness if the other twin has schizophrenia is about 50%. Many genes have been weakly associated with the development of schizophrenia; however, no clear association exists for any one gene. There is probably no single "schizophrenic gene." Recent data, however, suggest that genes encoding dopamine receptors, serotonin receptors, and the enzyme that metabolizes dopamine, catechol-O-methyltransferase (COMT), may be implicated in the etiology of schizophrenia.[2] Environmental stimuli or triggers along with genetic liability may contribute to the expression of the illness. Some data suggest that intrauterine exposure to viral or bacterial infections may be a risk factor; however, more research is needed in this area.

PATHOPHYSIOLOGY

The oldest theory associated with the pathophysiology of schizophrenia is the dopamine hypothesis, which proposes that psychosis is due to excessive dopamine in the brain. This hypothesis was formed in the late 1950s, following the discovery that chlorpromazine, the first antipsychotic drug, acted as a postsynaptic dopamine antagonist. There is evidence from many pharmacologic challenge studies that drugs that lead to an increase in dopamine (e.g., cocaine and amphetamines) increase psychotic symptoms, while drugs that decrease dopamine (as do all current antipsychotic medications) decrease psychotic symptoms. A wide array of scientific work over the last several decades, including functional magnetic resonance imaging (MRI), positron emission tomography (PET), computed tomography (CT), and studies of dopamine metabolites have revealed a more complicated picture with both hyperdopaminergic, as well as hypodopaminergic brain regions. Hypodopaminergic activity observed in the prefrontal lobe is thought to relate to the core negative symptoms associated with schizophrenia. Thus, a more modern reworking of the dopamine hypothesis is the "dysregulation hypothesis" which takes these findings into account.[3] It is possible, however, that the dopamine abnormalities hypothesized to underlie the etiology of schizophrenia may represent compensatory changes that occur secondary to other pathophysiologic abnormalities intrinsic to the illness. Despite the accumulation of knowledge surrounding dopamine's etiologic relationship to schizophrenia, other neurotransmitter systems have been implicated. Some investigators have suggested that a combined dysfunction of the dopamine and glutamate transmitter systems may better explain the disorder.[4] There has also been a great deal of speculation regarding a role for serotonin receptor antagonism in antipsychotic efficacy,[5] as many second-generation antipsychotics (SGAs) are active at serotonin receptors. Serotonin receptor binding may be important to drug action, possibly by modulating dopamine activity in **mesocortical** pathways. However, a compelling pathophysiologic theory relating to dopamine and serotonin receptor affinities does not yet exist. It is important to note that to date,



Clinical Presentation of Schizophrenia

General

❶ Schizophrenia is a chronic disorder of thought and affect, causing a significant disturbance in the individual's ability to function vocationally and interpersonally. The onset of symptoms in most cases is insidious, usually preceded by a prodromal phase characterized by gradual social withdrawal, diminished interests, changes in appearance and hygiene, changes in cognition, and bizarre or odd behaviors. Despite the tendency of the media to portray a stereotype, the clinical presentation of a person with schizophrenia is extremely varied. Hallmark symptoms include psychotic symptoms, negative symptoms, and cognitive impairments that last for at least 6 months.

Symptoms

Psychotic symptoms: These symptoms are sometimes called positive symptoms, as they are "added on to" a person's normal experience. They may include hallucinations (distortions or exaggeration of perception), delusions (fixed false beliefs), and thought disorder (illogical thought and speech). Hallucinations, most frequently auditory, can also be visual, olfactory, gustatory, and tactile. Auditory hallucinations may be experienced as voices or as thoughts that feel distinct from the person's own thoughts. The content of the hallucinations is variable but often they are threatening or commanding (i.e., commanding the person to perform a particular action). Patients may feel compelled to perform the commanded task or may experience much anxiety when they do not. Delusions frequently involve fixed false beliefs despite invalidating evidence, and may be bizarre in nature. Often they have paranoid themes, which may make the patient suspicious of others. The characteristic thought disorder of schizophrenia includes loosening of associations, **tangentiality**, **thought blocking**, **concreteness**, circumstantiality, and perseveration. Thinking and speech may be incomprehensible and illogical. Subtle disturbances in associative thinking may develop years before disorganized thinking (formal thought disorder).

Negative symptoms: So called because they are qualities "taken away" from the personality, include **i**mpoverished speech and thinking, lack of social drive, flatness of emotional expression, and apathy. Though quite ubiquitous, these symptoms are difficult to evaluate because they occur in a continuum with normality, and can be due to secondary causes, including medication side effects, mood disorder, environmental understimulation, or demoralization. When due to schizophrenia itself, they are termed primary negative symptoms or deficit symptoms. The best strategy for differentiating primary from secondary negative symptoms is to observe for their persistence over time, despite efforts at resolving the other causes. Approximately 10% to 15% of people with schizophrenia may present primarily with negative symptoms; these people may be referred to as having a deficit syndrome.

Cognitive symptoms: Neuropsychological research shows that patients with schizophrenia show abnormalities in the areas of attention, processing speed, verbal and visual memory, working memory, and problem solving. There is a loss of, on average, one standard deviation of preillness IQ, with the average IQ of between 80 and 84.

antipsychotics without any primary or secondary dopamine-modulating properties have been ineffective for the treatment of positive symptoms of schizophrenia.

CLINICAL PRESENTATION AND DIAGNOSIS

People with schizophrenia may appear uncooperative, suspicious, hostile, anxious, or aggressive due to their misinterpretation of reality. They may have poor hygiene and appear unkempt, as psychosis, as well as depressive symptoms, may lead to impaired self-care. Sleep and appetite are often disturbed. People with schizophrenia often have difficulty living independently in the community and have difficulty forming close relationships with others. Additionally, they have problems with initiating or maintaining employment. Rates of illness denial are high, as is non-compliance with medications, particularly early in the course of illness, increasing the risk for relapse and hospitalization. Comorbid medical disorders, such as type 2 diabetes and chronic obstructive pulmonary disease, are prevalent in schizophrenia due to sedentary lifestyles, poor dietary habits leading to obesity, and heavy cigarette smoking. Approximately

85% of people with schizophrenia smoke, and approximately 50% use drugs and alcohol, rates that are much higher than in the general population.[6]

❷ *There is no objective diagnostic or laboratory measure or brain imaging technique to diagnose schizophrenia. Biological markers are being investigated, but currently, the diagnosis is made by ruling out other causes of psychosis and meeting specified diagnostic criteria that are based on symptoms and functioning. Family history of psychiatric disorders is helpful in supporting the diagnosis. The commonly accepted diagnostic criteria for schizophrenia are from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*[7] (Table 34–1).

TABLE 34–1. Diagnostic Criteria for Schizophrenia

A. *Characteristic symptoms:* Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):[a]
- Delusions
- Hallucinations
- Disorganized speech (e.g., frequent derailment/incoherence)
- Grossly disorganized/catatonic behavior
- Negative symptoms (e.g., flat affect, alogia, avolition)

B. *Social/occupational dysfunction:* For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to onset (or when onset is in childhood or adolescence, failure to achieve the expected level of interpersonal, academic, or occupational achievement).

C. *Duration:* Continuous signs of disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet criterion A (i.e., active-phase symptoms), and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of disturbance may be manifested by only negative symptoms, or by two or more symptoms listed in category A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. *Ruling out other disorders:*
- Schizoaffective and mood disorder exclusion: Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either (1) no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.
- Substance/general medical condition exclusion: The disturbance is not due to the direct physiologic effects of a substance (e.g., drug of abuse or medication) or a general medical condition.
- Pervasive developmental disorder: If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

[a]Only one symptom from category A is required if delusions are bizarre or hallucinations consist of a voice maintaining a running commentary on the person's behavior or thoughts, or two or more voices conversing. Adapted from reference 7 with permission.

COURSE AND PROGNOSIS

The onset of psychosis, whether insidious or acute, is marked by difficulties for patients, families, and clinicians. The severity of symptoms may be denied, and the nature of behavioral disturbances may be misunderstood. Patients may try to keep symptoms hidden from family and friends; they may remove themselves emotionally and geographically from social support networks. The onset of psychosis may be confounded by substance abuse. The gradual development of psychosis, combined with the frequent misunderstanding of symptoms, generally leads to a substantial time period between symptom onset and diagnosis and treatment. While not unequivocal, recent data suggest that people with fewer episodes of acute psychosis and those treated early on in their illness may have a better prognosis. Therefore, the first challenge of optimal therapy is to move treatment initiation closer to the onset of psychosis.

Although the course of schizophrenia is variable, the long-term prognosis for independent function is often poor. The course of illness is marked by intermittent acute psychotic episodes with a downward decline in psychosocial functioning. Over time, a patient may become more withdrawn, bizarre, and non-functional. Complete return to full premorbid functioning is uncommon. Many of the more dramatic and acute symptoms fade with time, but severe residual symptoms may persist. Family and friends often find this illness difficult to interpret and understand. Involvement with the law is fairly common for misdemeanors such as vagrancy, loitering, and disturbing the peace. The overall life expectancy is shortened primarily due to suicide, accidents, and the inability of self-care. The lifetime risk of suicide for people with schizophrenia is about 10%.[8] Persistent compliance with a tolerable drug regimen improves prognosis, though relapse without medication exceeds 50% annually.

TREATMENT

Desired Outcomes

❸ *The goal is for people with schizophrenia to receive, as early in their course as possible, comprehensive treatment designed to achieve functional outcomes. While in the past, the primary treatment goal was to decrease positive symptoms and the associated hostile and aggressive behaviors, newer approaches to treatment have a wider focus, treating not only positive symptoms, but also negative, depressive, and anxious symptoms. The aim is to not only reduce symptomatology and psychotic relapses, but also to improve functional and social outcomes.*[9] It is important to keep in mind that some symptoms respond earlier than others. Combativeness, hostility, sleep disturbances, appetite, and hallucinations may be some of the first symptoms to improve. Improvements in negative symptoms, cognitive functioning, social skills, and judgment generally require a longer period to improve.



Patient Encounter, Part 2

Past Psychiatric History

Though AG describes himself as being depressed "all my life" and remembers that he felt able to read peoples' minds in high school, he denied prior psychiatric treatment until his first hospitalization 2 years ago at the height of his paranoia. At that time, he believed there was a conspiracy against him. He lived in constant fear that his phone was tapped and his home was bugged. He felt he was being watched in public places, and therefore he began avoiding going out. He experienced voices commenting on his behavior and believed the television was talking to him and that shows were about him. At times he felt his "brain was being squeezed" for information, so that his mind was being read. He believed his girlfriend was having affairs, and he could not be reassured. He reported decreased appetite, difficulty sleeping, and suicidal ideation. His toxicology screen and blood alcohol test in the emergency department were negative. In the hospital he was given a diagnosis of major depressive disorder with psychotic features. He was started on olanzapine 10 mg/day for psychosis and fluoxetine 20 mg/day for depression, with some improvement.

Past Medical History

He has no history of medical illness, head trauma, or seizure disorder.

Social History

He grew up in an upper middle class family, completed high school, and entered the Navy where he was discharged dishonorably due to not following rules. He began using alcohol in high school and continued to use other substances intermittently since then. He has held several jobs, the longest for 6 months. He thinks he might apply for disability.

Family Psychiatric History

His father had an alcohol problem.

Mental Status Exam

Appearance: Nicely dressed and groomed. No abnormal movements. Poor eye contact.
Speech: Quiet and somewhat monotonous.
Mood: Nervous.
Affect: Guarded and mildly anxious with restricted range.
Thought content: Adequate historian but with a tendency to leave out detail. Experiences hearing others call his name, and interpreting the car lights coming down his street as meaning people are out to get him. He denies suicidal or homicidal thoughts.
Thought processes: Logical but vague.
Cognition: Grossly intact.
Insight and judgment: Mixed, as he can at times question his thinking, but at other times has full conviction of his beliefs. He is currently taking his medication and cooperating with the evaluation appointments.

- Given this additional information, how was your differential changed?
- What would the goals of outpatient treatment be?
- What pitfalls are likely to occur during outpatient treatment?

Over the past few years, partial recovery and remission have become an increasingly prominent paradigm for conceptualizing the treatment of schizophrenia. In working toward these goals, a range of interventions must be incorporated into long-term treatment strategies, including not only pharmacologic interventions, but psychosocial therapies as well. Current treatment planning is increasingly focused on functional outcomes by providing treatment and recovery-oriented services to people with schizophrenia. Also, newer trends such as evidence-based practice, whereby new information from the published literature gets incorporated into clinicians' prescribing behavior, have led to the use of interventions that promote a remission or recovery attitude.[10] Moreover, recent attempts have been made to address and measure patient satisfaction with treatments and instill hope and optimism in order to attempt to empower patients.

Unfortunately, this new paradigm is in the earliest stages of implementation, and despite these advances and recent treatment improvements, long-term outcomes currently remain poor, and many patients fail to receive comprehensive care.

General Approach to Treatment

A person presenting with the initial episode of psychosis requires a comprehensive assessment and careful diagnosis, as psychosis is not pathognomonic for schizophrenia. The differential diagnosis includes a wide array of neurologic, psychiatric, and general medical conditions (Table 34–2). Often, people present with a short history of psychopathology and cannot recall historical information accurately. This lack of information, along with frequent comorbid substance abuse, medical illnesses, and psychosocial stressors often confound the case. Patients presenting with psychotic symptoms, particularly those in their initial episode, should have a thorough medical and laboratory (electrolytes, blood urea nitrogen, serum creatinine, urinalysis, liver and thyroid function profile, syphilis serology, serum pregnancy test, and urine toxicology) evaluation, including a careful review of systems and a physical exam that includes a neurologic evaluation. At the minimum, in accordance with the American Psychiatric Association Practice Guidelines[11] and the Expert Consensus Guideline Series for Schizophrenia,[12] psychotic patients should have a medical workup at the time of admission to rule out other diagnoses or contributing factors.

❹ *Since early detection and intervention in schizophrenia is important for maximizing outcomes, treatment with antipsychotic medications should begin as soon as psychotic symptoms are recognized. Antipsychotic medications are the cornerstone of therapy for people with schizophrenia, and most patients are on lifelong therapy since non-adherence and discontinuation of antipsychotics are associated with high relapse rates.* If other symptoms are present such as depression and anxiety, these symptoms should also be aggressively treated. Additionally, psychosocial treatments should be used concomitantly to improve patient outcomes.

Nonpharmacologic Therapy

❺ *Psychosocial support is needed to help improve functional outcomes*. Only 30% of patients respond robustly to antipsychotics, another 30% respond partially, and another 30% have a minimal response. Patients who do respond often continue to have residual symptoms such as **amotivation**, isolation, and impaired social functioning, thus limiting their participation in social, vocational, and educational endeavors. Psychosocial interventions are based on the premise that increased psychosocial functioning will lead to improvements in subjective feelings of self-esteem and life satisfaction. However, generalizability from studies in this area are confounded by differences in treatment settings, severity of illness, insurance status of patients, and the presence of comorbid conditions. A few of the best-supported and most promising approaches to psychosocial rehabilitation are social skills training (SST), cognitive-behavioral therapy (CBT), and cognitive remediation (CR). These treatments are used most appropriately as targeted treatments for social and cognitive impairments and not as sole treatments for psychotic symptoms.[13] Most psychosocial studies have been carried out in the United Kingdom, and findings are not yet widely utilized in the United States. Nonetheless, there are substantial data to support that family education and vocational support help to improve long-term functional outcomes.

TABLE 34–2. Disorders That May Present with Psychotic Symptoms

Addison's disease	Huntington's disease
Asperger's disorder	Major depression
Autism	Posttraumatic stress disorder
Bipolar disorder	Sarcoidosis
Cancer	Seizure disorder
Cushing's disease	Substance abuse
Delirium	Syphilis
Dementia	Thyrotoxicosis
Head trauma	Viral encephalitis

Pharmacologic Therapy

There are more choices of antipsychotic medications than ever before. Generally, all people with schizophrenia should be treated with antipsychotics, and adjunctive medications should be used when necessary to treat specific symptoms or comorbid diagnoses. Medications specifically targeting negative symptoms and cognitive deficits are actively being investigated. Because each schizophrenic patient presents differently, each treatment regimen should be individually tailored. After a period of nearly 20 years during which only first-generation antipsychotics (FGAs; typical antipsychotics) were available, six new antipsychotics have been marketed in the United States since 1990. These agents, known as second-generation antipsychotics (SGAs; atypical antipsychotics), include risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), ziprasidone (Geodon), aripiprazole (Abilify), and clozapine (Clozaril). Clozapine, the prototype of this class of medications, is reserved as second-line therapy due to its unusual side-effect profile (see below). ❻ *As a class the SGAs offer greater tolerability, with less risk of* ***extrapyramidal side effects*** *(EPSs) and* ***tardive dyskinesia*** *(TD; see below), and possibly better treatment for mood symptoms, negative symptoms, and cognitive deficits. There are some data to show that they are associated with lower rates of relapse*. Unfortunately, these medications are more expensive than older medications and have similar efficacy for psychotic symptoms, thus pharmacoeconomic cost:benefit profiles provide information essential for designing appropriate therapeutic regimens. The FGAs are currently used in less than 10% of the schizophrenic population, primarily in patients who cannot afford newer medications and those who have responded well and tolerated these medications in the past.

Second-Generation (Atypical) Antipsychotics

While FGAs exert most of their effect through dopamine receptor blockade at the dopamine (D_2) receptor, the SGAs

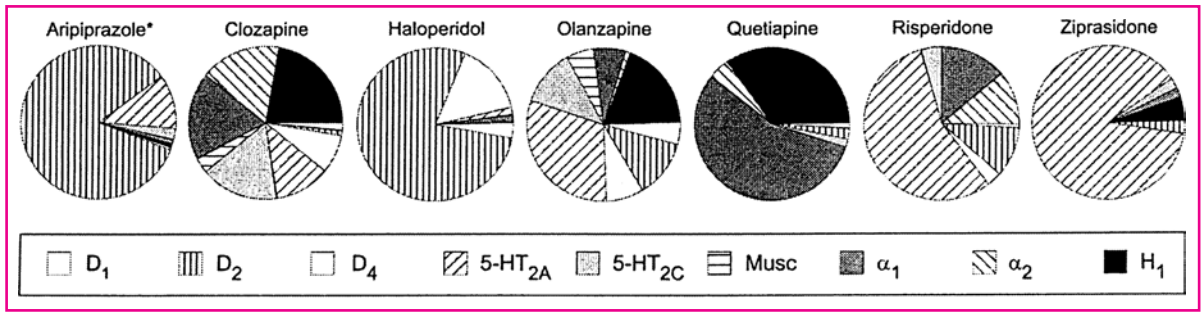


FIGURE 34–1. Profiles for receptor binding of second-generation antipsychotics and haloperidol. [a]Partial agonist activity at D_2 receptors, whereas all others are D_2 antagonists. D, dopamine receptor; H_1, histamine receptor; 5-HT, serotonin receptor; Musc, muscarinic receptor; α_1 and α_2, α_1 and α_2 receptors. (Adapted and reprinted from The Journal of Clinical Psychiatry and Physicians Post Graduate Press. Collaborative Working Group on Clinical Trial Evaluations. J Clin Psychiatry 1998; 59[Suppl 12]:7, and Pharmacologic Treatment of Schizophrenia. Caddo, OK. Professional Communications, Inc, 2003: 52, with permission.)

may work through a more complicated mechanism, as SGAs have greater affinity for serotonin receptors than for dopamine receptors (Fig. 34–1). Despite being very heterogeneous with regard to receptor binding, the overall efficacy among the SGAs is similar.[14] Recently new comparative data among SGAs and FGAs (lower doses) have reported that overall efficacy is similar between groups, which suggests a reevaluation of the place of FGAs in therapy is needed.[14] Only clozapine, however, has demonstrated superior efficacy for some patients (see section below on treatment-resistant patients). An important distinction of the SGAs as a class is their lower propensity to cause EPS and TD. The annual risk of TD is considered to be less than 1.5% per year in adults (less than 54 years old) taking SGAs as compared to approximately a 5%-per-year risk in those taking FGAs.[15] Pharmacologic profiles and side-effect profiles, however, are very different among the agents. Table 34–3 lists the SGA agents, recommended dosing, and dosage forms available. Table 34–4 lists the side-effect profiles of the SGAs and haloperidol. Clozapine is discussed in the section on treatment-resistant patients.

Risperidone

Risperidone, a benzisoxazole derivative, was the first SGA to be marketed following the release of clozapine. It has high binding affinity to both serotonin ($5\text{-}HT_{2A}$) and D_2 receptors and binds to α_1 and α_2 receptors, with very little blockade of cholinergic receptors.[16] Multicenter registry trials found risperidone efficacy to be at least equal to that of haloperidol while producing significantly fewer extrapyramidal symptoms.[17] Risperidone is the only SGA approved for relapse prevention and is associated with significantly lower relapse rates than long-term haloperidol treatment.[18] At clinically effective doses (less than or equal to 6 mg/day), EPSs are low, although higher doses are clearly associated with a greater incidence of EPS. Risperidone is associated with serum prolactin elevations that are similar to or greater than those seen with the FGAs. Elevated prolactin levels can, but

TABLE 34–3. Second-Generation (Atypical) Antipsychotics

Second-Generation Antipsychotic	Usual Target Dose (mg/day)	Maximal Dose Likely to Be Beneficial (mg/day)	Available Dosage Forms
Aripiprazole (Abilify)	15–30	30	• 2-, 5-, 10-, 15-, 20-, and 30-mg tablets • 1 mg/mL oral solution • 10- and 15-mg discmelt orally disintegrating tablets • IM 9.75 mg/1.3 mL
Clozapine (Clozaril)	400	500–800	• 25- and 100-mg tablets • FazaClo (orally disintegrating tablets) 25 and 100 mg
Olanzapine (Zyprexa)	15–20	30-40[a]	• 2.5-, 5-, 7.5-, 10-, 15-, and 20-mg tablets • Zyprexa Zydis (orally disintegrating tablets) 5,10,15, and 20 mg • IM 10–mg vial (after reconsitution, approx. 5 mg/mL)
Quetiapine (Seroquel)	400–600	800–1200[a]	• 25-, 100-, 200-, and 300-mg tablets
Risperidone (Risperdal)	2–4	6	• 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg tablets • 1 mg/mL (30 mL) solution • Risperidal M-tab (orally disintegrating tablets) 0.5, 1, and 2 mg • Risperdal Consta long-acting injectable 25-, 37.5-, and 50-mg vial/kit
Ziprasidone (Geodon)	100–120	160–240[a]	• 20-, 40-, 60-, and 80-mg capsules • IM 20 mg/mL

[a]Outside product labeling guidelines.

TABLE 34–4. Comparative Side Effects among the Second-Generation Antipsychotics and Haloperidol

Side Effect	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Aripiprazole	Haloperidol
Anti-cholinergic side effects (dry mouth, constipation, blurred vision, urinary hesitancy)	+++	±	++ (higher doses)	+	±	±	±
EPS at clinical doses	±	+	±	±	±	±	++
Dose-dependent EPS	0	++	+	0	+	±	+++
Orthostatic hypotension	+++	++	+	++	+	+	+
Prolactin elevation	0	+++	+	±	+	0	++
QTc prolongation	+	±	±	±	+	±	±
Sedation	+++	+	+	++	+	+	+
Seizures	++	±	±	±	±	±	±
Weight gain	+++	++	+++	++	+	+	±
Glucose dysregulation	++	+	++	+	±	±	±
Lipid abnormalities	+++	+	+++	++	±	±	±

0, absent; ±, minimal; +, mild or low risk; ++, moderate; +++, severe; EPS, extrapyramidal side effects.

do not always, lead to clinical symptoms such as hormonal problems (e.g., amenorrhea, galactorrhea, and gynecomastia) or sexual dysfunction. Risperidone is associated with mild to moderate weight gain and mild elevations in lipid and glucose may occur. However, patients chronically treated with other antipsychotics such as olanzapine may have declines in cholesterol and triglyceride levels when changed to risperidone monotherapy.[14]

Olanzapine

Olanzapine has greater affinity for 5-HT_{2A} than for D_2 receptors. In addition, the compound has affinity at the binding sites of D_4, D_3, 5-HT_3, 5-HT_6, α_1-adrenergic, muscarinic ($M_{1–5}$), and histamine (H_1) receptors.[19] Multicenter clinical trials have reported that the effectiveness of olanzapine is at least equal to that of haloperidol for the treatment of positive symptoms[20,21] and equal or superior to haloperidol for the treatment of negative symptoms. The premarketing clinical trials reported no significant differences in efficacy among dosage groups. However, the higher dose range appeared to offer the greatest benefits for both positive and negative symptoms when compared to haloperidol (20 mg). Among the first-line antipsychotic agents, olanzapine is associated with the longest time to treatment discontinuation, a finding that suggests that olanzapine may somewhat differ from the other SGAs in effectiveness.[14] Olanzapine has a low rate of EPS and causes slight, transient prolactin elevations. However, clinically significant weight gain occurs with olanzapine across the dosage range. The degree of weight gain is similar to that seen with clozapine and greater than that observed with the other SGAs. Olanzapine is also associated with hypertriglyceridemia, increased fasting glucose, and new-onset type 2 diabetes (i.e., metabolic syndrome), and among the first-line SGAs, it is associated with the greatest elevations in these metabolic parameters.[14]

Quetiapine

Structurally quetiapine is related to clozapine and olanzapine. Quetiapine has high affinity for 5-HT_{2A} receptors and lower affinity for D_2 and D_1 receptors. This drug has some affinity for α_1, α_2, and H_1 receptors, and very little for muscarinic receptors. The efficacy of quetiapine for psychosis was established in two controlled trials, which found that maximum benefits occurred at 300 mg per day or greater.[22,23] The most effective doses of quetiapine may be higher than 500 mg/day. Quetiapine has not been shown to be superior to haloperidol in any symptom dimension; however, it has beneficial effects for anxious and depressive symptoms. Because of its low D_2 occupancy, motor side effects and prolactin elevations are usually not seen with quetiapine. Sedation may occur but is generally transient. Mild weight gain and minor elevations in triglycerides can occur.

Ziprasidone

Ziprasidone was developed specifically to be a compound that blocks D_2 receptors, but also binds with even greater affinity to central 5-HT_{2A} receptors. As a result, ziprasidone has a binding affinity ratio of 11:1 for 5-HT_{2A}:D_2 receptors. Ziprasidone also has a relatively high affinity for 5-HT_{2C}, 5-HT_{1D}, α_1-adrenergic, and D_1 receptors.[24] Several short-term, placebo-controlled, premarketing clinical trials led to the recommended dose range of 40 to 160 mg daily with food.[25,26] Current dosing suggests that efficacy may be greater at doses over 200 mg/day. Liability for EPS, weight gain, and lipid elevations were very low in the clinical trials. Ziprasidone is associated with some prolongation of the QTc interval in adults. However, drug overdose data and studies of pharmacokinetic interactions have thus far shown little evidence that significant QTc prolongation may occur.

Aripiprazole

Aripiprazole was formulated in the early 1980s to function as a potential dopamine modulator, with both antagonist and agonist activity at the D_2 receptor. It is the first D_2 partial agonist available for the treatment of schizophrenia and is sometimes referred to as a third-generation antipsychotic. This novel mechanism is



Patient Encounter, Part 3

Soon after his discharge from the hospital, AG stopped taking his olanzapine. He had gained a lot of weight, and he didn't believe the medication was helping. He continued to have difficulties maintaining employment and being involved socially. With encouragement from his girlfriend, AG sought treatment again and was started on risperidone 2.5 mg a day. He continued to experience paranoia, still feeling unable to function up to his potential at work, and still tending to be reclusive. A new therapist supported his involvement in Alcoholics Anonymous, and with AG began to question the depression diagnosis. She referred him to a center specializing in schizophrenia where the diagnosis was clarified as schizophrenia, paranoid type, continuous with depressive episode, single episode, alcohol dependence, early full remission; and polysubstance abuse, early full remission.

- List a reason why risperidone was selected as the next antipsychotic choice for AG.
- Describe nonpharmacologic treatment strategies that may be appropriate for AG.
- Discuss a risperidone dosing plan and list side effects AG may experience on this medication.

termed a "dopamine system stabilizer," functioning as an antagonist in a hyperdopaminergic state and as an agonist when in a hypodopaminergic state. Aripiprazole is also a partial agonist at 5-HT_{1A} receptors, an antagonist at 5-HT_{2A} receptors, and also has affinity for D_3 receptors. Additionally, it has a moderate affinity for α_1 and H_1 receptors with no appreciable affinity for the M_1 receptor.[27] The recommended starting dose is 10 to 15 mg daily given without regard to meals. No titration is required, as the starting dose is an effective dose. The recommended dosing range is 10 to 30 mg/day; doses greater than 30 mg have not been systematically evaluated. Doses less than 10 mg/day have not been consistently found to be effective. Side effects are low with sedation and nausea and vomiting occurring the most frequently. Elevations in weight, lipids, and glucose are generally negligible to minor.

First-Generation (Typical) Antipsychotics

First-generation antipsychotics (FGAs), also referred to as conventional, traditional, or typical antipsychotic agents, are high-affinity D_2 receptor antagonists. During chronic treatment, these agents block 65% to 80% of D_2 receptors in the striatum and block dopamine receptors in the other dopamine tracts in the brain as well.[28] Clinical response is generally associated with 60% D_2-receptor blockade, while 70% and 80% are associated with hyperprolactinemia and EPS, respectively. This group of antipsychotics was widely used from the 1950s to the 1990s, until the SGAs began to replace these agents as first-line therapy.

Dosages for these agents are frequently given as **chlorpromazine equivalent** dosages, which are defined as the dosage of any of the FGAs equipotent with 100 mg of chlorpromazine. The target dose recommendation is 400 to 600 chlorpromazine equivalents, unless the patient's history indicates that this dose may result in intolerable side effects. Generally maintenance therapy should provide a dose of 300 to 600 chlorpromazine equivalents for maximum efficacy. Information on dosing and available dosage forms is provided in Table 34–5. All FGAs are equally efficacious in groups of patients when used in equipotent doses. However, individual variation does occur, such that a patient may not respond equally to each antipsychotic. Selection of a particular antipsychotic should be based on patient variables, such as the need to avoid certain side effects

TABLE 34–5. First-Generation (Typical) Antipsychotics

Class	Agent (Brand Name)	Dosage Range (mg/day)	Chlorpromazine Equivalents (mg)	Available Formulations
Butryphenone	Haloperidol (Haldol)	5–30	2	T, LC, I
Dibenzoxazepine	Loxapine (Loxitane)	25–100	10	C
Diphenylbutylpiperidone	Pimozide (Orap)	1–10	1–2	T
Indole	Molindone (Moban)	25–100	10	T
Phenothiazines	Chlorpromazine (Thorazine)	300–800	100	T, LC, I, R
	Fluphenazine (Prolixin)	2–40	2	T, L, I
	Mesoridazine (Serentil)	150–500	50	T, LC
	Perphenazine (Trilafon)	8–64	10	T, LC
	Thioridazine (Mellaril)	300–800	100	T, LC
	Trifluoperazine (Stelazine)	15–30	5	T
Thioxanthenes	Thiothixine (Navane)	5–40	4	C

Low-potency antipsychotics include thioridazine, mesoridazine, and chlorpromazine.
High-potency antipsychotics include haloperidol, fluphenazine, thiothixine, and pimozide.
T, tablet; C, capsule; C-SR, controlled- or sustained-release; I, injection; L, liquid solution, elixir, or suspension; LC, liquid concentrate, R, rectal suppository.

or interactions with concomitant medications. Previous patient or family history of response is also helpful in the selection of a particular agent.

Decanoates

Long-acting, depot preparations are available for two FGAs (fluphenazine decanoate and haloperidol decanoate) in the United States. These compounds are esterified antipsychotics formulated in sesame seed oil for deep intramuscular injection. Because these are long-acting preparations, patients should be exposed to the oral form of the drug first to ensure tolerability. With initial dosing of haloperidol decanoate, oral supplementation may temporarily be necessary, as the drug accumulates over many weeks, not reaching steady state until 4 to 5 dosing intervals have elapsed. The pharmacokinetic profiles of the depot agents are useful parameters for strategic dosing. Patients may be dosed with fluphenazine decanoate on a 1- to 3-week interval, while haloperidol decanoate is usually dosed once a month. Conversion from oral to depot and maintenance dosing recommendations are shown in Table 34–6. Based on these recommendations, a reasonable estimate is that 12.5 mg (0.5 mL) of fluphenazine decanoate given every 2 weeks is approximately equivalent to 10 mg/day of fluphenazine orally. A maintenance haloperidol decanoate dose of 150 mg every 4 weeks is approximately equivalent to 10 mg/day of oral haloperidol. Initial decanoate injections should be preceded by a small test dose.

Side Effects of First-Generation Antipsychotics

FGAs cause a wide range of adverse events, affecting many organ systems. In general, the low-potency agents are less likely to cause EPS than the high-potency agents. Neuroleptic malignant syndrome (NMS), a life-threatening emergency characterized by severe muscular rigidity, autonomic instability, and altered consciousness, can occur uncommonly with all the FGAs. Rapid dose escalation, the use of high-potency FGAs at higher doses, and younger patients are associated with a higher risk of NMS. When NMS is diagnosed or suspected, antipsychotics should be discontinued and supportive and symptomatic treatment begun (e.g., antipyretics, cooling blanket, intravenous fluids, oxygen, monitoring of liver enzymes, and complete blood cell count). Dopamine agonists (i.e., bromocriptine) should be considered in moderate to severe cases. Additionally, dermatologic side effects, photosensitivity, and cataracts may occur with the phenothiazine agents. Sedation is caused from H_1-receptor antagonism, anticholinergic side effects (constipation, blurred vision, dry mouth, and urinary retention) are caused from M_1-receptor antagonism, and α_1-receptor blockade is associated with orthostatic hypotension and tachycardia (Table 34–7.) QTc prolongation may occur with lower-potency FGAs such that thioridazine has a black box warning for QTc prolongation.

The other group of major adverse effects associated with FGAs are EPS and include akathisia (restlessness), dystonia (muscle spasm), and pseudoparkinsonism (akinesia, tremor, and rigidity). These fairly common motor side effects are caused by dopamine antagonism in the nigrostriatal pathways. Akathisia is the most frequently occurring motor side effect, with approximately 20% to 40% of people treated with FGA drugs experiencing an objective or subjective feeling of restlessness. The onset of akathisia is usually 5 to 10 days after the first dose or increase in dosage, but it can occur later. Younger people and those taking high doses of high-potency antipsychotics are at greater risk for the development of akathisia. Acute dystonic reactions are abrupt in onset and are usually seen within 24 to 96 hours after a first dose or increase in dosage. Characteristic signs and symptoms include abnormal positioning or spasm of the muscles of the head, neck, limbs, or trunk. Dystonia may occur in 10% to 20% of patients. Younger patients are at highest risk. Pseudoparkinsonism resembles idiopathic Parkinson's disease, and features may be present in up to 30% to 60% of people treated with FGAs. The onset of symptoms is usually seen within 1 to 2 weeks following initiation of dosing or a dose increase. Risk factors include older age, female gender, high doses, and possibly those with depressive symptoms.[29] Using

TABLE 34–6. First-Generation (Typical) Antipsychotic Dosing of Decanoate Preparations

Drug	Starting Dose	Maintenance Dose	Comments
Haloperidol decanoate	20 × oral haloperidol daily dose; in the elderly use 10–15 × oral haloperidol daily dose Generally 100–450 mg/month Initial dose should not exceed 100 mg regardless of previous dose requirements (if greater than 100 mg give 3–7 days apart)	10–15 × oral haloperidol dose, generally 50–300 mg/month	With initial dosing, oral supplementation may temporarily be necessary; deep IM injection generally with 21-gauge needle; maximum volume per injection site should not exceed 3 mL Available in 5 mg/mL and 100 mg/mL (5-mL vials and 1-mL ampules)
Fluphenazine decanoate	1.2 × oral fluphenazine daily dose, generally 12.5–75 mg/2–3 weeks	Based on starting dose and clinical response Generally 12.5–25 mg dosed every 3–6 weeks	Can be administered IM or SC; 21-gauge needed, must be dry Should not exceed 100 mg; when dosing above 50 mg, should increase in increments of 12.5 mg Available in 25 mg/mL (5-mL vials)

IM, intramuscular, SC, subcutaneous.

TABLE 34–7. Side Effects of First-Generation (Typical) Antipsychotics

	EPS	Sedation	Anticholinergic Side Effects	Cardiovascular Side Effects	Seizure Effects/ QTc Prolongation
Chlorpromazine	XX	XXXX	XXX	XXXX	XX
Thioridazine	XX	XXXX	XXXX	XXXX	XXX
Mesoridazine	XX	XXX	XXX	XXX	XX
Loxapine	XXX	XXX	XX	XXX	X
Trifluoperazine	XXX	XX	XX	XX	X
Molindone	XX	X	XX	XX	X
Perphenazine	XXX	XX	XX	XX	X
Thiothixene	XXX	XX	XX	XX	X
Fluphenazine	XXXX	XX	XX	XX	X
Haloperidol	XXXX	X	X	X	X

EPS, extrapyramidal side effects; X, very low; XX, low; XXX, moderate; XXXX, high.

decanoate formulations to minimize peak levels may minimize the incidence of EPS.

TD is a movement disorder characterized by abnormal choreiform (rapid, objectively purposeless, irregular, and spontaneous movement) and athetoid (slow and irregular) movements occurring late in onset in relation to initiation of antipsychotic therapy. This adverse effect usually develops over several months or after at least 3 months of cumulative exposure to neuroleptic medications. The estimated average prevalence is 20% with a range of 13% to 36%. The incidence of new cases per treatment year with FGAs is approximately 5%.[30] TD is reversible in one-third to one-half of cases with the cessation of the antipsychotic. When the antipsychotic is tapered or discontinued, there is initially usual worsening of abnormal movements. Risk factors for TD include older age, longer duration of antipsychotic treatment, and higher rates of EPS, substance abuse, and mood disorders.

Treatment Guidelines and Algorithms

Due to the plethora of choices and the rising costs of SGAs, algorithms and treatment/consensus guidelines have been developed for the treatment of schizophrenia. The most widely accepted algorithm in the United States was developed as part of the Texas Implementation of Medication Algorithms (TIMA). A national panel of experts developed this algorithm, most recently updated in 2003.[31] Algorithms go beyond guidelines, providing a framework for clinical decision making at critical decision points. According to the TIMA schizophrenia algorithm, SGAs (except clozapine) should be utilized as first-line treatment. The choice of SGA is guided by consideration of the side-effect profiles and the clinical characteristics of the patient. Treatment should be continued for 4 to 6 weeks in order to assess response. If only partial response or non-response is noted, a trial of a second SGA should be initiated (Fig. 34–2). Other similar guidelines include the American Psychiatric Association Practice Guidelines for schizophrenia,[11] The Expert Consensus Guideline Series,[12] and the Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations.[32]

Treatment Adherence

Medication non-adherence in schizophrenia is common and often associated with symptom relapse.[33] Estimates of non-adherence on FGAs range from approximately 24% to 88% with a mean of approximately 50%.[34] Subjects who are non-compliant have approximately a four-fold greater risk of a relapse than those who are compliant. Adherence to antipsychotic regimens is problematic for many reasons. Neurocognitive deficits and paranoid symptoms may hamper compliance, and identification of non-compliance by caretakers and providers can be challenging. Frequently, there is no obvious connection between non-compliance and symptom exacerbation, as there may be no immediate consequences of missing a dose, and patients may relapse suddenly after only several weeks or months of non-adherence. Side effects from antipsychotics are also a major contributing factor to treatment non-adherence, with 25% to 66% of subjects citing adverse effects as the primary reason for non-adherence.[33] EPS, most notably akathisia, sexual dysfunction, and weight gain are adverse effects that commonly lead to non-adherence.[35] Several factors are associated with non-compliance, including younger age, grandiosity, substance abuse, and deficit symptoms. SGAs may be associated with somewhat better rates of adherence, most likely attributable to a lower incidence of **dysphoria** and EPS; however, rates of medication discontinuation remain high.[14,36] For patients who have relapsed several times due to non-adherence, have a history of dangerous behavior, or risk a significant loss of social/vocational gains when relapsed, treatment with long-acting formulations should be strongly encouraged. Risperidone is currently the only SGA with a long-acting formulation available. It uses a microsphere technology that maintains stable blood levels for about 2 weeks. Dosing is generally 25 to 75 mg every 2 weeks with oral supplementation in the first 3 weeks.

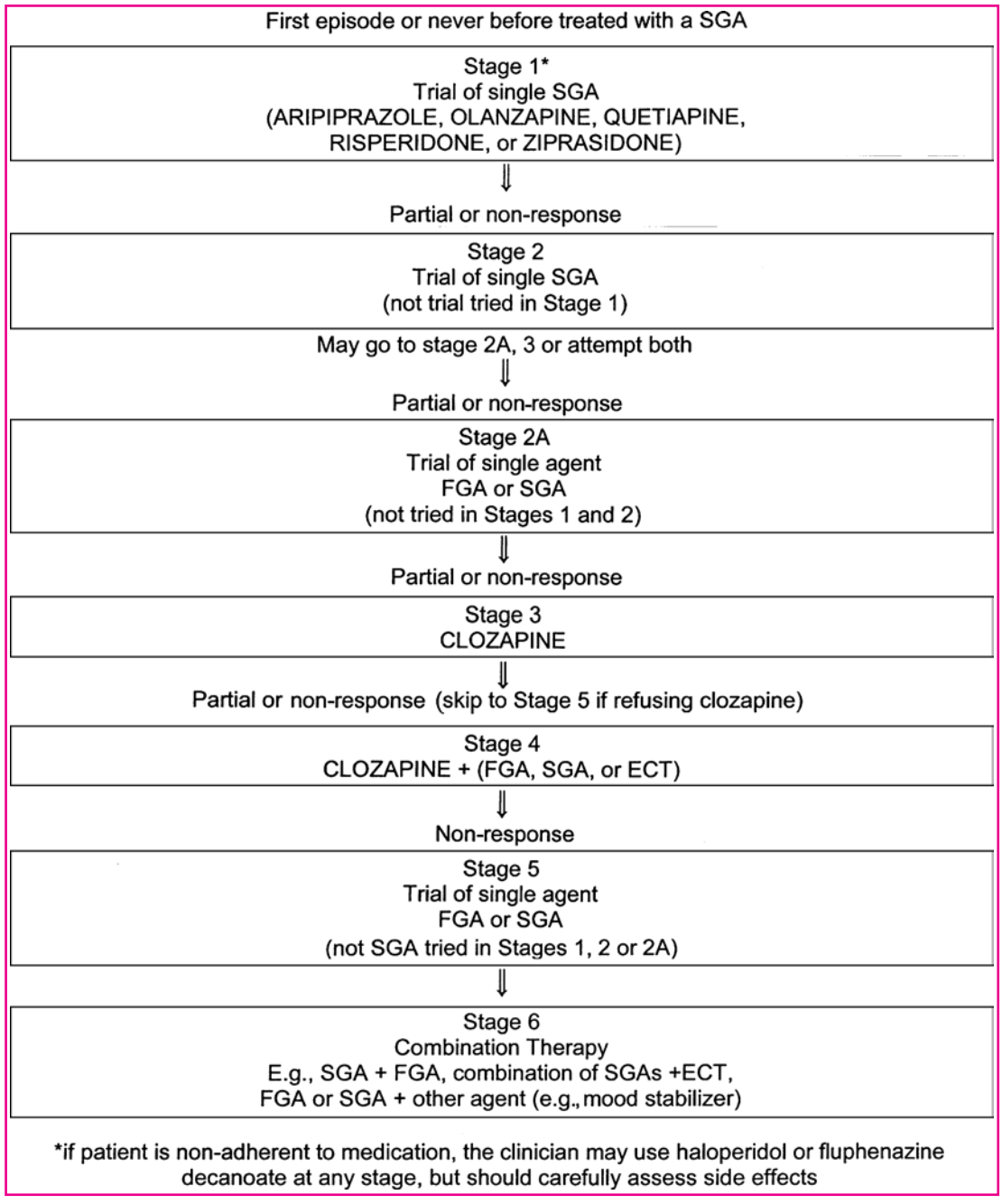


FIGURE 34–2. TIMA algorithm for antipsychotic treatment in schizophrenia. Choice of antipsychotic should be guided by considering the clinical characteristics of the patient and the efficacy and side-effect profiles of the medication. Any stage may be skipped depending on the clinical picture or history of antipsychotic failures. ECT, electroconvulsive therapy; FGA, first-generation antipsychotic; SGA, second-generation antipsychotic. (Adapted from www.dshs.state.tx.us/mhprograms/tmasczman.pdf.)

Patient-Specific Antipsychotic Selection

Patient-specific characteristics may help guide the selection of antipsychotic treatment. Based on expert consensus guidelines, Table 34–8 provides evidence-based suggestions for SGA selection to aid the clinician in individualizing treatment. FGAs continue to have a place in therapy for patients who cannot afford the SGAs or for those who have responded favorably to these agents in the past. Currently, however, SGAs are recommended as first-line therapy.

Special Populations

Adolescents

Epidemiologic data show that 10% to 30% of patients with schizophrenia develop their first psychotic symptoms prior to their eighteenth birthday. Onset between puberty and age of 18 is sometimes classified as early-onset schizophrenia (EOS) or intermediate onset schizophrenia, and those presenting with symptoms before puberty are classified as very early-onset

TABLE 34–8. Suggestions for First-Line Antipsychotic Therapy in Specific Patients

Clinical Condition	First-Line Treatment	Other Options
Diabetes or family history of diabetes	Aripiprazole, quetiapine, ziprasidone	Risperidone
Hyperlipidemia or significant family history of hyperlipidemia	Aripiprazole, ziprasidone	Risperidone, quetiapine
Hypertriglyceridemia or significant family history of elevated triglycerides	Aripiprazole, ziprasidone	Risperidone, quetiapine
Overweight or obese, or concerns about weight	Aripiprazole, ziprasidone	Risperidone, quetiapine
Current sexual dysfunction or concerns about sexual dysfunction	Aripiprazole, quetiapine, clozapine	Olanzapine, ziprasidone
Amenorrhea or problems with menstrual period	Aripiprazole, quetiapine, clozapine	Olanzapine, ziprasidone
Cardiac arrhythmias or current anti-arrhythmic treatment	**NOT** ziprasidone or clozapine	
Suicidal or history of frequent suicide attempts	Clozapine	
Current or past anti-cholinergic side effects	Risperidone, quetiapine, aripiprazole ziprasidone	Olanzapine (low dose)
EPS or severe EPS in the past	Quetiapine, aripiprazole, clozapine	Ziprasidone
Current tardive dyskinesia	Clozapine, quetiapine	Risperidone, olanzapine, ziprasidone
History of non-adherence	Long-acting risperidone	
Difficulty swallowing tablets/capsules	Risperidone or aripiprazole liquid, orally-disintegrating tablets (risperidone, olanzapine, clozapine)	Long-acting risperidone

EPS, extrapyramidal symptoms.
Data from references 11, 12, and 32 and 51.

schizophrenia (VEOS) or as having childhood-onset schizophrenia. The diagnosis of schizophrenia in children and adolescents is often difficult to make, and the differential diagnosis includes pervasive developmental disorders, attention-deficit/hyperactivity disorder, and language or communication disorders. The existence of prominent hallucinations or delusions, however, help make the diagnosis, as they are not a prominent part of the other disorders. Auditory hallucinations are common and occur in approximately 80% of children and adolescents with schizophrenia. Command hallucinations are the most frequently occurring type of hallucination. The content and context of delusions in children and adolescents vary by age. Younger children tend to have delusions that are less complex and fixed. Fifty-four to ninety percent of patients developing schizophrenia before age 18 have premorbid abnormalities such as withdrawal, odd traits, and isolation.[37]

Treatment for psychotic children and adolescents ideally involves an intensive and comprehensive program with a highly structured environment that includes special education and psychoeducation. Day treatment, hospitalization, or long-term residential treatment may be necessary. Pharmacologic treatment is indicated if psychotic symptoms cause significant impairments or interfere with other interventions. Children and adolescents are more vulnerable to EPS, particularly dystonias, than are adults. Due to concerns about EPS and TD, pharmacotherapy in children and adolescents should be initiated with SGAs. Agents with significant sedation and anti-cholinergic side effects are not preferred, as they can cause attention difficulties and cognitive dulling that may interfere with optimal school performance. Compared to adults, children and adolescents tend to gain more weight on these agents. Young patients should be started on lower doses than adults and should be titrated at a slower rate. Side effects should be monitored closely during initiation and throughout maintenance therapy. Informed consent, addressing the rationale for treatment and potential risks and benefits of therapy, should be obtained from the parents or guardians prior to treatment with any antipsychotic medication, and assent should be obtained from the child as well. Standardized clinician ratings such as the Positive and Negative Syndrome Scales derived from the Children's Psychiatric Rating Scale can be helpful in assessing the effects of antipsychotic therapy. Dosing in children and adolescents is initiated lower and titration is slower than in adults.

Elderly

Psychotic symptoms in late life (greater than 65 years of age) are generally a result of an ongoing chronic illness carried over from younger life; however, a small percentage of patients develop psychotic symptoms de novo, defined as late-life schizophrenia. The 6-month prevalence rate of schizophrenia in the elderly is around 1%. However, other illnesses presenting with psychotic symptoms are common in this population, as approximately one-third of patients with Alzheimer's disease, Parkinson's disease, and vascular dementia experience psychotic symptoms. The majority of data for antipsychotic use in the elderly comes from experience treating these other disease states.

Antipsychotics can be safe and effective for the treatment of psychosis in the elderly, if used at lower doses than those commonly used in younger adults. Older adults are particularly vulnerable to the side effects of FGAs. Parkinsonian symptoms

reportedly occur in over 50% of all elderly patients receiving these agents, and the cumulative annual incidence of TD in middle-aged and elderly patients is over 25%. With the SGAs, the risk appears to be approximately 4%.[38] The likelihood of reversing this potentially debilitating condition diminishes with age. Other adverse effects of these agents that are often intolerable in the older population include orthostatic hypotension and anticholinergic effects. For example, orthostasis, estimated to occur in 5% to 30% of geriatric patients, is a major contributing factor to the occurrence of falls that often leads to fractures, injuries, and loss of independence. Low-potency antipsychotics and clozapine are more likely to cause significant drops in orthostatic blood pressure. Antipsychotics may cause or worsen anticholinergic effects including constipation, dry mouth, urinary retention, and cognitive impairment. Cognitive impairment may lead to decreased independence, and a more rapid decline in cognitive functioning may occur in the elderly treated with antipsychotics than the younger adult population. Using lower doses and remaining vigilant to side effects is essential in this population. Recently published data reported a statistically significant increase in mortality rate due to stroke in elderly dementia patients who are treated with SGAs. All SGAs now carry this warning, and patients and families should be informed of this risk prior to treatment with these agents. Dosing in the elderly is initiated lower and titration is slower than in adults. Maximum doses are often one-half of adult doses.

Dually Diagnosed

The prevalence of substance dependence and abuse among persons with schizophrenia is significantly higher than in the general population. Conservative estimates of the proportion of schizophrenic patients abusing alcohol and/or illicit drugs range from one-third to as many as one-half.[39] The most common drugs of abuse are alcohol, cannabis, and cocaine. Although, the reasons for this high comorbidity are unclear, a number of theories have been postulated, including the possibility of a deficiency in the dopamine-mediated brain reward circuit. According to this theory, patients use substances as a way to replete dopamine in the reward centers of the brain. This pleasure-seeking behavior serves in part as the basis for what is termed the self-medication hypothesis, in which patients are described as "self-medicating" with substances sometimes as a way to counter depression, reduce anxiety, or induce sleep. Unfortunately, substance use often worsens the course and complicates the treatment of schizophrenia. Dually-diagnosed patients are more likely to be non-compliant with treatment. Characteristically, they have a poorer response rate to traditional antipsychotics, have more severe psychosis, and have higher rates of relapse and rehospitalization compared to patients who are not abusing substances. Some studies have found that EPS may occur more frequently in substance-abusing patients, and alcohol use is a risk factor for developing TD. There is a growing body of literature indicating that SGAs are effective in this population, and some studies have shown a reduction in the use of drugs and alcohol with SGAs.

Treatment-Resistant Patients

For approximately 20% to 30% of people with schizophrenia, drug treatment is ineffective. A standard definition of treatment resistance includes patients who have persistent positive symptoms despite treatment with at least two different antipsychotics given at adequate doses (at least 600 chlorpromazine equivalents) for an adequate duration (4 to 6 weeks). In addition, patients must have a moderately severe illness as defined by rating instruments, and have a persistence of illness for at least 5 years.[40] These patients are often highly symptomatic and require extensive periods of hospital care.

Clozapine

To date, clozapine remains the only drug with proven and superior efficacy in treatment-resistant patients, and it is currently the only drug approved for the treatment-resistant schizophrenic. Studies have shown a response of approximately 30% to 50% in these well-defined treatment-resistant patients. Clinical trials have consistently found clozapine to be superior to traditional antipsychotics for treatment-refractory patients, and it is efficacious even after non-response to other SGAs and in partially responsive patients. It is often rapidly effective even in those who have had a poor response to other medication for years. Recent studies have demonstrated that it has a beneficial effect for aggression and suicidality, which led to the Food and Drug Administration (FDA) approval for the treatment of suicidal behavior in people with psychosis.[41]

A great deal of interest has been generated in understanding what pharmacologic properties of clozapine contribute to its superior efficacy, but to date this has not been clearly elucidated. Clozapine has a low affinity for D_2 receptors, works also on D_1 receptors, and is a 5-HT_{2A} antagonist. Its unsurpassed efficacy suggests that there is a neuropharmacologic effect associated with clozapine that is to date unique to this agent.

Clozapine's use is limited by its association with the rare but life-threatening risk of agranulocytosis and seizures, as well as common unpleasant side effects including sedation, enuresis, anti-cholinergic effects, weight gain, and hypersalivation. The long-term hematologic monitoring (see monitoring section) required for prevention of agranulocytosis can represent a barrier to both patients and care providers. The optimal plasma level of clozapine is a minimum trough level of 300 to 350 ng/mL (300 to 350 μg/L or 918–1071 nmol/L), usually corresponding to a daily dose of 200 to 400 mg, although dosage must be individualized. According to published guidelines and recommendations, clozapine should be considered after two failed antipsychotic trials.[31] Fewer than 8% of new antipsychotic prescriptions are written for this medication annually in the United States.

Other Strategies

Approximately 30% of patients treated with clozapine will not respond, and another 30% will have only a partial response to the drug. Treatment options with other medications are limited

after clozapine non-response. For these patients, the best evidence points to augmentation using an FGA, SGA, or **electroconvulsive therapy** (ECT). The only available data support the combination of clozapine with risperidone; however, controlled trial results are mixed. Other potential strategies include combining antipsychotics with mood stabilizers (e.g., lithium, lamotrigine, valproate, and topiramate).[31]

Acutely Psychotic Patients

Psychiatric emergencies occur in a variety of settings, including emergency departments, psychiatric units, medical facilities, and outpatient settings. Most psychiatric emergencies require both pharmacologic and psychological interventions. Often, the psychiatrist must make decisions based on limited information and history. Intramuscular (IM) formulations are available for a number of FGAs and two SGAs (ziprasidone and olanzapine). These formulations are safe and effective in treating acute psychosis. These SGAs are now recommended as first-line therapy in agitated schizophrenia patients; however, IM lorazepam with or without concomitant oral (tablets, liquid, or disintegrating tablets) SGAs are also used. High dosing of FGAs, termed rapid neuroleptization, is no longer recommended.

Pregnancy and Lactation

When to use antipsychotics in pregnancy and during lactation remains a complicated decision based on a careful analysis of risks and benefits. Women with schizophrenia have a significantly greater risk for stillbirth, infant death, preterm delivery, low infant birth weight, and infants that are small for gestational age, even in unmedicated patients. Furthermore, women who experience a relapse in psychotic symptoms during pregnancy are at the greatest risk for birth complications.[42] Because risks related to psychotic relapse may be more detrimental than antipsychotic treatment to both mother and baby, antipsychotics are often continued during this period.

Essentially all antipsychotic medications pass through the placenta. The use of these drugs requires critical attention to the timing of the exposure, the dose and duration of use, and fetal susceptibility. When possible, discontinuing antipsychotics for the first trimester is the safest option, as weeks 6 to 10 are the most vulnerable period for organ formation. Generally, monotherapy at the lowest effective dose for the shortest period necessary is the best strategy. High-potency FGAs are associated with a low risk for congenital abnormalities; however, limb defects and dyskinesias have been reported.[43] Low-potency phenothiazine antipsychotics may increase the risk of congenital abnormalities when used in the first trimester. According to the relevant literature published to date, there appears to be little risk associated with the first-line SGAs.[44] However, on the basis of available data, generalization is impossible, and each case and specific antipsychotic should be weighed on an individual basis. While SGAs are excreted in breast milk, most case reports have reported a low frequency of deleterious effects on the infant. Women taking SGAs may have enhanced fertility compared to women taking FGAs, as SGAs (except risperidone) are less likely to cause prolactin elevations leading to anovulation. Therefore, careful discussion with patients, including education about birth control, must occur.

Pharmacokinetics

Pharmacokinetic and pharmacodynamic issues are not generally a major concern with antipsychotic treatment; however, additive side effects may occur with combined treatment, and a few clinically significant drug interactions are notable (Table 34–9). All of the antipsychotics are highly protein-bound; however, protein-binding interactions are generally not clinically significant. Absorption of most antipsychotics is not affected by food, with the exception of ziprasidone, whose absorption is increased by 60% to 70% when given with meals. The absorption of quetiapine may be slightly increased when given with food.

All antipsychotics are metabolized by hepatic microsomal enzymes to water-soluble compounds that are excreted by the kidneys. The most important of the microsomal enzymes are the cytochrome P-450 (CYP450) enzymes, a group of enzymes that play a major role in oxidative drug metabolism. Although over 30 isoenzymes of the CYP450 system have been identified in humans, three play a significant role in the metabolism of antipsychotic medications: CYP4502D6, CYP4501A2, and CYP4503A3/4. Substances that inhibit or induce the function of these enzymes can change antipsychotic blood concentrations. For example cigarette smoking

TABLE 34–9. Metabolism and Drug Interactions with Antipsychotics

Antipsychotic	Major CYP450 Metabolic Enzyme	Other CYP450 Metabolic Pathways	Increase Antipsychotic Concentrations	Decrease Antipsychotic Concentrations
Clozapine	1A2	3A3/4, 2D6, 2C19	Fluvoxamine, ciprofloxacin, paroxetine	Cigarette smoking
Risperidone	2D6	3A3/4		
Olanzapine	1A2	2D6	Fluvoxamine, ciprofloxacin, paroxetine	Cigarette smoking
Quetiapine	3A3/4	2D6	Fluvoxamine, ketoconazole	Carbamazepine
Ziprasidone	3A3/4		Fluvoxamine, ketoconazole	Carbamazepine
Aripiprazole	3A3/4	2D6	Fluvoxamine, ketoconazole	Carbamazepine
Haloperidol	2D6, 3A3/4		Fluvoxamine, fluoxetine, ketoconazole	Carbamazepine
Thioridazine	2D6	1A2	Fluvoxamine	Cigarette smoking
Perphenazine	2D6		Fluvoxamine, fluoxetine, paroxetine	

CYP, cytochrome P-450 isoenzyme.

induces CYP4501A2, and therefore can decrease clozapine and olanzapine plasma concentrations. Table 34–9 lists the primary metabolic enzymes and some potential drug interactions for the antipsychotic medications. Clinicians should assess the clinical impact of the addition or discontinuation of these drugs in individual patients and should make appropriate adjustments when necessary. Unlike the other antipsychotics, ziprasidone is mostly metabolized by aldehyde oxidase, a metabolic system independent of the CYP450 system. Another recent discovery in drug metabolism of antipsychotics and their distribution involves the transmembrane energy-dependent efflux transporter, P-glycoprotein, which may limit a number of drugs from penetrating into the extracellular space.[45] Antipsychotics currently known to use this pathway include perphenazine, haloperidol, fluphenazine, quetiapine, risperidone, and olanzapine.[46]

Due to its propensity to cause prolongation of the QTc interval, the use of ziprasidone with other agents that prolong the QTc interval should be avoided. These other agents include, but are not limited to, anti-arrhythmic medications such as quinidine and sotalol, certain FGAs (chlorpromazine, droperidol, mesoridazine, pimozide, and thioridazine), and certain antibiotics (gatifloxacin, halofantrine, mefloquine, moxifloxacin, and pentamidine). Ziprasidone has not been shown to have clinically significant drug interactions with the CYP4503A3/4 inhibitors regarding increasing the QTc; however, higher doses, especially given with inhibitors of CYP4503A3/4 (e.g., ketoconazole and erythromycin), should be used cautiously. Other risk factors for prolongation of the QTc interval include comorbid diabetes, electrolyte disturbances (e.g., low sodium and potassium serum concentrations), heavy alcohol consumption, female gender, and congenital QTc disorder. Clinicians should also be vigilant to avoid pharmacodynamic interactions with any of the antipsychotics involving additive side effects from combination therapies. Side effects that may be worsened with combination therapies include sedation, hypotension, anti-cholinergic symptoms, and weight gain or metabolic abnormalities.

Adjunct Pharmacologic Treatments

The judicious use of pharmacologic therapies other than antipsychotics may be necessary in the treatment of schizophrenia. Concomitant medications may be indicated for the treatment of motor side effects, anxiety, depression, mood elevation, and possibly refractory psychotic symptoms. Anticholinergic medications (e.g., benztropine, 1 to 2 mg two times daily; trihexyphenidyl, 1 to 3 mg three times daily; and diphenhydramine, 25 to 50 mg two times daily) are used to effectively treat EPS, thereby improving the tolerability of these medications. They are usually prescribed prophylactically with high-D_2-binding agents or in patients at risk for EPS. β-Blockers (e.g., propranolol in doses of 30 to 120 mg/day) are sometimes effective for patients who develop akathisia. In some situations, such as on an inpatient unit, the concomitant use of benzodiazepines (e.g., lorazepam in doses of 1 to 3 mg/day) with the SGAs may be necessary for agitation and insomnia.

Antidepressants may be useful for patients with depressive symptoms that are not due to negative symptomatology or emotional blunting secondary to parkinsonian-type side effects. Sometimes it is necessary for the clinician to treat with an antidepressant to rule out depression, as it is not always possible to differentiate these conditions. Since suicide and depression are interconnected, aggressive treatment is necessary when depression is present. Selective serotonin reuptake inhibitors (SSRIs) are the preferred agents, but may inhibit the CYP450 enzymes, thus raising plasma concentrations of clozapine, olanzapine, and haloperidol. Mood stabilizers, such as lithium and the anticonvulsants, have long been used adjunctively with antipsychotics to treat the affective component of schizoaffective disorder. Valproate is currently the most commonly used mood stabilizer in schizophrenic patients, and its use in conjunction with clozapine may protect against a pre-epileptic condition known as myoclonic jerking. And finally, much research is currently underway to develop better treatments for primary negative symptoms and cognitive impairment; however, no approved treatments are yet available.

OUTCOME EVALUATION

Patient Education

Frequently, patients receive little education about schizophrenia and may not have a good understanding of their diagnosis. Meetings for purposes of medication management offer an opportunity to provide some education on the general illness. Discuss the nature and course of schizophrenia and be prepared to accept that the patient might have a different understanding of the nature of his or her illness. Key points to cover include:

- Involve families in the education and treatment plans, since family psychoeducation may decrease relapse, improve symptomatology, and enhance psychosocial and family outcomes.[47]
- Be clear that there is no cure for schizophrenia and that medications only help to decrease the symptoms.
- Explain common side effects of medications.
- Discuss rare but dangerous side effects which may also occur.
- Stress the importance of medication and treatment adherence for improving long-term outcomes in schizophrenia.

Symptom Monitoring

Develop a good working alliance with the patient. When a solid therapeutic foundation is not formed, patients are frequently reluctant to share their psychotic experiences. Frequently, patients fear that others will interpret their descriptions as "crazy." Alternatively, some care providers have told patients to "keep their beliefs to themselves," as a way to cope with their illness in the community. In these instances, it may take time to gain the patient's trust and to learn enough

about the details of their life experience to explore their more personal experiences. Once a solid working relationship and some knowledge of the patient's psychotic experiences exist, perform a more structured interview. Many assessments are available to more objectively rate positive and negative symptoms, level of function, and life satisfaction. The most commonly used scales include:

- The Positive and Negative Symptom Scale (PANSS)
- The Brief Psychiatric Rating Scale (BPRS)
- The Clinical Global Impression (CGI) scale

Using these scales on a regular basis, particularly when switching medications or changing doses, is a more reliable means of monitoring for improvement. Certainly symptom assessments cannot capture the full range of possible improvements a patient may experience, but they can be useful in deciding whether a medication is having substantial benefit.

Side Effect Monitoring

❼ *Regularly monitor patients for side effects and overall health status while taking antipsychotic medications.*[48,49] *Perform orthostatic blood pressure measurements at the initiation of antipsychotics and throughout treatment. Ask about impaired menstruation, libido, and sexual performance regularly. Encourage patients to have annual eye exams, as several of the antipsychotic medications have been associated with the premature development of cataracts. Check body weight, fasting glucose, glycosylated hemoglobin, and lipid profile at baseline, at 4 months after initiation of medication, and then yearly.*[50] For patients who are at higher risk of developing diabetes and those who gain weight, check body weight more often (Table 34–10). Encourage patients to act proactively against weight gain through healthier eating and exercise. Perform a *baseline electrocardiogram (ECG) for patients with preexisting cardiovascular disease and risk for arrhythmia*. With clozapine therapy there is a risk for the development of agranulocytosis, which is greatest in the first 6 months of treatment. Current guidelines require the monitoring of white blood cell counts (WBC) prior to drug dispensing (Table 34–11).

Commonly used rating scales to monitor for EPS include the Simpson Angus Scale (SAS) and the Extrapyramidal Symptom Rating Scale (ESRS). Akathisia is commonly monitored by the Barnes Akathisia Scale (BAS). The emergence of dyskinesias (writhing or involuntary movements) could represent the emergence of TD. Monitor for TD at least annually, and if FGAs are used patients should be evaluated at each visit. The most commonly used instrument to measure these symptoms is the Abnormal Involuntary Movement Scale (AIMS).



Patient Encounter, Part 4

With his care providers, AG discussed several possible medication choices. Because there had been improvement of auditory hallucinations on risperidone, the initial choice was made to increase the dose to target the ongoing paranoid thinking. AG was seen weekly to monitor for emergence of EPS or akathisia. He was able to tolerate an increase to 4 mg of risperidone daily with improvement in his paranoid thinking. He went on several interviews for jobs and accepted part-time employment at a coffee shop. When he complained of emergence of sexual dysfunction, his prolactin level was determined to be 42 ng/mL (42 µg/L). He discussed risks and benefits of therapy with his clinicians and decided to continue risperidone for now, as he had improved in his ability to work and get out more in the community. He remains interested in having an aripiprazole trial in the future, as he hopes he might more easily lose the weight he gained while taking olanzapine and resume normal sexual functioning. He is no longer taking an antidepressant, and though he has some low days, he does not meet the criteria for diagnosis of depressive episode. He continues to be free of substance abuse, and his girlfriend continues to support his treatment. He still hopes to return to work in his field of expertise someday.

- Based on the information above, create a care plan for this patient's treatment. Your plan should include: (1) a statement of the drug-related concerns and/or problems, (2) the goals of therapy, and (3) a plan for monitoring and follow-up to determine whether the goals have been achieved and adverse effects minimized.

TABLE 34–10. Monitoring Protocol for Patients on Second-Generation (Atypical) Antipsychotics

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 Years
Personal/family history[a]	X					X	
Weight	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting plasma lipids	X			X			X

[a]Of obesity, diabetes, dyslipidemia, hypertension, or cardiovascular disease.
From American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004;27: 596–601, with permission.

TABLE 34–11. Monitoring of White Blood Cell Count and Absolute Neutrophil Count during Clozapine Treatment

	Hematologic Values	Frequency of WBC and ANC Monitoring
Prior to clozapine initiation	Recommended levels: WBC greater than or equal to 3,500/mm^3 and ANC greater than or equal to 2,000/mm^3 No history of a **myeloproliferative disorder** or clozapine-induced agranulocytosis	
Initiation to 6 months	WBC greater than or equal to 3,500/mm^3 and ANC greater than or equal to 2,000/mm^3	Weekly for 6 months
6 to 12 months	WBC greater than or equal to 3,500/mm^3 and ANC greater than or equal to 2,000/mm^3	Every 2 weeks for 6 months
After 12 months of therapy	WBC greater than or equal to 3,500/mm^3 and ANC greater than or equal to 2,000/mm^3	Every 4 weeks
Clozapine discontinuation		Weekly for at least 4 weeks from day of discontinuation
Mild leukopenia or granulocytopenia	3,500/mm^3 greater than WBC greater than or equal to 3,000/mm^3 and/or 2,000/mm^3 greater than ANC greater than or equal to 1,500/mm^3	Twice weekly until returned to recommended levels
Moderate leukopenia or granulocytopenia	3,000/mm^3 greater than WBC greater than or equal to 2,000/mm^3 and/or 1,500/mm^3 greater than ANC greater than or equal to 1,000/mm^3	Interrupt therapy; monitor daily until WBC greater than 3,000/mm^3 and ANC greater than 1,500/mm^3, then twice weekly until back to recommended levels
Severe leukopenia or granulocytopenia or agranulocytosis	WBC less than 2,000/mm^3 and/or ANC less than 1,000/mm^3 ANC less than or equal to 500/mm^3	Discontinue treatment and do not rechallenge; monitor daily until WBC greater than 3,000/mm^3 and ANC greater than 1,500/mm^3, then twice weekly until back to recommended levels

ANC, absolute neutrophil count; WBC, white blood cell.
ANC = Absolute Neutrophil Count, 3500/mm^3 = 3.5 × 10^3/μL or 3.5 × 10^{9}L; 3000/mm^3 = 3 × 10^3/μL or 3 × 10^{9}L; 2000/mm^3 = 2 × 10^3/μL or 2 × 10^{9}L; 1500/mm^3 = 1.5 × 10^3/μL or 1.5 × 10^{9}L; 1000/mm^3 = 1 × 10^3/μL or 1 × 10^{9}L; 500/mm^3 = 0.5 × 10^3/μL or 0.5 × 10^{9}L.



Patient Care and Monitoring

1. Assess the patient's symptoms, review patient and family history, and obtain initial medical evaluation to rule out other causes of psychosis.
2. Periodically review patient data for consistency with diagnostic criteria, and regularly monitor changes in symptomatology.
3. Obtain a thorough history of prescription medication use, and determine what treatments have been helpful in the past, which treatments the patient is currently receiving, and previous side effects experienced.
4. Determine whether the patient is taking an appropriate antipsychotic drug and dose and whether the patient has other symptoms that may need to be treated.
5. Educate the patient, and the family if possible, about the disease state, medication treatments, possible side effects, and goals of treatment.
6. Develop a plan to assess the effectiveness of the current treatment regimen. Also, consider alternative treatments if current treatment is ineffective.
7. Encourage a healthy lifestyle, including eliminating or decreasing substance abuse and cigarette use, as well as appropriate nutritional counseling and exercise suggestions.
8. Determine the role of psychosocial treatments.
9. Evaluate the patient for the presence of adverse drug reactions, drug interactions, and allergies.
10. Monitor the appropriate laboratory measures to prevent or minimize metabolic abnormalities and other side effects.
11. Stress the importance of adherence with the treatment regimen, and maintain treatment even if the patient is feeling well.

ABBREVIATIONS

5-HT:	serotonin
AIMS:	Abnormal Involuntary Movement Scale
ANC:	absolute neutrophil count
BAS:	Barnes Akathisia Scale
BPRS:	Brief Psychiatric Rating Scale
CBT:	cognitive-behavioral therapy
CGI:	Clinical Global Impression scale
COMT:	catechol-O-methyltransferase
CR:	cognitive remediation
CT:	computed tomography
CYP450:	cytochrome P-450 isoenzyme
D:	dopamine
DSM-IV-TR:	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
ECG:	electrocardiogram
ECT:	electroconvulsive therapy
EOS:	early-onset schizophrenia
EPS:	extrapyramidal side effects
ESRS:	Extrapyramidal Symptom Rating Scale
FDA:	Food and Drug Administration
FGA:	first-generation antipsychotic
H:	histamine
IM:	intramuscular
M:	muscarinic
MRI:	magnetic resonance imaging
NMS:	neuroleptic malignant syndrome
PANSS:	Positive and Negative Symptom Scale
PET:	positron emission tomography
PORT:	Schizophrenia Patient Research Outcomes Team
SAS:	Simpson Angus Scale
SGA:	second-generation antipsychotic
SSRI:	selective serotonin reuptake inhibitor
SST:	social skills training
TD:	tardive dyskinesia
TIMA:	Texas Implementation of Medication Algorithms
VEOS:	very early-onset schizophrenia
WBC:	white blood cell

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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35 Major Depressive Disorder

Marshall Cates, Angela Ann Boggs, and Jacqueline Feldman



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Explain the etiology and pathophysiology of major depressive disorder.
2. Identify symptoms and clinical features of major depressive disorder.
3. Differentiate antidepressants according to pharmacologic properties, adverse-effect profiles, pharmacokinetic profiles, drug interaction profiles, and dosing features.
4. Predict adverse-effect profiles of antidepressants based on pharmacology.
5. State the goals of pharmacotherapy in major depressive disorder.
6. Educate patients and caregivers on the proper use of antidepressants.

Key Concepts

❶ Classic views as to the cause of major depressive disorder focus on the monoamine neurotransmitters norepinephrine (NE), serotonin (5-HT), and to a lesser extent, dopamine (DA) in terms of both synaptic concentrations and receptor functioning.

❷ It is not uncommon for a patient to experience only a single major depressive episode, but most patients with major depressive disorder will experience multiple episodes.

❸ One extremely important outcome in the treatment of major depressive disorder is the prevention of suicidal attempts.

❹ Sexual dysfunction is common and challenging to manage and often leads to non-compliance with serotonergic medications.

❺ Each antidepressant has a response rate of approximately 60% to 80%, and no antidepressant medication or class has been reliably shown to be more efficacious than another.

❻ It is widely accepted that it takes approximately 2 to 4 weeks of treatment before improvement is seen in emotional symptoms of depression, such as sadness and anhedonia. Furthermore, it may take as long as 6 to 8 weeks of treatment to see the full effects of antidepressant therapy.

❼ Since the typical major depressive episode lasts 6 months or longer, if antidepressant therapy is interrupted for any reason following the acute phase, the patient may relapse into the depressive episode. When treating the first depressive episode, antidepressants must be given for an additional 4 to 9 months in the continuation phase for the purpose of preventing relapse.

❽ Pediatric patients should be observed closely for suicidality, worsened depression, agitation, irritability, and unusual changes in behavior, especially during the initial few months of therapy or at times of dosage changes. Furthermore, families and caregivers should be advised to monitor patients for such symptoms.

❾ Lack of patient understanding concerning optimal antidepressant drug therapy frequently leads to partial compliance or non-compliance with therapy; thus, the primary purpose of antidepressant counseling is to enhance compliance and improve outcomes.

My spirit is broken,
my days are cut short,
the grave awaits me.
—*Job 17:1*

Contrary to popular belief, major depression is not a fleeting "bad day," is not the result of personal weaknesses or character flaws, and does not respond to volitional efforts simply to feel better. Rather, major depressive disorder (MDD) is a serious medical condition with a biologic foundation, and it responds to biologic and psychological treatments. Individuals who suffer from MDD experience significant and pervasive symptoms that can affect such things as mood, thinking, physical health, work, and relationships. Unfortunately, suicide is often the result of MDD that has not been diagnosed and treated adequately.

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Patient Encounter, Part 1

ML, a 28-year-old white woman, comes into your clinic for the first time complaining of decreased sleep, pain, and lack of energy. On interviewing her, you learn that she is also having frequent crying spells and no longer participates in the bowling league, which she used to enjoy every weekend. She fears that she is about to be fired from her job because of numerous sick days and the inability to concentrate on tasks when she is at work, and she claims that she is already under a great deal of financial stress owing to the fact that her husband lost his job several months ago. She states that she has been suffering from these problems for the past two months and is feeling frustrated and hopeless. She admits to drinking about three to four beers per night in order to relax and fall asleep.

- What information is suggestive of MDD?
- What medical or psychiatric issues could be contributing to her symptoms?
- Does she have risk factors for depression?
- What additional information do you need to know before creating a treatment plan for this patient?

Owing to increased awareness of the illness and the advent of newer and safer antidepressant medications, the past two decades have seen improvements in the screening, diagnosis, and treatment of MDD. The willingness of generalist practitioners to involve themselves in the identification and treatment of MDD is noteworthy. To that end, antidepressants have become some of the most commonly prescribed drugs, and they account for 10 of the top 100 prescription drugs dispensed in the United States.[1] Despite recent increases in the treatment of MDD, inadequate treatment remains a serious concern.[2]

EPIDEMIOLOGY

MDD is quite common; lifetime and 12-month prevalence estimates are 16.2% and 6.6%, respectively. Thus, approximately 35 million United States adults will experience MDD in their lifetime.[2] Females are approximately twice as likely as males to experience MDD.[2] Although MDD may begin at any age, the average age at onset is the mid-20s.[3] Interestingly, MDD appears to occur earlier in life in people born in more recent decades.[2] Most patients with MDD also suffer from comorbid psychiatric disorders, especially anxiety disorders and substance-use disorders.[2]

MDD causes serious impairment. According to the World Health Organization (WHO), depression is the leading cause of disability (based on years lived with disability) and the fourth leading contributor to the global burden of disease (based on disability adjusted life years).[4] Those with 12-month MDD reported a mean of about 35 days in the past year in which they were unable to work or carry out usual activities.[2]

ETIOLOGY/PATHOPHYSIOLOGY

The exact cause of MDD remains unknown, but it is probably multifactorial. Biologic, psychological, and social theories abound, and many practitioners suggest that the development of depression often is predicated on the complex synthesis of genetic predisposition, psychological stressors, and biologic pathophysiology. Although knowledge certainly continues to accumulate in this area, there are currently no accepted unifying theories that explain these various factors adequately.

Genetics

The occurrence of MDD shows a familial pattern because first-degree relatives of MDD patients are about three times more likely to develop MDD compared with first-degree relatives of normal control individuals. Adoption studies and twin studies reveal that the familial aggregation of MDD is due to genetic influences.[5]

Life Stress

Depression can occur despite the absence of major life stressors, and conversely, major life stressors do not invariably cause depression. Nevertheless, there is an undeniable association between life stressors and depression, and there appears to be a significant interaction between life stressors and genetic liability in causing depression.[6] Although acute stressors may precipitate depression, chronic stressors have a longer risk period, cause longer episodes, and are more likely to lead to **relapse** and **recurrence.**[6]

Monoamine Neurotransmitter and Receptor Hypotheses

❶ *Classic views as to the cause of MDD focus on the monoamine neurotransmitters norepinephrine (NE), serotonin (5-HT), and to a lesser extent, dopamine (DA) in terms of both synaptic concentrations and receptor functioning.* The monoamine hypothesis asserts that depression is due to a deficiency of monoamine neurotransmitters. The major supporting evidence for this hypothesis is that existing antidepressants increase synaptic monoamine concentrations through various mechanisms (see Pharmacology section). One argument against the monoamine hypothesis is that depressed patients do not consistently exhibit decreased monoamine concentrations. Another problem is that whereas monoamine levels are altered within hours of the introduction of antidepressant therapy, there is a latency period of weeks before the actual antidepressant effect typically is evident.[7–9]

The neurotransmitter receptor hypothesis suggests that depression is related to abnormal functioning of neurotransmitter receptors. In this model, antidepressants presumably exert therapeutic effects by altering receptor sensitivity. In fact,

chronic administration of antidepressants has been shown to cause desensitization, or down-regulation, of β-adrenergic receptors and various 5-HT receptors. Importantly, the time required for changes in receptor sensitivity corresponds to the onset of action of antidepressant therapy.[7–9]

While such models of depression are quite useful in conceptualizing the mechanisms behind antidepressant activity, they are assuredly an oversimplification of the actual pathophysiologic process of the disorder. Depression probably involves a complex dysregulation of monoamine systems, and these systems, in turn, modulate and are modulated by other neurobiologic systems. Thus, the underlying cause of depression may well extend beyond dysfunction of the monoamine system.[10]

Other Neurobiologic Hypotheses

Various other hypotheses have been proposed to help explain the cause of depression. These hypotheses are related to such things as the role of non-monoamine neurotransmitters [e.g., glutamate and gamma-aminobutyric acid (GABA)], neuroendocrine systems (e.g., the hypothalamic-pituitary-adrenal axis), neurosteroids (e.g., allopregnanolone), and neuronal plasticity [e.g., brain-derived neurotrophic factor (BDNF)].[11] Researchers are even starting to gain insight on the intracellular level with findings related to messenger cascades and gene expression.[12]

CLINICAL PRESENTATION AND DIAGNOSIS

The diagnosis of a major depressive episode requires the presence of a certain number of depressive symptoms (five) for a minimum specified duration (2 weeks) that cause clinically significant effects (Table 35–1).[3]

TABLE 35–1. Diagnostic Criteria for Major Depressive Episode[3]

At least five of the following symptoms have been present during the same 2-week period and represent a change from previous functioning:

- Depressed mood[a]
- Markedly diminished interest or pleasure in usual activities[a]
- Increase or decrease in appetite or weight
- Increase or decrease in amount of sleep
- Increase or decrease in psychomotor activity
- Fatigue or loss of energy
- Feelings of worthlessness or guilt
- Diminished ability to think, concentrate, or make decisions
- Recurrent thoughts of death, suicidal ideation, or suicide attempt

The symptoms cause clinically significant distress or impairment in functioning.

The symptoms are not due to the direct physiologic effects of a substance or medical condition.

[a]One of these two symptoms must be present.
With permission.



Clinical Presentation

Patients typically present with a combination of emotional, physical, and cognitive symptoms:

- Emotional
  - Sadness
  - **Anhedonia**
  - Pessimism
  - Feeling of emptiness
  - Irritability
  - Anxiety
  - Worthlessness
  - Thoughts of death/suicidal ideation (SI)
- Physical
  - Disturbed sleep
  - Change in appetite/weight
  - Psychomotor changes
  - Decreased energy
  - Fatigue
  - Bodily aches and pain
- Cognitive
  - Impaired concentration
  - Indecisiveness
  - Poor memory

Occasionally, severely depressed patients also will present with psychotic symptoms:

- Hallucinations
- Delusions

Some patients present with "atypical features" of depression:

- Reactive mood (i.e., mood improves in response to positive events)
- Significant increase in appetite/weight gain
- Hypersomnia
- Heavy feelings in arms or legs
- Sensitivity to interpersonal rejection

HINT: In order to remember the nine diagnostic symptoms for a major depressive episode, learn the following mnemonic: Depression = SIG E CAPS (depression, sleep, interest, guilt, energy, concentration, appetite, psychomotor, suicide).

In turn, the diagnosis of MDD is based on the presence of one or more major depressive episodes during a person's lifetime.[3]

Differential Diagnosis

Major depressive episodes also occur in the context of bipolar disorder. The key difference is that persons with bipolar disorder also experience manic, hypomanic, and/or mixed episodes (see Chap. 36) during the course of their illness, whereas persons with MDD experience only major depressive episodes.[3]

The presence of a significant medical disorder can produce depressive symptoms via either psychological or physiologic mechanisms. Examples include hypothyroidism, anemia, infections, electrolyte disturbances, cardiovascular diseases, neurologic disorders, and many others.[9] Various psychiatric conditions, such as substance-use disorders and anxiety disorders, have been associated with depression as well.[9] The use of central nervous system (CNS) depressants, such as benzodiazepines and narcotics, is associated with increased propensity for depression.[13] Medical drugs that reportedly cause depressive symptoms or depressive-like side effects include corticosteroids, contraceptives, gonadotropin-releasing hormone agonists, interferon-α, interleukin-2, mefloquine, propranolol, and sotalol.[14]

COURSE/PROGNOSIS

Symptoms of a major depressive episode usually develop over days to weeks, but mild depressive and anxiety symptoms may last for weeks to months prior to the onset of the full syndrome. Left untreated, major depressive episodes typically last 6 months or more, but a minority of patients experience chronic episodes that can last for at least 2 years. Approximately two-thirds of patients will recover fully from major depressive episodes and return to usual mood and full functioning, whereas the other third will have partial remission and may continue to experience detrimental effects.[3]

The course of MDD varies markedly from patient to patient. ❷ *It is not uncommon for a patient to experience only a single major depressive episode, but most patients with MDD will experience multiple episodes.* Some patients experience isolated episodes separated by many years, others have clusters of episodes, and still others will suffer more frequent episodes as they age. The number of prior episodes predicts the likelihood of developing subsequent episodes such that by the time a patient experiences a third major depressive episode, there is about a 90% chance that he or she will have a fourth one. MDD is associated with a high mortality rate because about 15% of patients ultimately will commit suicide.[3]

TREATMENT

Desired Outcomes

The obvious goal of therapy for the depressed patient is the resolution of depressive symptoms and a return to **euthymia.** Once symptoms have resolved, then the purpose of ongoing therapy is to prevent relapse and recurrence of depressive symptoms. ❸ *One extremely important outcome in the treatment of MDD is the prevention of suicidal attempts.* Other essential outcomes include improvement of the patient's quality of life, normalization of functioning in areas such as work and relationships, avoidance or minimization of adverse effects, and reduction of health care costs.[15]



Patient Encounter, Part 2: The Medical History, Physical Exam and Diagnostic Tests

The work-up on ML reveals

PMH
- Chronic back pain since motor vehicle accident 3 years ago.

PPH
Non-contributory

FH
- Mother with diabetes mellitus and MDD.
- Father is alive and well with no medical problems.
- Brother is a recovered alcoholic.

SH
Works as a secretary for a construction company. For the past several months has been drinking three to four beers per night. She denies smoking cigarettes or using illicit substances.

Current Meds
- Lo/Ovral 1 tablet every day
- Oxycontin 10-mg tablet twice daily

ROS
- Decreased energy
- Decreased sleep
- All others non-contributory

PE
Height: 5 ft, 2 in (157 cm); weight: 116 lbs (52.7 kg); weight loss of 10 lbs (4.5 kg) over past 2 months

MSE
- Depressed mood
- Decreased concentration
- Thoughts of dying, but no suicidal ideation

Labs
Within normal limits. Pregnancy test negative.

- Given this additional information, what is your assessment of the patient's condition?
- Identify your treatment goals for the patient.
- What non-phamacologic and pharmacologic alternatives are available for this patient?

Nonpharmacologic/Alternative Therapies

Interpersonal therapy and cognitive behavioral therapy are types of psychotherapy that have well-documented efficacy for the treatment of MDD. Psychotherapy alone is an initial treatment option for mild to moderate cases of depression, and it may be useful when combined with pharmacotherapy in the treatment of more severe cases of depression. In fact, the combination of psychotherapy and pharmacotherapy can be more effective than either treatment modality alone in cases of severe or recurrent MDD. Psychotherapy can be especially helpful for patients with significant psychosocial stressors, interpersonal difficulties, or comorbid personality disorders.[16]

Electroconvulsive therapy (ECT) is a highly efficacious treatment for MDD. The **response** rate is about 80% to 90% and even exceeds 50% for patients who have failed pharmacotherapy.[16,17] ECT may be particularly beneficial for MDD that is complicated by psychotic features, severe suicidality, refusal to eat, pregnancy, or contraindication/non-response to pharmacotherapy.[16,17] ECT is typically a very safe treatment alternative, but various cautions do exist, and the chief side effects are confusion and memory impairment.[16]

St. John's wort (*Hypericum perforatum*) is an herbal medication that has shown some efficacy in mild to moderate depression but minimal efficacy for moderate to severe depression.[18] Many patients may believe that herbal medications, being "natural" products, are devoid of adverse effects and drug interactions; however, St. John's wort can cause gastrointestinal irritation, headache, fatigue, and nervousness,[17] and it triggers drug interactions through induction of CYP3A4, as well as other potential mechanisms.[19] The safety and efficacy of St. John's wort combined with standard antidepressant medications remain unknown.[16]

Light therapy is an alternative treatment for depression associated with seasonal (e.g., winter) exacerbations. Possible side effects include eye strain, headache, insomnia, and hypomania.[16,17] Also, potentially vulnerable patients, such as those with photosensitivity or a history of skin cancer, should be evaluated carefully prior to therapy.[16]

Vagus nerve stimulation (VNS) may be used for adult patients with **treatment-resistant depression.** A pulse generator is surgically implanted under the skin of the left chest, and an electrical lead connects the generator to the left vagus nerve. Stimulation of this nerve sends signals to the brain. This therapy is intended to be used along with traditional therapies, such as pharmacotherapy and ECT.[20]

Transcranial magnetic stimulation is a non-invasive and well-tolerated procedure that has shown promise as a novel antidepressant treatment.[21] Some data show that physical exercise may reduce depressive symptoms, but well-controlled studies are needed to clarify its role in the treatment of depression.[18]

Pharmacologic Therapy

Clinical Distinctions

Given that there are now about 25 antidepressant medications, one apparent clinical perplexity is for the clinician to distinguish the various agents. But each antidepressant has its unique blend of characteristics, and in fact, even individual drugs within the same class have important differences.[22]

General Pharmacology

Table 35–2 demonstrates the differing pharmacologic properties of the antidepressant medications,[7–9] whereas Table 35–3 delineates the results of those pharmacologic actions.[7,8] Monoamine oxidase inhibitors (MAOIs) inhibit the enzyme responsible for the intraneuronal breakdown of 5-HT, NE, and DA. Tricyclic antidepressants (TCAs) possess both 5-HT reuptake inhibition (SRI) and NE reuptake inhibition (NRI) properties but unfortunately also block the so-called "dirty receptors", including α_1-adrenergic, histamine-1, and muscarinic cholinergic receptors, which do not contribute to efficacy but do cause problematic adverse effects. The selective serotonin reuptake inhibitors (SSRIs) are classified as such because SRI is the predominant effect. Bupropion is an NE and DA reuptake inhibitor (NDRI). Venlafaxine and duloxetine are 5-HT and NE reuptake inhibitors (SNRIs) but are also weak inhibitors of DA reuptake. Compared with venlafaxine, which has primarily SRI activity, duloxetine has more balanced SRI and NRI activities and has a higher affinity for the reuptake sites. Nefazodone and trazodone are 5-HT antagonists/reuptake inhibitors (SARIs). Their SRI activity is not as pronounced as that of SSRIs, but they potently block 5-HT_{2A} receptors, which allows more 5-HT to interact at postsynaptic 5-HT_{1A} sites. In addition, trazodone blocks histaminergic and

TABLE 35–2. Primary Pharmacologic Actions of Antidepressants[a7–9]

Action	MAOIs	TCAs	SSRIs	Bupropion	Venlafaxine	Duloxetine	Trazodone	Nefazodone	Mirtazapine
Monoamine oxidase inhibition	X								
Serotonin reuptake inhibition		X	X		X	X	X	X	
Norepinephrine reuptake inhibition		X		X	X	X			
Dopamine reuptake inhibition				X					
α_2-Adrenergic receptor blockade									X
Serotonin-2A receptor blockade							X	X	X
Serotonin-2C receptor blockade									X
Serotonin-3 receptor blockade									X
α_1-Adrenergic receptor blockade		X					X	X	
Histamine-1 receptor blockade		X					X		X
Muscarinic cholinergic receptor blockade		X							

[a]Please see text for discussion of more secondary pharmacologic actions.
MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

TABLE 35–3. Efficacy/Adverse-Effect Profiles Based on Pharmacology[7,8]

Pharmacologic Action	Result
Serotonin reuptake inhibition (SRI)	Antidepressant and antianxiety efficacy (via interaction of serotonin at 5HT-1A receptors) Anxiety, insomnia, sexual dysfunction (via interaction of serotonin at 5HT-2A receptors) Anxiety, anorexia (via interaction of serotonin at 5HT-2C receptors) Nausea, GI problems (via interaction of serotonin at 5HT-3 receptors)
Norepinephrine reuptake inhibition (NRI)	Antidepressant efficacy Tremor, tachycardia, sweating, jitteriness, increased blood pressure
Dopamine reuptake inhibition (DRI)	Antidepressant efficacy Euphoria, psychomotor activation, aggravation of psychosis
α_2-Adrenergic receptor blockade	Increase in serotonergic and noradrenergic activity—see actions of SRI and NRI above
Serotonin-2A receptor blockade	Antianxiety efficacy Increased REM sleep, decreased sexual dysfunction
Serotonin-2C receptor blockade	Antianxiety efficacy Increased appetite/weight gain
Serotonin-3 receptor blockade	Antinauseant, decreased GI problems
α_1-Adrenergic receptor blockade	Orthostatic hypotension, dizziness, reflex tachycardia
Histamine-1 receptor blockade	Sedation, weight gain
Muscarinic cholinergic receptor blockade	Dry mouth, blurred vision, constipation, urinary hesitancy, sinus tachycardia, memory problems

α-adrenergic receptors, whereas nefazodone possesses weak NRI and α-adrenergic blocking properties. Finally, mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA). It blocks presynaptic α_2 receptors, both autoreceptors on noradrenergic neurons and heteroreceptors on serotonergic neurons, with resulting increases in NE and 5-HT synaptic concentrations, respectively. Mirtazapine also blocks various postsynaptic serotonergic receptors and histamine-1 receptors.[7–9]

Adverse Effects

The important adverse effects of the various antidepressants are often a function of their underlying pharmacologic profiles[7,8] (Table 35–3). TCAs cause problematic sedative, anticholinergic, and cardiovascular adverse effects owing to their interaction with "dirty receptors." While these adverse effects generally are considered to be common and bothersome, they can be quite serious in certain cases. For example, constipation in its extreme form can lead to paralytic ileus. It is very important to note that TCAs have a quinidine-like effect on the heart, which makes them quite toxic in overdose situations. The average lethal dose in a young adult is only 30 mg/kg, which is typically less than a 1-month's supply of medicine.[7,9,22,23]

The adverse-effect profile of the SSRIs reveals the strong serotonergic influence of these drugs. Sexual dysfunction (e.g., delayed or absent orgasms), CNS stimulation (e.g., nervousness and insomnia), and gastrointestinal disturbances (e.g., nausea and diarrhea) are frequent serotonergic adverse effects.[7,9,22,23] ❹ *Sexual dysfunction is common and challenging to manage and often leads to non-compliance with serotonergic medications.*[24] Various strategies have been used by clinicians to deal with antidepressant-induced sexual dysfunction, including waiting for symptoms to subside, reducing the dosage, permitting periodic "drug holidays," prescribing adjunctive therapy, and switching antidepressants.[25] However, waiting for symptoms to subside usually does not work because sexual dysfunction may very well persist throughout the duration of therapy, and both reducing the dose and using drug holidays have the potential for weakening the therapeutic effects of the medications. Thus, clinicians often prescribe adjunctive therapy, such as dopaminergic drugs (e.g., bupropion or amantadine), 5-HT_2 antagonists (e.g., cyproheptadine and nefazodone), and phosphodiesterase inhibitors (e.g., sildenafil), or simply switch to antidepressants with far less chance of causing these effects, such as bupropion, mirtazapine, and nefazodone.[24,25]

Bupropion causes insomnia, nightmares, decreased appetite, anxiety, and tremors, but the most concerning adverse effect is seizures. Because of the risk for seizures, patients who should not receive the drug include those with a CNS lesion or those with a history of seizures, head trauma, or bulimia. The daily dose of bupropion should not exceed 450 mg/day, and any single dose of the immediate-release formulation should not exceed 150 mg/day Occurrences of insomnia and/or nightmares often respond to moving the last daily dose from bedtime to late afternoon.[7,9,22,23]

The adverse effects of SNRIs look fairly similar to those of SSRIs. Nausea can be particularly troublesome with venlafaxine, which sometimes necessitates using lower starting dosages than usual and giving the medication with food. A dose-related elevation in blood pressure can occur at higher doses, probably owing to the NRI effects. Blood pressure monitoring should be conducted for patients receiving venlafaxine therapy. As a rule, duloxetine should not be prescribed to patients with extensive alcohol use or evidence of chronic liver disease owing to the potential for hepatic injury.[9,22,26,27]

Trazodone routinely causes sedation, which is why it is used far more often as an adjunct with other antidepressants for sleep than as a primary agent for the treatment of depression. Priapism is a rare but serious adverse effect in males who take trazodone. In addition, orthostatic hypotension and dizziness are more common with trazodone than with nefazodone because the latter agent has a weaker effect at α-adrenergic receptors and also has a balancing of adrenergic effects owing

TABLE 35–4. Relative Incidence of Adverse Effects of Various Newer Antidepressants[9,13,28]

Drug	Sedation	Activation	Weight Gain	Weight Loss	GI Upset	Sexual Dysfunction
Bupropion	Min	High	Min	Low	Mod	Min
Citalopram	Min	Min	Min	Min	High	High
Fluoxetine	Min	High	Min	Min	High	High
Mirtazapine	Mod	Min	Low	Min	Min	Min
Nefazodone	Low	Min	Min	Min	Low	Min
Paroxetine	Low	Low	Min	Min	High	High
Sertraline	Min	Mod	Min	Min	High	High
Venlafaxine	Low	Mod	Min	Min	High	High

Min, minimal; mod, moderate.
High greater than Mod greater than Low greater than Min.

to weak NRI activity. Unfortunately, nefazodone has been associated with development of hepatotoxicity, which has led to a black-box warning and a great reduction in its use.[7,9,22,23]

Mirtazapine can cause sedation and weight gain by virtue of blocking histamine-1 receptors. Despite being partially a serotonergic drug, it rarely causes serotonergic-related adverse effects because it blocks the various postsynaptic 5-HT receptors. Although it carries a black-box warning for neutropenia owing to a handful of cases reported during clinical trials, it is questionable whether neutropenia is any more problematic with this agent versus other antidepressants.[9,22,23]

The relative incidence of adverse effects among some of the newer antidepressant agents are shown in Table 35–4.[9,13,28]

Pharmacokinetic Parameters

Pharmacokinetic parameters of the newer antidepressants are shown in Table 35–5.[9,29] Several antidepressants are not very highly protein bound, and the most notable of these is venlafaxine. The elimination half-lives of nefazodone and venlafaxine are relatively short compared with the other agents. Conversely, fluoxetine has a very long half-life (i.e., many days) with chronic dosing, and its active metabolite (norfluoxetine) has an even longer half-life. Owing to the extremely long half-life of fluoxetine and its active metabolite, the clinician must be aware that about 5 weeks are required to either reach steady-state levels or to wash out after discontinuation of therapy. Sertraline and citalopram are the other SSRIs with active metabolites, but these metabolites (desmethylsertraline and desmethylcitalopram, respectively) are only about one-eighth as potent as the parent compounds in terms of SRI activity.

TABLE 35–5. Pharmacokinetic Parameters of Newer Antidepressants

Drug	Protein Binding (%)	Half-Life (hours)	Active Metabolite(s)
Bupropion	84	10–21	Yes
Citalopram	80	33	Yes
Duloxetine	90	9–19	No
Escitalopram	56	27–32	No
Fluoxetine	94	4–6 days with chronic dosing; 4–16 days (active metabolite)	Yes
Fluvoxamine	77	15–26	No
Mirtazapine	85	20–40	No
Nefazodone	99	2–4	Yes
Paroxetine	95	21	No
Sertraline	98	27	Yes
Venlafaxine	27	5	Yes

Data from references 9 (with permission) and 29.

Drug Interactions

The major drug interactions of antidepressants are shown in Table 35–6.[9,19,30] Antidepressants cause both pharmacodynamic (e.g., additive pharmacologic effects) and pharmacokinetic (e.g., changes in drug levels) interactions with other medications.

The usual pharmacodynamic interactions involve the "dirty receptors" blocked by some antidepressants. Hence especially TCAs can cause significant additive effects with drugs that cause sedation, hypotension, or anticholinergic effects. Similarly, nefazodone and mirtazapine can interact with other drugs that cause hypotensive and sedative effects, respectively. By far the most concerning pharmacodynamic interactions are hypertensive crisis and serotonin syndrome, which are both potentially life-threatening when they occur. Hypertensive crisis is characterized by sharply elevated blood pressure, occipital headache, stiff or sore neck, nausea, vomiting, and sweating. It may result during MAOI therapy if the patient takes a sympathomimetic drug, such as ephedrine, pseudoephedrine, phenylephrine, or phenylpropanolamine, or if the patient consumes foods rich in tyramine, such as tap beers, aged cheeses, fava beans, yeast extracts, liver, dry sausage, sauerkraut, or tofu.[23] There are extensive lists of foods and drinks that are permitted and not permitted during therapy with MAOIs, and these always should be provided to patients for their safety. Furthermore, since many over-the-counter products contain sympathomimetics, patients always

TABLE 35–6. Drug Interactions of Antidepressants[a9,19,30]

Antidepressants	Type of Interaction	Examples of Interacting Drugs
TCAs Trazodone Mirtazapine	Pharmacodynamic—additive sedation	Benzodiazepines Alcohol Antihistamines
TCAs Trazodone	Pharmacodynamic—additive hypotensive effects	Prazosin Antipsychotics
TCAs	Pharmacodynamic—additive anticholinergic effects	Phenothiazines Benztropine
TCAs	Pharmacodynamic—additive cardiac toxicity	Thioridazine Quinidine
TCAs	Pharmacodynamic—decreased antihypertensive effect	Guanethidine Clonidine Methyldopa
Bupropion	Pharmacodynamic—increased seizure risk	TCAs Phenothiazines
MAOIs	Pharmacodynamic—hypertensive crisis	Tyramine-rich foods Sympathomimetics
MAOIs TCAs SSRIs SNRIs SARIs	Pharmacodynamic—serotonin syndrome	Serotonergic antidepressants Meperidine Dextromethorphan Tramadol
Fluvoxamine	Pharmacokinetic—CYP1A2 inhibition	TCAs Clozapine Theophylline
Fluoxetine Fluvoxamine Sertraline	Pharmacokinetic—CYP2C inhibition	TCAs Phenytoin Warfarin Tolbutamide
Fluoxetine Paroxetine Duloxetine Sertraline	Pharmacokinetic—CYP2D6 inhibition	TCAs Haloperidol Risperidone Codeine Propranolol Propafenone
Nefazodone Fluoxetine Fluvoxamine	Pharmacokinetic—CYP3A4 inhibition	TCAs Alprazolam Verapamil Carbamazepine Lovastatin

[a]Not an all-inclusive list.
MAOI, monoamine oxidase inhibitor; SARI, serotonin antagonist and reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

should be told to consult with their clinician and/or pharmacist prior to using these drugs. Serotonin syndrome is characterized by confusion, restlessness, fever, abnormal muscle movements, hyperreflexia, sweating, diarrhea, and shivering.[31] It may result when a serotonergic agent is added to any serotonergic antidepressant, but the MAOIs are strongly associated with severe cases of serotonin syndrome.[31] Serotonin syndrome is complicated by the general unawareness of clinicians of its diagnosis,[31] as well as the fact that many drugs are not obviously serotonergic in nature, such as dextromethorphan, meperidine, and tramadol.

Several antidepressants, including most of the SSRIs, nefazodone, and duloxetine, are known to inhibit various cytochrome P-450 isoenzymes, thereby elevating plasma levels of substrates for those isoenzymes and thus potentially leading to increased adverse effects or toxicity of those drugs. The propensity to cause these drug interactions will vary with the particular antidepressant and the precise isoenzyme[9,19,30] (Table 35–6).

Dosing

As can be seen in Table 35–7, antidepressants are available in several different dosage forms.[13,16–18,29,32] The extended-release

TABLE 35–7. Dosing of Antidepressants in Adult Patients[13,16–18,29,32]

Generic Name	Brand Name	Generic	Dosage Forms	Initial Dose (mg/day)	Usual Dosage Range (mg/day)	Usual Dosing Schedule
MAOIs						
Phenelzine	Nardil	No	Tablet	15–30	15–90	Twice daily
Tranylcypromine	Parnate	No	Tablet	10–20	30–60	Twice daily
TCAs and Tetracyclics						
Amitriptyline	Elavil[a]	Yes	Tablet	25–50	100–300	Once daily
Amoxapine	Asendin[a]	Yes	Tablet	25–50	100–400	Once to twice daily
Clomipramine	Anafranil	Yes	Capsule	25	100–250	Once daily
Desipramine	Norpramin	Yes	Tablet	25–50	100–300	Once daily
Doxepin	Sinequan	Yes	Capsule, solution	25–50	100–300	Once daily
Imipramine	Tofranil	Yes	Tablet, capsule (PM)	25–50	100–300	Once daily
Maprotiline	Ludiomil[a]	Yes	Tablet	50–75	100–225	Once to twice daily
Nortriptyline	Pamelor	Yes	Capsule, solution	25	50–150	Once daily
Protriptyline	Vivactil	No	Tablet	5–10	15–60	Once daily
Trimipramine	Surmontil	No	Capsule	25–50	100–300	Once daily
SSRIs						
Citalopram	Celexa	Yes	Tablet, solution	20	20–60	Once daily
Escitalopram	Lexapro	No	Tablet, solution	10	10–20	Once daily
Fluoxetine	Prozac	Yes	Tablet, capsule; solution	10–20	20–80	Once daily
	Prozac Weekly	No	Delayed-release capsule	—	90	Once weekly
Fluvoxamine	Luvox[a]	Yes	Tablet	50	50–300	Twice daily
Paroxetine	Paxil	Yes	Tablet, suspension	10–20	20–50	Once daily
	Paxil CR	No	Controlled-release tablet	12.5–25	25–62.5	Once daily
Sertraline	Zoloft	No	Tablet, concentrate	25–50	50–200	Once daily
NDRI						
Bupropion	Wellbutrin	Yes	Tablet	150–200	300–450	Twice to thrice daily
	Wellbutrin SR	Yes	Sustained-release tablet	150	300–400	Twice daily
	Wellbutrin XL	No	Extended-release tablet	150	300–450	Once daily
SNRIs						
Duloxetine	Cymbalta	No	Capsule	40–60	40–60	Once to twice daily
Venlafaxine	Effexor	No	Tablet	37.5–75	75–375	Twice daily
	Effexor XR	No	Extended-release capsule	37.5–75	75–225	Once daily
SARIs						
Nefazodone	Serzone[a]	Yes	Tablet	100–200	300–600	Twice daily
Trazodone	Desyrel	Yes	Tablet	50–150	200–600	Twice daily
NaSSA						
Mirtazapine	Remeron	Yes	Tablet, disintegrating tablet (SolTab)	15	15–45	Once daily

[a]Brand name no longer available in the United States.
MAOI, monoamine oxidase inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; NDRI, norepinephrine and dopamine reuptake inhibitor; SARI, serotonin antagonist and reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

formulations of venlafaxine and bupropion allow for once-daily dosing. The delayed-release capsule of fluoxetine can be given once weekly, which can be started 7 days after the last regular-release capsule or tablet. Liquid dosage forms and disintegrating tablets of various antidepressants are ideal for patients who have difficulty swallowing tablets or capsules or those who otherwise may attempt to "cheek" their medication.

The starting dose is the usual therapeutic dose for most of the SSRIs, duloxetine, and mirtazapine, whereas there is usually need for at least some upward titration of venlafaxine, bupropion, and nefazodone. A particular disadvantage of TCAs is that the customary way of dosing them involves meticulous upward titration from a small starting dose to a wide usual therapeutic dosage range. On the other hand, one advantage is that plasma levels may be used to help guide dosing, especially for those that have well-defined therapeutic plasma level ranges, including nortriptyline (50–150 ng/mL or mcg/L, or 190–570 nmol/L), desipramine (100–160 ng/mL or mcg/L, or 375–600 nmol/L), amitriptyline (75–175 ng/mL or mcg/L, 255–595 nmol/L), and imipramine (greater than 200 ng/mL or mcg/L, or 714 nmol/L).[28]

Efficacy of Pharmacotherapy

❺ *Each antidepressant has a response rate of approximately 60% to 80%, and no antidepressant medication or class has been reliably shown to be more efficacious than another.*[7,22] MAOIs may be the most effective therapy for atypical depression, but MAOI use continues to wane because of problematic adverse effects, dietary restrictions, and possibility of fatal drug interactions.[22,28] There is some evidence that dual-action antidepressants, such as TCAs and SNRIs, may be more effective for inpatients with severe depression than are the single-action drugs such as SSRIs,[22,28] but the more general assertion that multiple mechanisms of action confer efficacy advantages is quite controversial.[33]

Selection of Medication

Figure 35–1 depicts a well-known algorithm for the pharmacologic treatment of non-psychotic MDD—the Texas Medication Algorithm Project.[34] Notable aspects of this algorithm include the preferential use of newer antidepressants in the earlier stages of treatment and sequential trials of antidepressant monotherapy prior to the use of combination therapy (see Managing Partial Response or Non-response). It has been shown that patients undergoing treatment guided by this algorithm fared better than those who received treatment as usual during a 1-year period, as measured by clinician-rated symptoms, self-reported symptoms, and overall mental functioning.[35] Antipsychotic medication should be combined with antidepressant medication in cases of depression with psychotic features.[16]

Various factors must be taken into account when selecting antidepressant therapy for a particular patient. The most reliable predictor of response is the patient's past history of response (e.g., efficacy, side effects, and overall satisfaction) to antidepressants. To a lesser extent, the past history of a first-degree relative's response to antidepressants may be used to predict a patient's response. Adverse-effect profiles should be considered because compliance is influenced greatly by tolerability. In this regard, a frank discussion should occur with the patient in order to determine which adverse effects are acceptable and which are not. The clinician must be careful to contemplate potential drug-drug interactions and disease-state interactions. For instance, a patient with seizure disorder would be an inappropriate candidate for bupropion therapy. The presence of comorbid psychiatric conditions can help the clinician to determine the best antidepressant to choose for a patient. For example, an SSRI can treat both MDD and panic disorder, obviating the need for separate medication therapy. The patient must be willing and able to comply with dosing schedules (e.g., upward titration of TCAs or twice-daily dosing of nefazodone) and special instructions (e.g., diet with MAOI therapy) associated with certain antidepressants. Another patient-specific factor is the potential for accidental or intentional overdosing because certain antidepressants (e.g., TCAs) are quite toxic in those situations. Finally, the patient should be able to comfortably afford the chosen medication or else compliance is at risk.[22]

Time Course of Response

Unfortunately, antidepressants do not produce a clinical response immediately. Improvement in physical symptoms, such as sleep, appetite, and energy, can occur within the first week or so of treatment. Although a recent meta-analysis suggests earlier effects of antidepressant treatment,[36] ❻ *it is widely accepted that it takes approximately 2 to 4 weeks of treatment before improvement is seen in emotional symptoms of depression, such as sadness and anhedonia. Furthermore, it may take as long as 6 to 8 weeks of treatment to see the full effects of antidepressant therapy.*[7,22,23]

Managing Partial Response or Non-response

Approximately one-third of patients with MDD do not respond satisfactorily to their first antidepressant medication.[37] In such cases, the clinician must evaluate the adequacy of antidepressant therapy, including dosage, duration, and patient compliance.[17] Treatment reappraisal also should include verification of the patient's diagnosis and reconsideration of clinical factors that could be impeding successful therapy, such as concurrent medical conditions (e.g., thyroid disorder), comorbid psychiatric conditions (e.g., alcohol abuse), and psychosocial issues (e.g., marital stress).[16]

For patients who have experienced a partial response, extending the medication trial and/or using higher doses within the recommended dosage range of the antidepressant may be helpful.[16] Another option is to employ augmentation therapy, i.e., adding another medication that generally is not used as an antidepressant.[37] Augmenting agents with clear efficacy include lithium and thyroid hormone (e.g., liothyronine), whereas initial enthusiasm has lessened to some extent for the serotonergic drugs buspirone and pindolol owing to negative findings in controlled trials.[38] Efficacy has been suggested for dopaminergic drugs (e.g., pramipexole), psychostimulants (e.g., methylphenidate), and atypical antipsychotics (e.g., olanzapine), whereas various other medications, such as anticonvulsants (e.g., valproic acid), modafanil, and estrogen, have anecdotal evidence to support their use.[38] A third option is to make use of combination therapy, whereby another antidepressant, typically from a different pharmacologic class, is added to the first antidepressant medication. Examples include combining bupropion and SSRIs and combining TCAs and SSRIs.[38,39]

Switching to a different antidepressant is a common strategy for patients who have had no response to initial antidepressant therapy but also is acceptable in cases of partial response.[16] Relative to augmentation/combination, advantages of switching include improved compliance, decreased costs, and less concern over drug interactions, whereas disadvantages include loss of time ("reset the clock") and loss of any improvement seen with the initial drug.[39] When switching from one antidepressant to another, clinicians may choose to stay within the same class (e.g., sertraline to fluoxetine) or go outside of the class (e.g., paroxetine to venlafaxine).[37,39]

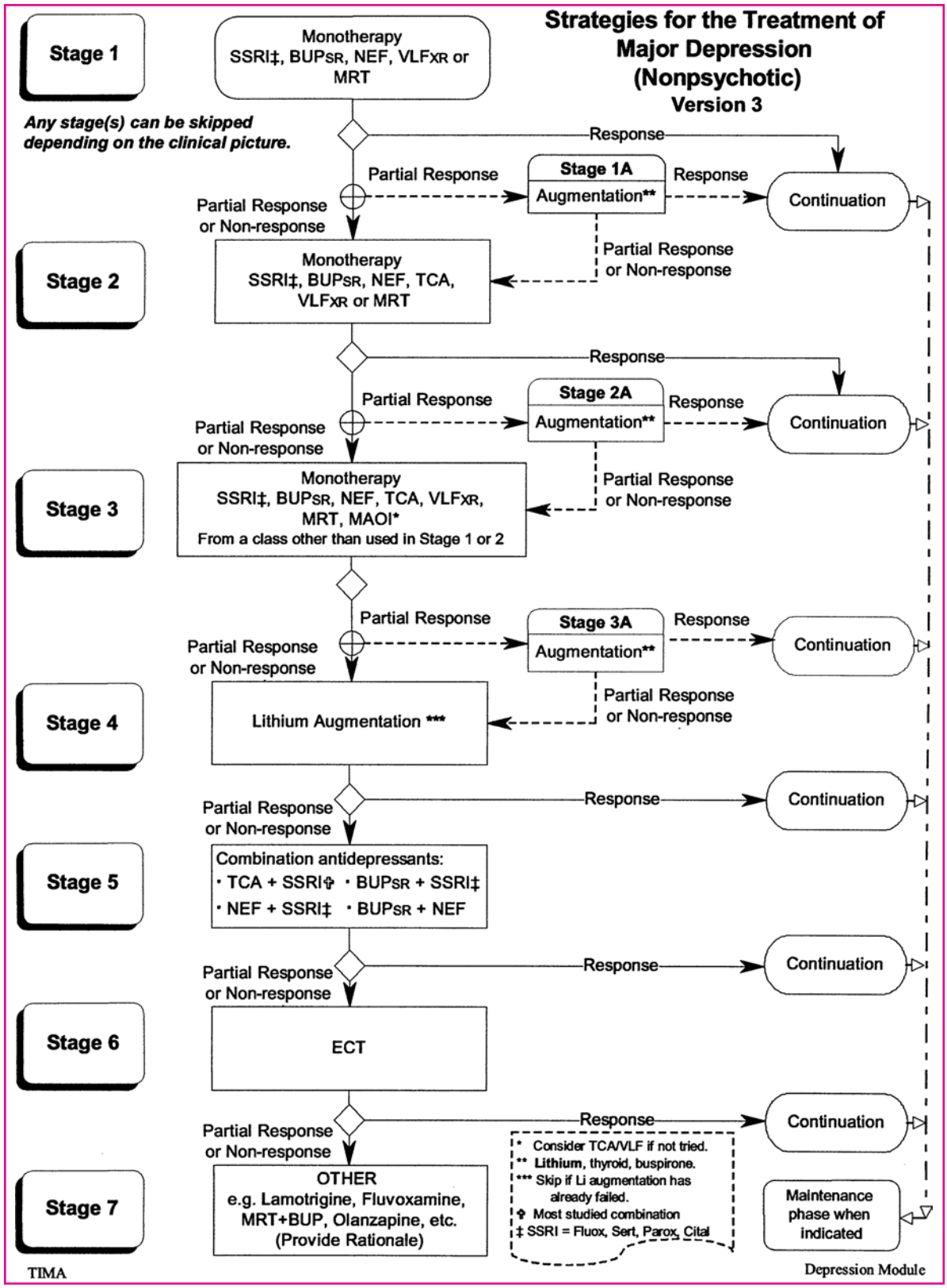


FIGURE 35–1. Strategies for the treatment of non-psychotic major depression.[34] (Used, with permission)

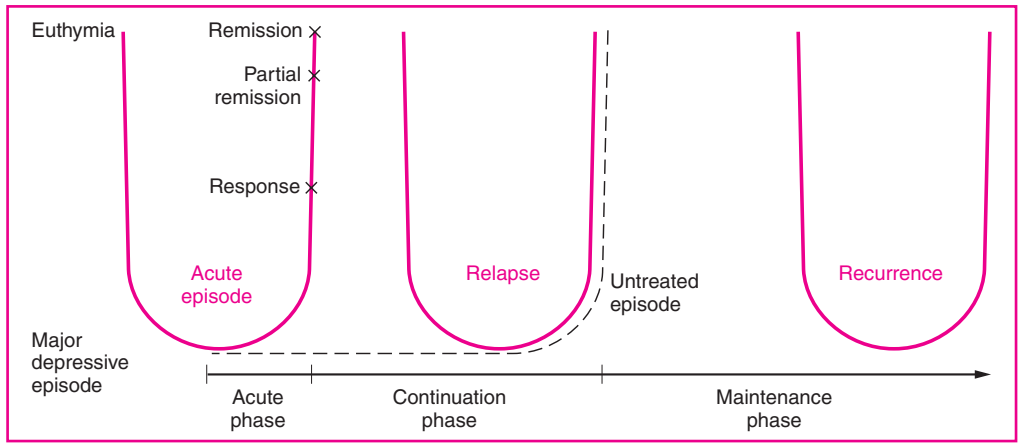


FIGURE 35–2. The course of depression and phases of treatment.[7,8]

Nonpharmacologic interventions in cases of treatment non-response include adding or changing to psychotherapy or initiating ECT.[16]

Duration of Therapy

Treatment of MDD can be conceptualized as a series of three phases: acute, continuation, and maintenance[7,8,16] (Fig. 35–2). During a major depressive episode, a clinician will initiate antidepressant therapy for the purpose of attaining **remission** of symptoms. This acute phase of treatment typically lasts 6 to 12 weeks. ❼ *Since the typical major depressive episode lasts 6 months or longer, if antidepressant therapy is interrupted for any reason following the acute phase, the patient may relapse into the depressive episode. When treating the first depressive episode, antidepressants must be given for an additional 4 to 9 months in the continuation phase for the purpose of preventing relapse.* Maintenance treatment takes place after the normal course of a major depressive episode in order to prevent recurrence, which is the development of future episodes. This phase can last for years, if not for a lifetime. Whereas all patients who suffer a major depressive episode should receive both acute and continuation treatment, not all of them will require maintenance treatment. The reason for this is because not all patients experience multiple major depressive episodes, and even in many cases in which they do, many years may separate the episodes. Therefore, the clinician must consider various factors in determining whether an individual patient requires maintenance treatment. A major factor is the number of prior episodes experienced by the patient. As discussed earlier, the more episodes experienced, the more likely future episodes will occur. This has led many clinicians to adopt the "three strikes and you're on" approach, whereby a patient with a history of three or more major depressive episodes is given lifelong maintenance treatment because of the very high (i.e., 90%) chance of experiencing additional episodes. Other factors to consider are the severity of previous episodes, especially if suicidal attempts were made or psychotic features were present, and patient preference.[16] In general, the dose of the antidepressant required in the acute phase of treatment should be sustained during the continuation and maintenance phases.[16]

Discontinuation of Therapy

When the clinician and patient are ready to attempt discontinuation of therapy, whether at the end of the continuation phase or during the maintenance phase, it is best to do so via gradual taper of the antidepressant. This is done for two reasons. First, almost all antidepressants can produce withdrawal syndromes if discontinued abruptly or tapered too rapidly, especially antidepressants with shorter half-lives (e.g., venlafaxine, paroxetine, and fluvoxamine).[17] These withdrawal syndromes can cause sleep disturbances, anxiety, fatigue, mood changes, malaise, gastrointestinal disturbances, and a host of other symptoms[17] and often are confused with depressive relapse or recurrence.[16] In general, a tapering schedule involving a small dosage decrement (e.g., paroxetine 5 mg) every 3 to 5 days should prevent significant withdrawal symptoms.[17] Second, depressive symptoms may return on taper or discontinuation of the antidepressant. If antidepressant therapy is discontinued abruptly and depressive symptoms return weeks later, then the lag time to onset of action must be observed once the antidepressant is restarted ("reset the clock"); however, if gradual tapering is carried out, then early signs of depression can be countered with a return to the original dosage and a potentially quicker response.[16] Depending on the patient's illness and the clinical circumstances, tapering of the antidepressant can be extended for weeks or even months because of the concern over relapse or recurrence.

Special Considerations

Pregnant/Breast-Feeding Patients

It is a common misconception that pregnancy protects against depression (i.e., the "glow" of pregnancy). Depression actually is quite common in pregnancy, especially for women with a history of recurrent depression. Both maternal and fetal well-being must be taken into account when weighing the benefits and risks of using antidepressant therapy during pregnancy.[40] In general, studies have not demonstrated an increased risk of miscarriage or congenital malformations with antidepressant use,[40] but the prescribing information for paroxetine was changed recently to reflect the findings of epidemiologic studies in which an increased risk of congenital malformations, in particular atrial or ventricular septal defects, was seen in infants born to women taking the drug during the first trimester of pregnancy.[41] Antidepressants have been reported occasionally to cause perinatal sequelae, such as poor neonatal adaptation, respiratory distress, feeding problems, and jitteriness.[40] Data concerning the long-term neurobehavioral effects of in utero antidepressant exposure remain quite limited.[40] Fluoxetine, citalopram, and TCAs have the greatest reproductive safety data and should be considered first-line treatments when pharmacotherapy is indicated.[40]

There will be at least some drug exposure to the infant from nursing mothers taking antidepressant medications. Although there have been rare anecdotal reports of adverse effects (i.e., respiratory depression and seizure-like episodes) in infants exposed to antidepressants through breast milk, no rigorous study has confirmed adverse effects of these drugs, and it is generally accepted that the benefits of breast-feeding outweigh the risks to the infant of antidepressant exposure. However, the decision needs to be made on an individual basis.[42]

Geriatric Patients

It is generally agreed that depression in older adults is underrecognized and undertreated.[43] Although not uncommon in community samples, MDD is particularly prevalent among those living in long-term care facilities.[15,43] Barriers to recognition of geriatric depression include the tendency toward "masked" presentations, i.e., complaints of physical symptoms (e.g., pain and gastrointestinal problems) instead of mood symptoms, the frequent presence of medical illnesses, and the overlap of mood and cognitive symptoms with those of dementia.[15,43] Age-related pharmacokinetic and pharmacodynamic changes cause geriatric patients to be more sensitive to the effects of antidepressant medications.[15] Thus, lower starting doses of antidepressants with slow upward titrations as tolerated are recommended for geriatric patients.[13,16,43] SSRIs are chosen frequently to treat geriatric depression because of their overall favorable adverse-effect profiles and low toxicity, whereas most TCAs are avoided owing to problematic anticholinergic, cardiovascular, and sedative properties.[43] Desipramine and nortriptyline are two TCAs that are more tolerable in terms of these adverse effects and thus may be used in geriatric depression.[43] Other newer antidepressants, such as bupropion, venlafaxine, nefazodone, and mirtazapine, are alternatives for the treatment of geriatric patients as well.[43]



Patient Encounter, Part 3: Creating a Care Plan

Based on the information presented, create a care plan for ML. Your plan should include: (1) a statement of the drug-related needs and/or problems, (2) the goals of therapy, (3) a patient-specific detailed therapeutic plan, and (4) a plan for follow-up to determine whether the goals have been achieved.

Pediatric Patients

Antidepressant medications appear to be useful for certain children and adolescents, particularly those who have severe or psychotic depression, fail psychotherapeutic measures, or experience chronic or recurrent depression. SSRIs generally are considered the initial antidepressants of choice, although comorbid conditions may favor alternative agents. Clinicians should be aware of the possibility of "behavioral activation" with the SSRIs, including such symptoms as impulsivity, silliness, daring conduct, and agitation.[44] Desipramine should be used with caution in this population because of several reports of sudden death, and a baseline and follow-up electrocardiogram (ECG) may be warranted when this medication is used to treat pediatric patients.[9]

The Food and Drug Administration (FDA) has warned that antidepressants increase the risk of suicidality (i.e., suicidal thinking and behavior) in children and adolescents. A large analysis of clinical trials revealed that the risk of such events was 4% for antidepressant medications versus 2% for placebo, although no completed suicides occurred in the trials. Because of this increased risk, antidepressants have black-box warnings concerning the matter, and patient medication guides are required to be distributed with each prescription or refill of antidepressant medications. ❽ *Pediatric patients should be observed closely for suicidality, worsened depression, agitation, irritability, and unusual changes in behavior, especially during the initial few months of therapy or at times of dosage changes. Furthermore, families and caregivers should be advised to monitor patients for such symptoms.*[45]

Suicidal Patients

The FDA is in the process of analyzing data to determine whether there is an increased risk of suicidality in adult patients similar to that seen in pediatric patients (see above). Even though the suicidality risk for adults taking antidepressant medications

TABLE 35–8. Patient Counseling[28,47]

Counseling Point	Clinical Rationale
Mechanism of action—The medication works by affecting certain chemicals in the brain.	Patient may feel that depression is a character weakness or personality flaw instead of a biologic disorder.
Lack of addiction potential—Although the medication affects certain chemicals in the brain, it is not addicting.	Patient may worry that since the antidepressant is psychoactive, it must be addicting.
Need for routine use—The medication will only work if it is taken as prescribed every day.	Patient may try taking the medication on an as-needed basis.
Delayed onset of action—It may take several weeks to see significant improvement in symptoms.	Patient may prematurely discontinue therapy prior to onset of beneficial effects.
Prolonged duration of therapy—The medication should be taken for at least 6 to 12 months; do not discontinue it without consulting with the prescriber.	Patient may prematurely discontinue therapy after symptoms have remitted, which could lead to relapse or recurrence.
Adverse effects—Mention common and expected adverse effects as well as what to do should they occur.	Patient may be more likely to discontinue therapy and distrust the prescriber if adverse effects occur without forewarning.
Avoidance of alcohol/CNS depressants—Use of alcohol or other CNS depressants could cause worsened depression and additive adverse effects with the medicine.	Patient may be unaware of the possible consequences of drinking alcohol or taking other drugs with antidepressants.
Risk of suicidality—Be alert to symptoms of worsening depression and suicidality.	Patient may become suicidal while taking the antidepressant.

Data from references 28 and 47.

is currently unknown, similar monitoring for suicidality and clinical worsening that is mandated for pediatric patients should be followed for adult patients.[46]

The clinician should bear in mind the toxic potential for the various antidepressant medications when patients already have or develop suicidality. The TCAs and MAOIs have narrow therapeutic indices, whereas the SSRIs, SNRIs, nefazodone, and mirtazapine have wide therapeutic indices.[22]

Patient Counseling

Major counseling points and the clinical rationale behind them are outlined in Table 35–8.[28,47] ❾ *Lack of patient understanding concerning optimal antidepressant drug therapy frequently leads to partial compliance or non-compliance with therapy; thus, the primary purpose of antidepressant counseling is to enhance compliance and improve outcomes.*[47]

Recent Developments

The FDA recently approved selegiline (Emsam®) as the first transdermal patch for use in treating MDD.[48] Despite belonging to the MAOI class of antidepressants, the lowest dose of the patch, 6 mg/24 hours, can be used without the usual dietary restrictions associated with MAOI use.[48] Patients receiving the higher doses, 9 and 12 mg/24 hours, should follow the usual dietary restrictions.[48] Patients are advised to change the patch daily. Also, drug labeling advises patients and clinicians about the possibility of increased absorption of medication if the patch is exposed to direct heat.[48] A mild skin reaction at the site of patch placement is a common side effect. As with oral MAOIs, decreased blood pressure and light-headedness are possible.[48]

OUTCOME EVALUATION

- Review the patient's medication profile to ensure that there are no potential/actual pharmacotherapy problems related to dosing, disease-state precautions or contraindications, drug-drug interactions, unnecessary therapeutic duplication, etc.
- Verify the extent of compliance with pharmacotherapy.
- Assess the response to pharmacotherapy, especially with regard to suicidality and those symptoms that cause significant subjective distress and/or functional impairment.
- Determine whether the patient is experiencing adverse effects of pharmacotherapy. Although general questioning (e.g., "Are you having any side effects?") may reveal some problems with therapy, it is better to use direct questioning concerning adverse effects that are most common and/or most problematic (e.g., "Have you noticed any change in your sexual functioning?").
- Provide counseling to enhance patient understanding of MDD and its pharmacotherapy.



Patient Care and Monitoring

1. Assess the patient's severity of symptoms to determine if patient-directed therapy is appropriate or whether a psychiatrist should evaluate the patient.
2. Obtain a thorough history of prescription, nonprescription, natural, and illicit drug product use. Rule out medications or medical disorders that may cause or mimic depressive symptoms.
3. Review *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition, Text Revision (DSM-IV-TR) criteria to determine an appropriate diagnosis.
4. Determine appropriate pharmacologic and psychological treatments (e.g., cognitive-behavioral therapy), including what has been helpful to the patient in the past.
5. Educate patient and/or caretaker about the disease state, lifestyle modifications, and medication therapy.
   - What risk factors are present that could contribute to depression?
   - What lifestyle modifications could be made to improve condition (e.g. exercise)?
   - How should the medication be taken?
   - What potential adverse effects may occur?
   - Which drugs may interact with their therapy?
   - Educate on warning signs and prevention of suicidal and/or homicidal ideation.
6. Develop a plan to assess effectiveness of pharmacologic therapy after 4 weeks of being on a clinically effective dose.
7. Evaluate the patient for the presence of adverse drug reactions, drug allergies, and drug interactions.
8. Assess improvement in quality-of-life measures such as physical, psychological, and social functioning and well-being.
9. If the patient does not respond, determine if the patient is taking the appropriate medication and dose.
10. Recommend changes in therapy if the patient does not respond.
11. Determine long-term maintenance therapy.

ABBREVIATIONS

BDNF:	brain-derived neurotrophic factor
DA:	dopamine
DRI:	dopamine reuptake inhibitor
DSM-IV-TR:	*Diagnostic and Statistical Manual of Mental Disorders.* 4th ed., text revision
ECT:	electroconvulsive therapy
5-HT:	serotonin
GABA:	gamma-aminobutyric acid
MAOI:	monoamine oxidase inhibitor
MDD:	major depressive disorder
NaSSA:	noradrenergic and specific serotonergic antidepressant
NDRI:	norepinephrine and dopamine reuptake inhibitor
NE:	norepinephrine
NRI:	norepinephrine reuptake inhibitor
SARI:	serotonin antagonist and reuptake inhibitor
SI:	suicidal ideation
SNRI:	serotonin and norepinephrine reuptake inhibitor
SRI:	serotonin reuptake inhibition
SSRI:	selective serotonin reuptake inhibitor
TCA:	tricyclic antidepressant
VNS:	vagus nerve stimulation

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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36 Bipolar Disorder

Brian L. Crabtree and Martha J. Faulkner



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Explain the pathophysiologic mechanisms underlying bipolar disorder.
2. Recognize the symptoms of a manic episode and depressive episode in patients with bipolar disorder.
3. Identify common comorbidities of bipolar disorder.
4. Recognize the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria for bipolar disorder as well as the subtypes of bipolar I disorder, bipolar II disorder, and cyclothymic disorder.
5. List the desired therapeutic outcomes for patients with bipolar disorder.
6. Explain the use of drugs as first-line therapy in bipolar disorder, including appropriate dosing, expected therapeutic effects, potential adverse effects, and important drug-drug interactions.
7. Recommend individualized drug therapy for acute treatment and relapse prevention based on patient-specific data.
8. Recommend monitoring methods for assessment of therapeutic and adverse effects of drugs used in the treatment of bipolar disorder.
9. Recommend treatment approaches for special populations of patients with bipolar disorder, including pediatric patients, geriatric patients, and pregnant patients.
10. Educate patients with bipolar disorder about their illness, drug therapy required for effective treatment, and the importance of adherence.

Key Concepts

❶ Patients presenting with depressive or elevated mood features and a history of abnormal or unusual mood swings should be assessed for bipolar disorder.

❷ The diagnosis of bipolar disorder is made based on clinical presentation, a careful diagnostic interview, and review of the history. There are no laboratory examinations, brain imaging studies, or other procedures that confirm the diagnosis.

❸ Goals of treatment are to reduce symptoms, induce remission, prevent relapse, improve patient functioning, and minimize adverse effects of drug therapy.

❹ Psychotherapy is needed to improve functional outcomes.

❺ The primary treatment modality for manic episodes is mood-stabilizing agents, often combined with antipsychotic drugs.

❻ The primary treatment for depressive episodes in bipolar disorder is mood-stabilizing agents, often combined with antidepressant drugs.

❼ The primary treatment for relapse prevention is mood-stabilizing agents.

❽ Education of the patient regarding benefits and risks of drug therapy and the importance of adherence to treatment must be integrated into pharmacologic management.

Bipolar disorder is a mood disorder characterized by one or more episodes of mania or **hypomania**, often with a history of one or more major depressive episodes.[1] It is a chronic illness with a course characterized by relapses and improvements or remissions. Mood episodes can be manic, depressed, or mixed. They can be separated by long periods of stability or can cycle

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Patient Encounter, Part 1

MW, a 43-year-old Caucasian female, is a married mother of two boys and is moderately obese. She is wearing a short skirt, low-cut blouse, and heavy makeup, and is somewhat disheveled. She is mildly agitated, speaking rapidly, has fair eye contact, and appears tired and anxious. Her chief complaint: "I am about to get fired from my job, and I can't seem to get any sleep."

- What diagnoses are suggested by this patient's presentation?
- What additional information is needed to clarify the diagnoses?

rapidly. They occur with or without psychosis. Disability and other consequences of bipolar disorder can be devastating to patients, including an increased risk of suicide. Correct diagnosis and treatment are essential as early as possible in the course of the illness to prevent complications and maximize response to treatment. Both pharmacologic and nonpharmacologic treatments are required for maximum benefit.

EPIDEMIOLOGY AND ETIOLOGY

Epidemiology

Bipolar disorders have been categorized into bipolar I disorder, bipolar II disorder, and bipolar disorder, not otherwise specified (NOS). Bipolar I disorder is characterized by one or more manic or **mixed mood episodes**. Bipolar II disorder is characterized by one or more major depressive episodes and at least one hypomanic episode. Hypomania is an abnormally and persistently elevated, expansive, or irritable mood, but not of sufficient severity to cause significant impairment in social or occupational function and does not require hospitalization. Most epidemiologic studies have looked at bipolar disorder of all types (bipolar I and bipolar II), or the bipolar spectrum, which includes all clinical conditions thought to be closely related to bipolar disorder. The lifetime prevalence of bipolar I disorder is estimated to be between 0.3% and 2.4%. The lifetime prevalence of bipolar II disorder ranges from 0.2% to 5%. When including the bipolar spectrum, the lifetime prevalence is between 3% and 6.5%.[1]

Bipolar I disorder affects men and women equally; bipolar II seems to be more common in women. Rapid cycling and mixed mania occur more often in women. Individuals with bipolar disorder commonly have another psychiatric disease with 78% to 85% reporting another Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) diagnosis during their lifetime. The most common comorbid conditions include anxiety, substance abuse, and eating disorders.[2]

The mean age of onset of bipolar disorder is 20, although onset may occur in early childhood to the mid-40s.[1] If the onset of symptoms occurs after 60 years of age, the condition is probably secondary to medical causes. Early onset of bipolar disorder is associated with greater comorbidities, more mood episodes, a greater proportion of days depressed, and greater lifetime risk of suicide attempts, compared to bipolar disorder with a later onset. Substance abuse and anxiety disorders are more common in patients with an early onset. Patients with bipolar disorder also have higher rates of suicidal thinking, suicidal attempts, and completed suicides.

Etiology

The precise etiology of bipolar disorder is unknown. Thought to be genetically based, bipolar disorder is influenced by a variety of factors that may enhance gene expression. These include trauma, environmental factors, anatomic abnormalities, exposure to chemicals or drugs, and others.[3–5] Neurochemical abnormalities in bipolar disorder may be caused by these factors, as discussed further in the pathophysiology section.

PATHOPHYSIOLOGY

Neurochemical

The pathophysiology of bipolar disorder has been poorly understood, but imaging techniques such as positron emission tomography (PET) scans and functional magnetic resonance imaging (fMRI) are now being used to elucidate the cause. Research in the 1970s focused on neurotransmitters such as norepinephrine, dopamine, and serotonin. One hypothesis was that bipolar disorder is caused by an imbalance of cholinergic and catecholaminergic neuronal activity. Serotonin (5-HT) has been suggested to modulate catecholamine activity. Dysregulation of this relationship could cause a mood disturbance.[6] An early theory was that elevation of norepinephrine (NE) and dopamine (DA) caused mania, and a reduction caused depression, but this theory is now considered overly simplistic.[7] Other neurotransmitters are involved and interact with multiple neurochemical and neuroanatomic mechanisms and pathways. The pathophysiology of bipolar disorder has also been hypothesized from the mechanisms of action of lithium and other mood stabilizers. Lithium, valproate, and carbamazepine all have similar effects on neuronal growth that are reversible by inositol, supporting the hypothesis that bipolar disorder is related to inositol depletion.[8]

Genetic

Results of family and twin studies suggest a genetic basis for bipolar disorder.[4] The lifetime risk of bipolar disorder in relatives of a bipolar patient is 40% to 70% for a monozygotic twin and 5% to 10% for another first-degree relative.



Patient Encounter, Part 2: The Medical History, Physical Exam, and Laboratory Exam

The interview reveals the following additional information about MW:

PMH
Para 2, gravida 2

Hx
Sexually transmitted disease (unspecified) as a teen and in her twenties, but has been monogamous since her last marriage in her mid-thirties; she states, "It has not always been easy to stay with my husband"; she feels sexually attracted to many men.

Past Psychiatric Hx
Hospitalized at age 15 for physical aggression towards parents, suicidality, and running away; does not remember if she was placed on medication or if she was given a diagnosis; admits history of sleep disturbance that alternates between hyposomnia and hypersomnia and moodiness, when she shifts from feeling "on top of the world" to very depressed, "like I'm a nobody."

FH
Father was an alcoholic and died in his 50s of cirrhosis; mother is alive and has an anxiety disorder and emphysema; brother was incarcerated for attempted murder and drug trafficking; sister has an anxiety disorder and self-medicates with marijuana

SH
Obtained GED; smokes 2 packs of cigarettes per day; has had multiple jobs and two previous marriages; currently works as a salesperson in an auto parts store; lives with her husband who is a mechanic, and two elementary school–aged sons

Substance Abuse Hx
In late teens into mid-twenties, heavy abuse of stimulants, barbiturates, and alcohol; currently smokes marijuana three times per week and states "it calms me down and helps me sleep"; occasionally drinks on weekends

Meds
Antacids as needed for heartburn, ibuprofen as needed for headache

ROS
(+) Increased energy, irritability, and anger outbursts, racing thoughts, decreased need for sleep; (–) heart palpitations, weight loss, nausea, vomiting, diarrhea

PE
VS: Blood pressure 130/88 mm Hg, pulse 88 beats per minute, respiratory rate 20/minute, temperature 37.0°C (98.6°F)
HEENT: Neck supple; thyroid smooth, symmetrical, non-tender, moveable
CV: RRR, normal S_1, S_2; no murmurs, rubs, gallops, or heaves
Abd: Soft, non-tender, non-distended; (+) bowel sounds, no hepatosplenomegaly

Labs
WNL except + tetrahydrocannabinol (THC).

- Considering this additional information, what is the most likely diagnosis?
- What are the key pieces of information leading you to this conclusion?



Clinical Presentation and Diagnosis[1,3,7]

General
The patient may present in a hypomanic, manic, depressed, or mixed state, and may or may not be in acute distress.

Symptoms
Mood and affect:
- Mood elevation
- Expansive mood
- Irritable mood
- Depression
- Hopelessness
- Suicidality

Physical/behavioral:
- Agitation
- Impulsivity
- Aggression
- Rapid, pressured speech
- Decreased need for sleep
- Insomnia (sometimes for days or weeks)
- Hypersexuality
- Increased physical energy
- Inflated self-esteem, boasting, grandiosity
- Heightened interest in pleasurable activities with high risk of negative consequences (e.g., spending sprees and promiscuity)
- Fatigue
- Hypersomnia

Thought Processes, Content, and Perceptions:
- Racing thoughts, flight of ideas (FOI), distractibility
- Delusions of grandeur; ideas of reference (IOR): persecution, wealth, religion

Psychosocial:
- Substance use
- Disrupted relationships
- Job loss

Laboratory and Other Diagnostic Assessments
❷ *There are no objective laboratory tests or procedures to diagnose bipolar disorder, but such testing can be done to rule out other medical diagnoses.*

- Perform urinalysis, urine toxicology, thyroid function, and white blood cell count in the elderly to rule out urinary tract infection
- A mood disorder questionnaire is completed by the patient that asks about common symptoms of bipolar disorder, problems caused by the symptoms, and family history in a yes-or-no answer format. It is then scored by the clinician.

Suicidality risk is increased in the presence of:

- Substance abuse
- Prior suicide attempts and lethality of attempts
- Access to a means of suicide
- Command hallucinations/psychosis
- Severe anxiety
- Family history of attempted or completed suicide

CLINICAL PRESENTATION AND DIAGNOSIS

Diagnosis of Bipolar Disorder

Bipolar disorder can be conceptualized as a continuum or spectrum of mood disorders and is not comprised solely of bipolar I disorder.[9] They include four subtypes: bipolar I (periods of major depressive, manic, and/or mixed episodes); bipolar II (periods of major depression and hypomania); cyclothymic disorder (periods of hypomanic episodes and depressive episodes that do not meet all criteria for diagnosis of a major depressive episode); and bipolar disorder, NOS. The defining feature of bipolar disorders is one or more manic or hypomanic episodes in addition to depressive episodes that are not caused by any medical condition, substance abuse, or other psychiatric disorder.[1]

Initial and subsequent episodes of bipolar disorder are mostly depressive,[10] although this varies depending on type of bipolar disorder. In males, the initial episode in bipolar I disorder is more likely to be mania, and the number of manic episodes is equal to or greater than depressive episodes.[1] Often misdiagnosed and underdiagnosed, bipolar I and II disorders were correctly diagnosed only 20% of the time, whereas 31% received the misdiagnosis of unipolar depression.[11] It is helpful to utilize a screening tool such as the mood disorder questionnaire.[12]

DSM-IV-TR criteria for the diagnosis of bipolar disorder are summarized in Table 36–1.

Bipolar I Disorder

Bipolar I disorder diagnosis necessitates at least one episode of mania, for at least 1 week or longer, with a persistently elevated, expansive, or irritable mood with related symptoms of decreased need for sleep, excessive energy, racing thoughts, a propensity to be involved in high-risk activities, and excessive talkativeness.[1] Bipolar I depression can be misdiagnosed as major depressive disorder; therefore, it is essential to rule out past episodes of hypomania or mania. If bipolar depression is mistaken for major depressive disorder and the patient is treated with antidepressants, this can precipitate a manic episode or induce rapid cycling of depression and mania.

Bipolar II Disorder

The distinguishing feature of bipolar II disorder is depression with past hypomanic episodes that often are not recalled by the individual as being unusual. Irritability and anger episodes are also common. Collateral information is essential to obtain the entire history (i.e., there cannot have been a prior full manic episode).[1,14]

Cyclothymic Disorder

Cyclothymic disorder is a chronic mood disturbance generally lasting at least 2 years (1 year in children and adolescents) and characterized by mood swings including periods of hypomania and depressive symptoms. Hypomanic symptoms include inflated self-esteem or **grandiosity** (non-delusional), decreased need for sleep, pressure of speech, **flight of ideas**, distractibility, and increased involvement in goal-directed activities, not causing severe impairment in social or occupational functioning or requiring hospitalization. Psychotic features are not found in cyclothymic disorder.[1]

Suicide

Patients with bipolar disorder have a high risk of suicide. Factors that increase that risk are early age at disease onset, high number of depressive episodes, comorbid alcohol abuse, personal history of antidepressant-induced mania, and family history of suicidal behavior.[15] In those with bipolar disorder, 1 of 5 suicide attempts are lethal, in contrast to 1 of 10 to 1 of 20 in the general population.

Differential Diagnosis

Schizophrenia and bipolar disorder often share certain symptoms, including psychosis in some patients. The prominence of mood symptoms and the history of mood episodes distinguish bipolar disorder and schizophrenia. In addition, the psychosis of schizophrenia occurs in the absence of prominent mood symptoms.

Personality disorders are inflexible and maladaptive patterns of behavior that deviate markedly from expectations of society. These patterns are stable over time, pervasive and rigid, and lead to distress or impairment in the individual's life. Onset is in adolescence or early adulthood.[1] Personality disorders and bipolar disorder may be comorbid, and patients with personality disorders may have mood symptoms. The two diagnoses are distinguished, however, by the predominance of mood symptoms and the episodic course of bipolar disorder, in contrast to the stability and persistence of the behavioral patterns of personality disorders.

Delirium is characterized by a disturbance of consciousness and a change in cognition that develops over a short period of time, usually hours or days. The course can fluctuate over the course of the day, usually worsening in the evening. Underlying medical problems such as urinary tract infections in the elderly, substance abuse, or withdrawal symptoms in adults may precipitate delirium.[1]

Dementia is the loss of function in multiple cognitive domains that occurs over a longer period of time, usually months to years. Diagnostic features include memory impairment and at least one of the following: aphasia (deterioration of speech), apraxia (impaired ability to execute motor activities despite intact motor abilities, sensory function, and comprehension of the required task), agnosia (failure to recognize or identify objects despite intact sensory function), or disturbances in executive functioning.[1]

TABLE 36–1. Evaluation and Diagnostic Criteria of Mood Episodes

Diagnostic work-up depends on clinical presentation and findings	• Mental status examination • Psychiatric, medical, and medication history • Physical and neurologic examination • Basic laboratory tests: complete blood count, blood chemistry screen, thyroid function, urinalysis, urine drug screen • Psychological testing • Brain imaging: magnetic resonance imaging and functional scan; alternative: computed tomography scan, positron emission tomography scan • Lumbar puncture • Electroencephalogram

Diagnosis

Episode	Impairment of Functioning or Need for Hospitalization[a]	DSM-IV-TR Criteria[b]
Major depressive	Yes	Greater than 2-week period of either depressed mood or loss of interest or pleasure in normal activities, associated with at least five of the following symptoms: • Depressed, sad mood (adults); may be irritable mood in children • Decreased interest and pleasure in normal activities • Decreased appetite, weight loss • Insomnia or hypersomnia • Psychomotor retardation or agitation • Decreased energy or fatigue • Feeling of guilt or worthlessness • Impaired concentration and decision making • Suicidal thoughts or attempts
Manic	Yes	Greater than 1-week period of abnormal and persistent elevated mood (expansive or irritable), associated with at least three of the following symptoms (four if the mood is only irritable): • Inflated self-esteem (grandiosity) • Decreased need for sleep • Increased talking (pressure of speech) • Racing thoughts (flight of ideas) • Distractible (poor attention) • Increased activity (either socially, at work, or sexually) or increased motor activity or agitation • Excessive involvement in activities that are pleasurable but have a high risk for serious consequences (buying sprees, sexual indiscretions, poor judgment in business ventures)
Hypomanic	No	At least 4 days of abnormal and persistent elevated mood (expansive or irritable); associated with at least three of the following symptoms (four if the mood is only irritable): • Inflated self-esteem (grandiosity) • Decreased need for sleep • Increased talking (pressure of speech) • Racing thoughts (flight of ideas) • Increased activity (either socially, at work, or sexually) or increased motor activity or agitation • Excessive involvement in activities that are pleasurable but have a high risk for serious consequences (buying sprees, sexual indiscretions, poor judgment in business ventures)
Mixed	Yes	Criteria for both a major depressive episode and manic episode (except for duration) occur nearly every day for at least a 1-week period
Rapid cycling	Yes	Greater than 3 major depressive or manic episodes (manic, mixed, or hypomanic) in 12 months

[a]Impairment in social or occupational functioning; need for hospitalization due to potential self-harm, harm to others, or psychotic symptoms.
[b]The disorder is not due to a medical condition (e.g., hypothyroidism) or substance-induced disorder (e.g., antidepressant treatment, medications, electroconvulsive therapy).
From Fankhauser MP, Freeman MP. Bipolar disorder. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1261, with permission.

Comorbid Psychiatric and Medical Conditions

Psychiatric

Lifetime prevalence rates of psychiatric comorbidity co-existing with bipolar disorder are 42% to 50%.[16] Comorbidities, especially substance abuse, make it difficult to establish a definitive diagnosis and complicate treatment. Comorbidities also place the patient at risk for a poorer outcome, high rates of suicidality, and onset of depression.[2] Psychiatric comorbidities include:

- Personality disorders
- Alcohol and substance abuse or dependence
- Anxiety disorders, including panic disorder, obsessive-compulsive disorder, and social phobia
- Eating disorders
- Attention-deficit/hyperactivity disorder

Medical comorbidities include:

- Migraine
- Multiple sclerosis
- Cushing's syndrome
- Brain tumor
- Head trauma

TREATMENT

Desired Outcomes

❸ *Desired outcomes for the treatment of bipolar disorder are to:*

- Reduce the symptoms of mania
- Reduce the symptoms of bipolar depression
- Prevent the recurrence of a manic or depressive episode
- Avoid or minimize adverse treatment effects
- Promote treatment adherence
- Maintain or improve quality of life and improving function

General Approach to Treatment

Treatment algorithms for manic and depressive episodes of bipolar disorder are included in Table 36–2.



Patient Encounter, Part 3: Creating a Care Plan

Based on all information presented, create a care plan for this patient's bipolar disorder. Your plan should include: (1) a statement of the drug-related needs and/or problems, (2) the goals of therapy, (3) a patient-specific therapeutic plan, and (4) a plan for follow-up to assess therapeutic response and adverse effects.

Although not all patients achieve asymptomatic remission, this is a goal of treatment. The mainstay of drug therapy is mood-stabilizing drugs, summarized below. A person entering treatment for a first mood episode in bipolar disorder must have a complete assessment and careful diagnosis to rule out non-psychiatric causes. A variety of conditions can cause similar symptoms (Table 36–3). Since early and accurate diagnosis is essential to maximizing response to treatment, pharmacologic and nonpharmacologic therapy should begin as soon as possible. Treatment is often lifelong. Comorbid conditions should likewise be addressed aggressively.

Suicidality Risk

Assess for the safety of others and potential for violence. If accompanied by friends or family with whom the patient is living, ask them to remove from the home all guns, caustic chemicals, medications, and objects the person might use to harm self or others. Risk factors for suicide include severity of depression, feelings of hopelessness, comorbid personality disorder, and a history of a previous suicide attempt.[19]

Nonpharmacologic Therapy

❹ *Interpersonal, family, or group therapy with a licensed psychiatric nurse practitioner/clinical nurse specialist, psychologist, social worker, or counselor assists individuals with bipolar disorder to establish and maintain a daily routine and sleep schedule and to improve interpersonal relationships.*[3,20] *These therapies may help treat and protect against manic episodes.*

Cognitive-behavioral therapy (CBT) is a type of psychotherapy that combines cognitive and behavioral theories. It stresses the importance of recognizing patterns of cognition (thought) and how thoughts influence subsequent feelings and behaviors. Other people, situations, and events external to the individual are not seen as the sources of thoughts and behaviors. An advantage of CBT is that patients are taught self-management skills to change their negative thoughts in order to feel and function better, even if external circumstances do not change.

Electroconvulsive therapy (ECT) is the application of prescribed electrical impulses to the brain for the treatment of severe depression, mixed states, psychotic depression, and treatment-refractory mania in patients who are at high risk of suicide. It also may be used in pregnant women who cannot take carbamazepine, lithium, or divalproex.

Psychoeducation for patients, their families, and groups regarding chronicity of bipolar disorders; self-management through sleep hygiene, nutrition, exercise, and stress reduction; and abstinence from alcohol or drugs is critical to the success of supporting the individual in managing bipolar disorder. The development of a crisis intervention plan is essential.

TABLE 36–2. Algorithm and Guidelines for the Acute Treatment of Mood Episodes in Patients with Bipolar I Disorder

Acute Manic or Mixed Episode

General guidelines

- Assess for secondary causes of mania or mixed states (e.g., alcohol or drug use)
- Taper off antidepressants, stimulants, and caffeine if possible
- Treat substance abuse
- Encourage good nutrition (with regular protein and essential fatty acid intake), exercise, adequate sleep, stress reduction, and psychosocial therapy
- Optimize the dose of mood-stabilizing medication(s) before adding on benzodiazepines; if psychotic features are present, add on antipsychotic; ECT used for severe or treatment-resistant manic/mixed episodes or psychotic features

Mild to moderate symptoms of mania or mixed episode

First, initiate and/or optimize mood-stabilizing medication: lithium[a] or valproate[a] or atypical antipsychotic (e.g., olanzapine, quetiapine, risperidone)

Alternative anticonvulsants: carbamazepine, lamotrigine,[b] or oxcarbazepine

Second, if response is inadequate, consider adding a benzodiazepine (lorazepam or clonazepam) for short-term adjunctive treatment of agitation or insomnia if needed

Third, if response is inadequate, consider a two-drug combination:

- Lithium **plus** an anticonvulsant or an atypical antipsychotic
- Anticonvulsant **plus** an anticonvulsant or atypical antipsychotic

Moderate to severe symptoms of mania or mixed episode

First, two-drug combinations: lithium[a] or valproate[a] **plus** an atypical antipsychotic (e.g., olanzapine, quetiapine, risperidone) for short-term adjunctive treatment of psychotic features (e.g., delusions or hallucinations)

Alternative anticonvulsants: carbamazepine, lamotrigine,[b] or oxcarbazepine

Second, if response is inadequate, consider adding a benzodiazepine (lorazepam or clonazepam) for short-term adjunctive treatment of agitation or insomnia if needed; lorazepam is recommended for catatonia

Third, if response is inadequate, consider a three-drug combination:

- Lithium **plus** an anticonvulsant **plus** an atypical antipsychotic
- Anticonvulsant **plus** an anticonvulsant **plus** an atypical antipsychotic

Fourth, if response is inadequate, consider ECT for mania with psychosis or catatonia;[d] or add clozapine for treatment-refractory illness

Fifth, if response is inadequate, consider adding adjunctive therapies[e]

Acute Depressive Episode

General guidelines

- Assess for secondary causes of depression (e.g., alcohol or drug use)
- Taper off antipsychotics, benzodiazepines or sedative-hypnotic agents if possible
- Treat substance abuse
- Encourage good nutrition (with regular protein and essential fatty acid intake), exercise, adequate sleep, stress reduction, and psychosocial therapy
- Optimize the dose of mood stabilizing medication(s) before adding on lithium, lamotrigine, or antidepressant (e.g., bupropion or an SSRI); if psychotic features are present, add on an antipsychotic; ECT used for severe or treatment-resistant depressive episodes or for psychosis or catatonia

Mild to moderate symptoms of depressive episode

First, initiate and/or optimize mood-stabilizing medication: lithium[a] or lamotrigine[b]

Alternative anticonvulsants: carbamazepine, oxcarbazepine, or valproate

Moderate to severe symptoms of depressive episode

First, two-drug combinations: lithium[a] or lamotrigine[b] **plus** an antidepressant[c]; lithium plus lamotrigine

Alternative anticonvulsants: carbamazepine, oxcarbazepine, or valproate

Second, if response is inadequate, consider adding an atypical antipsychotic for short-term adjunctive treatment of psychotic features (e.g., delusions or hallucinations) if needed

Third, if response is inadequate, consider a three-drug combination:

- Lithium **plus** an anticonvulsant **plus** an antidepressant
- Lamotrigine[b] **plus** an anticonvulsant **plus** an antidepressant

Fourth, if response is inadequate, consider ECT for treatment-refractory illness and depression with psychosis or catatonia[d]

Fifth, if response is inadequate, consider adding adjunctive therapies[e]

[a]Utilize standard therapeutic serum concentration ranges; if partial response or breakthrough episode, adjust dose to achieve higher serum concentrations without causing intolerable adverse effects; valproate is preferred over lithium for mixed episodes and rapid cycling; lithium and/or lamotrigine is preferred over valproate for bipolar depression.

[b]Lamotrigine is not approved for the acute treatment of depression, and the dose must be started low and slowly titrated up to decrease adverse effects if used for maintenance therapy of bipolar I disorder. A drug interaction and a severe dermatologic rash may occur when lamotrigine is combined with valproate (i.e., lamotrigine doses must be halved from standard dosing titration).

[c]Antidepressant monotherapy is not recommended for bipolar depression. Bupropion, selective serotonin reuptake inhibitors (SSRIs; e.g., citalopram, escitalopram, or sertraline), and serotonin-norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine) have shown good efficacy and fewer adverse effects in the treatment of unipolar depression; monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) have more adverse effects (e.g., weight gain) and may have a higher risk of causing antidepressant-induced mania; fluoxetine, fluvoxamine, nefazodone, and paroxetine inhibit liver metabolism and should be used with caution in patients on concomitant medications that require cytochrome P450 clearance; paroxetine and venlafaxine have a higher risk for causing a discontinuation syndrome.

[d]Electroconvulsive therapy (ECT) is used for severe mania or depression during pregnancy and for mixed episodes; prior to treatment, anticonvulsants, lithium, and benzodiazepines should be tapered off to maximize therapy and minimize adverse effects.

[e]There are minimal or no efficacy data for some adjunctive (add-on) therapies: α_2-adrenergic agonists, calcium channel blockers, gabapentin, tiagabine, topiramate, and zonisamide; topiramate may have efficacy as an adjunctive agent with standard agents for maintenance therapy, based on initial trials.

From Fankhauser MP, Freeman MP. Bipolar disorder. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1266, with permission.

TABLE 36–3. Secondary Causes of Mania[18]

General Medical Conditions
Alzheimer's disease
Cerebral infarction
Cerebral tumors
Closed head injury
Cushing's syndrome
Hemodialysis
Hepatic encephalopathy
Huntington's disease
Hyperthyroidism
Ictal or post-ictal mania
Multiple sclerosis
Neurosyphilis
Systemic lupus erythematosus
Vitamin B deficiency
Medications
Corticosteroids
Diltiazem
Levodopa
Oral contraceptives
Zidovudine
Illicit Substances
Anabolic steroids
Hallucinogens
Stimulants (cocaine, amphetamines)

The following Web sites provide additional information:

- National Association of Cognitive Behavioral Therapists—http://www.nacbt.org
- National Association for the Mentally Ill—http://www.nami.org/ Hometemplate.cfm
- National Institutes for Mental Health, Bipolar Disorder—http://www.nimh.nih.gov/healthinformation/bipolarmenu.cfm

Pharmacologic Therapy

❺ *Pharmacotherapy is the cornerstone of acute and maintenance treatment of bipolar disorder. Mood-stabilizing drugs are the usual first-choice treatments and include lithium, divalproex, carbamazepine, and lamotrigine. Atypical antipsychotics other than clozapine are also approved for treatment of acute mania.* Lithium, lamotrigine, olanzapine, and aripiprazole are approved for maintenance therapy. Drugs used with less research support and without Food and Drug Administration (FDA) approval include topiramate and oxcarbazepine. Benzodiazepines are used adjunctively for mania.

❻ *Antidepressants may be used for bipolar depression, but usually along with a mood-stabilizing agent to prevent a mood switch to mania, and only after the patient has failed to respond adequately to optimal mood-stabilizing therapy.*[21] Combinations of two mood-stabilizing drugs or a mood-stabilizing drug and either an antipsychotic or antidepressant drug are common, especially in acute mood episodes.

❼ *Mood-stabilizing drugs are considered the primary pharmacotherapy for relapse prevention.* Olanzapine and aripiprazole are also approved for maintenance therapy.

Table 36–4 includes a summary of current drug therapy for bipolar disorder. An algorithm for treatment of bipolar mania is shown in Table 36–2.

Mood-Stabilizing Drugs

The ideal mood-stabilizing drug has four desired effects: treatment of acute mania, treatment of acute bipolar depression, prevention of manic relapse, and prevention of bipolar depression relapse. All currently approved mood-stabilizing drugs have demonstrated efficacy over placebo for one or more of these effects, but there are differences among them with regard to specific patient populations. Choice of treatment is dictated by individual patient characteristics and history. Few studies have compared mood-stabilizing drugs to each other in systematic clinical trials. Effect sizes across placebo-controlled trials of individual agents are generally similar. Lithium is often considered the first-choice drug for the classic presentation of bipolar disorder. Treatment of childhood bipolar disorder is less well researched. Only lithium is FDA-approved in children and adolescents as young as age 12. Treatment of bipolar disorder during pregnancy is a particular challenge because of the risks of drug exposure in utero.

Lithium

Lithium was the first approved mood-stabilizing drug. It remains a first-line agent and sets the standard for efficacy against which other drugs are usually measured. It has antimanic efficacy, prevents bipolar disorder relapse, and has more modest efficacy for bipolar depression.[22] It remains the only drug supported by multiple controlled trials in mania, depression, and relapse prevention. In most studies, lithium's efficacy is equivalent to that of the anticonvulsant mood-stabilizers and the atypical antipsychotic drugs.[17] It is most effective for patients with few previous episodes, symptom-free interepisode remission, and a family history of bipolar disorder with good response to lithium. Patients with rapid cycling bipolar disorder are less responsive to lithium, however, than to other mood-stabilizing drugs such as divalproex.[26] Additionally, its effect on bipolar depression is less robust than for mania.[27] It may also be less effective in patients with mixed mood episodes (symptoms of mania and depression occurring simultaneously) and in mania secondary to non-psychiatric illness.

Increasing evidence shows an effect of lithium on suicidal behavior that is superior to other mood-stabilizing drugs.[28] Lithium reduces the risk of deliberate self-harm or suicide by about 70%.

Mechanism of Action Lithium's pharmacologic mechanism of action is not well understood and probably involves multiple effects. Possibilities include altered ion transport, increased intraneuronal catecholamine metabolism, neuroprotection or increased brain-derived neurotrophic factor, inhibition of second messenger systems, and reprogramming of gene expression.[29]

TABLE 36–4. Product Formulation, Dosage, and Information, and Clinical Use of Agents Used in the Treatment of Bipolar Disorder[3,22–25]

Generic Name	Brand Names	Formulations	Dosages	Clinical Use
Lithium Salts				
FDA-approved for use in bipolar disorder				
Lithium carbonate	Eskalith Eskalith CR Lithobid Generic	Capsule: 300 mg ER tablet: 450 mg ER tablet: 300 mg Tablet: 300 mg Capsule: 150, 300, 600mg	900–2400 mg/day in 2–4 divided doses, preferably with meals; there is wide variation in the dosage needed to achieve therapeutic response and 12-hour serum lithium concentration (i.e., 0.6–1.2 mEq/L or mmol/L for maintenance therapy and 1.0–1.5 mEq/L or mmol/L for acute mood episodes taken 12 hours after the last dose); single daily dosing is effective and causes fewer adverse renal effects	Monotherapy or in combination with other drugs for the acute treatment of mania and for maintenance treatment
Lithium citrate	Generic	300 mg (8 mEq)/5 mL		
Anticonvulsants				
FDA-approved for use in bipolar disorder				
Carbamazepine	Equetro	Capsule: 100, 200, 300 mg SR; may open capsule but do not crush or chew beads; take with food Tablet: 200 mg	Start at 100–200 mg bid; increase by 200 mg every 3–4 days 200–1800 mg/day in 2–4 divided doses	Monotherapy or in combination with other drugs for the acute treatment of mania or mixed episodes for bipolar I disorder.
	Tegretol	Chewable tablet: 100 mg Suspension: 100 mg/5 mL	Target serum concentration is 4–12 mcg/mL (17–51 µmol/L)	
	Tegretol XR	ER tablet: 100, 200, 400 mg		
	Carbatrol	ER capsule: 200, 300 mg		
Divalproex sodium	Depakote	Enteric-coated, delayed-release tablet: 125, 250, 500 mg Sprinkles: 125 mg	750–3000 mg/day (20–60 mg/kg per day) in 2–3 divided doses for delayed-release divalproex or valproic acid Extended release divalproex may be given once daily at bedtime	Monotherapy or in combination with other drugs for the acute treatment of mania and for maintenance treatment.
	Depakote ER	Extended-release tablet: 250, 500 mg		
Valproic acid	Depakene, generic	Capsules: 250 mg	A loading dose of divalproex (20–30 mg/kg per day) can be given, then 20 mg/kg per day and titrated to a serum concentration of 50–125 mcg/mL (346–866 µmol/L)	
Valproic acid syrup	Depakene, generic	250 mg/5 mL		
Lamotrigine	Lamictal	Tablet: 25, 100, 150, 200 mg	50–400 mg/day in divided doses. Dosage should be slowly increased by following prescribing information; if valproate is added to Lamictal, the Lamictal dosage should be reduced by half	Monotherapy or in combination with other drugs for the long-term maintenance treatment of bipolar depression; may have efficacy for prevention of bipolar depression
Anticonvulsants and Other Drugs Not FDA-Approved for Use in Bipolar Disorder				
Clonazepam	Klonopin	Tablet: 0.5, 1, 2 mg	0.5–20 mg/day in divided doses or one dose at bedtime Dosage should be slowly adjusted up and down according to response and adverse effects	Use in combination with other drugs for the acute treatment of mania or mixed episodes. Use as a short-term adjunctive sedative-hypnotic agent
Lorazepam	Ativan	Tablet: 0.5, 1, 2 mg Oral solution: 2 mg/mL Injection: 2, 4 mg/mL	2–4 mg/day in divided doses or just one dose at bedtime Dosage should be slowly adjusted up and down according to response and adverse effects	

(Continued)

TABLE 36–4. Product Formulation, Dosage, and Information, and Clinical Use of Agents Used in the Treatment of Bipolar Disorder[3,22–25] *(Continued)*

Generic Name	Brand Names	Formulations	Dosages	Clinical Use
Oxcarbazepine	Trileptal	Tablets: 150, 300, 600 mg Suspension: 300 mg/5 mL	300–1200 mg/day in two divided doses Doses should be slowly adjusted up and down according to response and adverse effects (e.g., 150–300 mg twice daily and increase by 300–600 mg/day at weekly intervals)	May cause fewer adverse drug-drug interactions than carbamazepine, but causes more gastrointestinal side effects and hyponatremia Evidence is limited regarding efficacy
Topiramate	Topamax	Tablet: 25, 100, 200 mg Sprinkle capsule: 15, 25 mg	50–200 mg/day in divided doses Dosage should be slowly increased to minimize adverse effects (e.g., 25 mg at bedtime for 1 week, then 25–50 mg/day increments at weekly intervals)	Not recommended for the acute treatment of mania or mixed episodes due to lack of efficacy; used as an adjunctive agent with established mood stabilizers
Atypical Antipsychotics **FDA approved for use in bipolar disorder**				
Aripiprazole	Abilify	Tablets: 5, 10, 15, 20, 30 mg	10–30 mg/day once daily	Use as monotherapy or in combination with lithium or valproate for the acute treatment of mania or mixed states for bipolar I disorder. Olanzapine and aripiprazole are approved for relapse prevention as well as for acute therapy
Olanzapine	Zyprexa	Tablets: 2.5, 5, 7.5, 10, 15, 20 mg	5–20 mg/day in 1 or 2 doses	
	Zyprexa, Zydis	Tablet, orally disintegrating: 5, 10, 15, 20 mg		
Quetiapine	Seroquel	Tablet 25, 100, 200, 300 mg	50–800 mg/day in divided doses or once daily when stabilized	
Risperidone	Risperdal	Tablet: 0.25, 0.5, 1, 2, 3, 4 mg Oral solution: 1 mg/mL	0.5–6 mg/day in 1 or 2 doses	Risperidone microspheres is not approved at present for bipolar disorder
	Risperdal Consta	Long-acting injectable: 25, 37.5, 50 mg		
Ziprasidone	Geodon	Capsule: 20, 40, 60 80 mg	40–160 mg/day in divided doses	

Dosing and Monitoring Lithium is usually initiated at a dosage of 600 to 900 mg per day. Although it is most commonly given in a divided dosage, once-daily dosing is acceptable, especially with sustained-release formulations, and can improve patient adherence and reduce some side effects. It has a narrow therapeutic index, meaning the toxic dosage is not much greater than the therapeutic dosage, and requires regular serum concentration monitoring as a guide to dosage titration and to minimize risk of adverse effects. At least weekly monitoring is recommended until the patient is stabilized, then in decreasing frequency. Well-maintained patients who tolerate lithium without difficulty can be monitored by serum concentration as infrequently as twice yearly. Dosage is titrated to achieve a serum lithium concentration of 0.6 to 1.4 mEq/L (0.6–1.4 mmol/L). Higher serum concentrations are usually required to treat an acute episode than to prevent relapse. However, serum lithium maintained above 0.8 mEq/L (0.8 mmol/L) may be more effective in preventing relapse than lower serum concentrations. The suggested therapeutic serum concentration range is based on a 12-hour post-dose sample collection, usually a morning trough in patients taking more than one dose per day. At least 2 weeks at a suggested therapeutic serum concentration is required for an adequate trial of lithium. Table 36–5 shows pharmacokinetic parameters and desired serum concentrations of mood-stabilizing drugs used for bipolar disorder.

TABLE 36–5. Pharmacokinetics and Therapeutic Serum Concentrations of Lithium and Anticonvulsants Used in the Treatment of Bipolar Disorder

	Lithium	Carbamazepine	Oxcarbazepine	Divalproex (DVPX) Sodium/Valproic Acid (VPA)	Lamotrigine
Gastrointestinal absorption					
Regular release	Rapid: 95–100% within 1–6 hours	Slow and erratic: 85–90%	Slow and complete: 100%	Rapid and complete (VPA)	Rapid: 98%
Syrup/suspension/ solution	Faster rate of absorption: 100%	Faster rate of absorption	Unknown	Faster rate of absorption than tablets	NA
Extended-release/ enteric-coated tablets	Delayed absorption: 60–90%	Delayed absorption: 89% of the suspension; and less than regular-release tablets	NA	Extended-release: 90% of intravenous dose. Delayed-release: 81–90% of intravenous dose Delayed absorption with delayed-release tablets; valproate is rapidlyconverted to VPA in the stomach, then is rapidly and almost completely absorbed from the GI tract	NA
Delay in absorption by food	Yes	No; reports of increased rate of absorption with fatty meals (extended-release capsule)	Unknown	Yes; food slows the rate of absorption but not the extent for DVPX	Bioavailability not affected by food
Time to reach peak serum concentrations	0.5–3 hours (regular-release) 4–12 hours (extended-release) 0.25–1 hours (oral solution)	4.5 hours (regular-release); 1.5 hours (suspension); 3–12 hours (extended-release tablets); 4.1–7.7 hours (extended-release capsules); higher peak concentrations with chewable tablets	4.5 hours (range of 3–13 hours)	1–4 hours (VPA) 3–5 hours (DVPX single dose) 7–14 hours (DVPX extended-release multiple dosing)	1–4 hours
Distribution					
Volume of distribution	Initial: 0.3–0.4 L/kg Steady-state: 0.7–1 L/kg	0.6–2 L/kg (adults)	10-monohydroxy carbazepine (metabolite): 49 L/kg	11 L/1.73 m^2 (total valproate); 92 L/1.73 m^2 (free valproate)	0.9–1.3 L/kg
Crosses the placenta	Yes; pregnancy risk category: D Risk of cardiac defects: 0.1–0.5%	Yes; pregnancy risk category: D	Yes; pregnancy risk category: C	Yes: pregnancy risk category: D Risk of neural tube defects: 1–5%	Yes; pregnancy risk category: C
Crosses into breast milk	Yes: 35–50% of mother's serum concentration; breast-feeding not recommended	Yes: ratio of concentration in breast milk to plasma is 0.4 for drug and 0.5 for epoxide metabolite; considered compatible with breast-feeding	Yes: both drug and active metabolite; breast-feeding not recommended	Yes: considered compatible with breast-feeding	Yes: breast-feeding not recommended
Protein binding	No	75–90%	40% of active metabolite	80–90% (dose dependent)	55%

(Continued)

TABLE 36–5. Pharmacokinetics and Therapeutic Serum Concentrations of Lithium and Anticonvulsants Used in the Treatment of Bipolar Disorder *(Continued)*

	Lithium	Carbamazepine	Oxcarbazepine	Divalproex (DVPX) Sodium/Valproic Acid (VPA)	Lamotrigine
Renal clearance	Yes: 10–40 mL/minute with 90–98% of dose excreted in urine; 80% of lithium that is filtered by the renal glomeruli is reabsorbed	Yes: 1–3% excreted unchanged in urine	Yes: 95% excreted in the urine less than 1% excreted unchanged	Yes: 30–50% excreted as glucuronide conjugate; less than 3% excreted unchanged	Yes: 94% excreted as glucuronide conjugate
Metabolism					
Hepatic metabolism	No	Yes: oxidation and hydroxylation induces liver enzymes to increase its metabolism and other drugs	Yes: oxidation and conjugation	Yes: oxidation and glucuronide conjugation	Yes: glucuronic acid conjugation Induces its own metabolism in normal volunteers
Metabolites	No	Yes: 10, 11-epoxide (active)	Yes: 10-monohydroxy carbazepine (active)	Yes (not active)	No
Kinetics	First-order	First-order after initial enzyme induction phase	First-order	First-order	First-order
Half-life ($t_{1/2}$)	18–27 hours (adult); greater than 36 hours (elderly or patients with renal impairment)	$t_{1/2}$ decreases over time due to autoinduction: 25–65 hours (initial) 12–17 hours (adult multiple dosing) 8–14 hours (children multiple dosing)	2 hours (parent) 9 hours (metabolite)	5–20 hours (adult)	25 hours; increases to 59 hours with concomitant valproic acid therapy
Cytochrome P-450 (CYP450) isoenzyme					
CYP450 substrate	No	2C8 and 3A3/4	Unknown	2C19	Unknown
CYP450 inhibitor	No	No	2C19	2C9, 2D6, and 3A3/4	Unknown
CYP450 inducer	No	1A2, 2C9/10, and 3A3/4	3A3/4	No	Unknown
Therapeutic serum/plasma concentrations					
Obtain blood level 10–12 hours postdose	1–1.5 mEq/L: for adult, acute mania 0.4–0.6 mEq/L: for elderly or medically ill 0.6–1.2 mEq/L: for adult, maintenance	4–12 mcg/mL: for adult, acute mania and maintenance 4–8 mcg/mL: for elderly or medically ill	No established therapeutic range; 12–30 mcg/mL for 10-hydroxy carbazepine based on epilepsy trials	50–125 mcg/mL: adult, acute mania and maintenance 40–75 mcg/mL: elderly or medically ill	No established therapeutic range: 4-20 mcg/mL based on epilepsy trials

NA, not applicable.
From Fankhauser MP, Freeman MP. Bipolar disorder. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1274–1275, with permission.

It is common for lithium to be combined with other mood-stabilizing drugs or antipsychotic drugs, if necessary, in order to achieve more complete remission of symptoms. Studies indicate that monotherapy is often insufficient to reach this goal.[17]

Adverse Effects The most common adverse effects are gastrointestinal upset, tremor, and polyuria,[30] which are dose-related. Nausea, dyspepsia, and diarrhea can be minimized by coadministration with food, use of sustained-release formulations, and giving smaller doses more frequently to reduce the amount of drug in the gastrointestinal tract at a given time. Tremor is present in up to 50% of patients. In addition to the approaches above, low-dose β-blocker therapy such as propranolol 20 to 60 mg/day often reduces the tremor.

Lithium impairs the kidney's ability to concentrate urine due to its inhibitory effect on vasopressin. This causes an increase in urine volume and frequency and a consequent increase in thirst. Polyuria and polydipsia occur in up to 70% of patients. A severe form of polyuria when urine volume exceeds 3 L/day is known as nephrogenic lithium-induced **diabetes insipidus**. It can be treated with amiloride or hydrochlorothiazide. If the latter is used, the lithium dosage should be reduced by 33% to 50% to account for the drug-drug interaction that could increase serum lithium and cause toxicity. Long-term lithium therapy can cause structural kidney changes such as glomerular sclerosis or tubular atrophy. Once-daily dosing of lithium is less likely to cause renal adverse effects than divided-daily dosing.

Lithium is concentrated in the thyroid gland and can impair thyroid hormone synthesis. Although goiter is uncommon, as many as 30% of patients develop at least transiently elevated thyroid-stimulating hormone values. Lithium-induced hypothyroidism is not usually an indication to discontinue the drug. Patients can be supplemented with levothyroxine if continuation of lithium is desired.[30]

Other common adverse effects include poor concentration, acneiform rash, alopecia, worsening of psoriasis, weight gain, metallic taste, and glucose dysfunction. Lithium causes a benign flattening or inversion of the T wave on the electrocardiogram (ECG). Less commonly, it can cause or worsen arrhythmias. Cardiologic evaluation is recommended for patients with preexisting cardiac disease who are candidates for lithium therapy. A benign leukocytosis is also common.[30]

Lithium and other mood-stabilizing drugs require baseline and routine laboratory monitoring to help determine medical appropriateness for initiation of therapy and monitoring of potential adverse effects. Guidelines for such monitoring are outlined in Table 36–6.

Acute lithium toxicity, which can occur at serum concentrations over 2 mEq/L, can be severe and life-threatening, necessitating emergency medical treatment. Symptoms include worsening of gastrointestinal distress to include severe vomiting and diarrhea; deterioration in motor coordination including a coarse tremor, ataxia, and dysarthria; and impaired cognition. In its most severe form, seizures, cardiac arrhythmias, coma, and kidney damage have been reported. Treatment includes discontinuation of lithium, intravenous fluids to correct fluid and electrolyte imbalance, and osmotic diuresis or hemodialysis. In case of overdose, gastric lavage is indicated. Clinical symptoms can continue well after the serum concentration is lowered, as clearance from the central nervous system is slower than from the serum. Factors predisposing to lithium toxicity include fluid and sodium loss due to hot weather or exercise or drug interactions that increase serum lithium.[30]

Drug Interactions Drug interactions involving lithium are common. Since lithium is not metabolized or protein bound, however, it is not associated with metabolic drug interactions that occur with other mood-stabilizing drugs. Common and significant drug interactions involve thiazide diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), and angiotensin-converting enzyme inhibitors (ACEIs). If a diuretic must be used with lithium and a thiazide is not required, loop diuretics such as furosemide are less likely to increase lithium retention. The ACEIs can abruptly increase serum lithium with the potential for acute and fatal toxicity, even after months of no effect. This combination is strongly discouraged.[35]

Divalproex Sodium and Valproic Acid

Divalproex sodium is comprised of sodium valproate and valproic acid. The delayed-release and extended-release formulations are converted in the small intestine into valproic acid, which is the systemically absorbed form. It was developed as an antiepileptic drug, but also has efficacy for mood stabilization and migraine headaches. It is FDA-approved for the treatment of the manic phase of bipolar disorder. It is generally equal in efficacy to lithium and some other drugs for bipolar mania. It has particular utility in bipolar disorder patients with rapid cycling, mixed mood features, and substance abuse comorbidity. Although not FDA-approved for relapse prevention, studies support this use, and it is widely prescribed for maintenance therapy. Divalproex can be used as monotherapy or in combination with lithium or an antipsychotic drug.[31]

Mechanism of Action The mechanism of action of divalproex is not well understood. It is known to affect ion transport and enhances the activity of γ-aminobutyric acid. Like lithium, it also has possible neuroprotective effects through enhancement of brain-derived neurotrophic factor.[31]

Dosing and Monitoring Divalproex is often initiated at 500 to 1000 mg per day, but studies indicate a therapeutic serum valproic acid concentration can be reached more quickly through a loading dose approach of 20 to 30 mg/kg per day. Using this approach, patients may respond with a significant reduction in symptoms within the first few days of treatment. The dosage is then titrated according to response, tolerability, and serum concentration. The most often referenced desired serum valproic acid concentration is 50 to 100 mcg/mL (346–693 μmol/L), but

TABLE 36–6. Guidelines for Baseline and Routine Laboratory Tests and Monitoring for Agents Used in the Treatment of Bipolar Disorder

	Baseline: Physical Exam & General Chemistry[a]	Hematologic Tests[c]		Metabolic Tests[b]		Liver Function Tests[d]		Renal Function Tests[e]		Thyroid Function Tests[f]		Serum Electrolytes[g]		Dermatologic[h]	
	Baseline	Baseline	6–12 months	Baseline	6–12 months	Baseline	6–12 months	Baseline	6–12 months	Baseline	6–12 months	Baseline	6–12 months	Baseline	3–6 months
Atypical antipsychotics[i]	X			X	X										
Carbamazepine[j]	X	X	X			X	X	X				X	X	X	X
Lamotrigine[k]	X													X	X
Lithium[l]	X	X	X	X	X			X	X	X	X	X	X	X	X
Oxcarbazepine[m]	X											X	X		
Valproate[n]	X	X	X	X	X	X	X							X	X

[a]Screen for drug abuse and serum pregnancy.
[b]Complete blood cell count (CBC) with differential and platelets.
[c]Fasting glucose, serum lipids, weight.
[d]Lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase.
[e]Serum creatinine, blood urea nitrogen, urinalysis, urine osmolality, specific gravity.
[f]Triiodothyronine, total thyroxine, thyroxine uptake, and thyroid-stimulating hormone.
[g]Serum sodium.
[h]Rashes, hair thinning, alopecia.
[i]Atypical antipsychotics: Monitor for increased appetite with weight gain (primarily in patients with initial low or normal body mass index); monitor closely if rapid or significant weight gain occurs during early therapy; cases of hyperlipidemia and diabetes reported.
[j]Carbamazepine: Manufacturer recommends CBC and platelets (and possibly reticulocyte counts and serum iron) at baseline, and that subsequent monitoring be individualized by the clinician (e.g., CBC, platelet counts, and liver function tests every 2 weeks during the first 2 months of treatment, then every 3 months if normal). Monitor more closely if patient exhibits hematologic or hepatic abnormalities or if the patient is receiving a myelotoxic drug; discontinue if platelets are less than 100,000/mm^3, if white blood cell (WBC) count is less than 3,000/mm^3 or if there is evidence of bone marrow suppression or liver dysfunction. Serum electrolyte levels should be monitored in the elderly or those at risk for hyponatremia. Carbamazepine interferes with some pregnancy tests.
[k]Lamotrigine: If renal or hepatic impairment, monitor closely and adjust dosage according to manufacturer's guidelines. Serious dermatologic reactions have occurred within 2–8 weeks of initiating treatment and are more likely to occur in patients receiving concomitant valproate, with rapid dosage escalation, or using doses exceeding the recommended titration schedule.
[l]Lithium: Obtain baseline electrocardiogram for patients over age 40 or if preexisting cardiac disease (benign, reversible T-wave depression may occur). Renal function tests should be obtained every 2–3 months during the first 6 months, then every 6–12 months; if impaired renal function, monitor 24-hour urine volume and creatinine every 3 months; if urine volume greater than 3 L/day, monitor urinalysis, osmolality, and specific gravity every 3 months. Thyroid function tests should be obtained once or twice during the first 6 months, then every 6–12 months; monitor for signs and symptoms of hypothyroidism; if supplemental thyroid therapy is required, monitor thyroid function tests and adjust thyroid dose every 1–2 months until thyroid function indices are within normal range, then monitor every 3–6 months.
[m]Oxcarbazepine: Hyponatremia (serum sodium concentrations less than 125 mEq/L) has been reported and occurs more frequently during the first 3 months of therapy; serum sodium concentrations should be monitored in patients receiving drugs that lower serum sodium concentrations (e.g., diuretics or drugs that cause inappropriate antidiuretic hormone secretion) or in patients with symptoms of hyponatremia (e.g., confusion, headache, lethargy, and malaise). Hypersensitivity reactions have occurred in approximately 25–30% of patients with a history of carbamazepine hypersensitivity and requires immediate discontinuation.
[n]Valproate: Weight gain reported in patients with low or normal body mass index. Monitor platelets and liver function during first 3–6 months if evidence of increased bruising or bleeding. Monitor closely if patients exhibit hematologic or hepatic abnormalities or in patients receiving drugs that affect coagulation, such as aspirin or warfarin; discontinue if platelets are Less than 100,000/mm^3/L or if prolonged bleeding time. Pancreatitis, hyperammonemic encephalopathy, polycystic ovary syndrome, increased testosterone, and menstrual irregularities have been reported; not recommended during first trimester of pregnancy due to risk of neural tube defects.
From Fankhauser MP, Freeman MP. Bipolar disorder. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1276, with permission.

it is not unusual for patients to require over 100 mcg/mL (693 μmol/L) for optimal efficacy. Some patients require high-milligram dosages in order to reach a desired serum concentration. The suggested serum concentration range is based on morning sampling, which is a trough value for patients taking divided-daily dosing. Serum concentration monitoring is recommended at least every 2 weeks until stabilized, then less frequently, sometimes as infrequently as twice yearly. The extended-release formulation can be taken once daily, usually at night. In this instance also, a morning blood sampling is recommended. The systemic bioavailability of extended-release divalproex is about 15% less than that of the delayed-release formulation. Patients who have difficulty swallowing large tablets can use the sprinkle formulation. Valproic acid is available in a syrup formulation, which is generally given three or four times per day.[31]

Adverse Effects The most common adverse effects of divalproex are gastrointestinal (loss of appetite, nausea, dyspepsia, and diarrhea), tremor, and drowsiness. Gastrointestinal distress can be reduced by coadministration with food. The delayed-release and extended-release formulations are less likely to cause gastric distress than the immediate-release valproic acid. This is an advantage for divalproex, along with fewer daily doses, which can improve patient adherence to treatment. Dosage reduction can reduce all of the common divalproex side effects. As with lithium, a low-dose β-blocker may alleviate the tremor. Weight gain is also common, occurring in up to 50% of patients on maintenance therapy.[31]

Other adverse effects that are less common include alopecia or a change in hair color or texture. Hair loss can be minimized by supplementation with a vitamin containing selenium and zinc. Polycystic ovarian syndrome associated with increased androgen production has been reported. Thrombocytopenia is not uncommon, and the platelet count should be monitored periodically. It is a dose-related adverse effect and usually asymptomatic, but the drug is usually stopped if the platelet count decreases to less than 100,000/mm^3 (100×10^3/μL or 100×10^9/L). More rare are hepatic toxicity and pancreatitis, which are not always dose-related. Severe gastrointestinal symptoms of hepatic or pancreatic toxicity include vomiting, pain, and loss of appetite. When these occur, the patient should be evaluated for possible hepatitis or pancreatitis. Divalproex has a wide therapeutic index. Acute toxicity for high dosages or overdosage is not life-threatening.[31]

Drug Interactions Drug interactions involving divalproex are common. It is a weak inhibitor of some of the drug-metabolizing liver enzymes and can affect the metabolism of other drugs. These include other antiepileptic drugs and tricyclic antidepressants. The interaction between divalproex and lamotrigine is particularly important. The risk of a dangerous rash due to lamotrigine is increased when given concurrently with divalproex. When lamotrigine is added to divalproex, the initial lamotrigine dosage should be reduced, and titrated more slowly than usual. When divalproex is added to lamotrigine, the lamotrigine dosage should be reduced by 50%. Conversely, the metabolism of divalproex can be increased by enzyme-inducing drugs such as carbamazepine and phenytoin, while divalproex may simultaneously slow metabolism of the other agents.[35]

Carbamazepine

Although long utilized as a mood-stabilizing drug, an extended-release formulation of carbamazepine has only recently received FDA approval for treatment of bipolar disorder. Like divalproex, it also has efficacy for mood stabilization, but is considered possibly less desirable as a first-line agent because of safety and drug interactions. It is sometimes reserved for patients who fail to respond to lithium or for patients with rapid cycling or mixed bipolar disorder. Carbamazepine can be used as monotherapy or in combination with lithium or an antipsychotic drug.[24,32]

Mechanism of Action The mechanism of action of carbamazepine is not well understood. It blocks ion channels and inhibits sustained repetitive neuronal excitation, but whether this explains its effect as a mood-stabilizing drug is not known.[32]

Dosing and Monitoring Carbamazepine is usually initiated at 400 to 600 mg/day. The sustained-release formulation can be given in two divided doses. In addition to a formulation that is completely sustained-release, an additional extended-release formulation contains a matrix of 25% immediate-release, 40% extended-release, and 35% enteric-release beads.[24] The suggested therapeutic serum concentration is 4 to 12 mcg/mL (17–51 μmol/L). As with divalproex, some patients require high-milligram dosages to achieve a desired serum concentration and therapeutic effect. The dosage can be increased by 200 to 400 mg per day as often as every 2 to 4 days to achieve the desired effect. Serum concentration monitoring is suggested at least every 2 weeks until stabilized, then less frequently.[32]

Adverse Effects The most common adverse effects are drowsiness, dizziness, ataxia, lethargy, and confusion. At mildly toxic serum concentrations, it also causes diplopia and dysarthria. These effects can be minimized through dosage adjustments, use of sustained-release formulations, and giving more of the drug late in the day. Gastrointestinal upset is also common. Carbamazepine has an antidiuretic effect similar to the syndrome of inappropriate antidiuretic hormone secretion and can cause hyponatremia. Mild elevations in liver enzymes can occur, but hepatitis is less common. Mild, dose-related leukopenia is not unusual and not usually an indication for stopping the drug. More serious blood count abnormalities such as aplastic anemia and agranulocytosis are rare, but life-threatening.[32] Suggested baseline and routine laboratory monitoring is reviewed in Table 36–6.

Drug Interactions Carbamazepine induces the hepatic metabolism of many drugs, including other antiepileptic drugs, antipsychotics, some antidepressants, oral contraceptives, and

antiretroviral agents. Carbamazepine is also an autoinducer (i.e., it induces its own metabolism). The dosage may require an increase after 1 month or so of therapy because of this effect. Conversely, the metabolism of carbamazepine can be slowed by enzyme-inhibiting drugs such as some antidepressants, macrolide antibiotics including erythromycin and clarithromycin, azole antifungal drugs including ketoconazole and itraconazole, and grapefruit juice. Carbamazepine should not be given concurrently with clozapine because of the added risk of agranulocytosis.[35]

Lamotrigine

Lamotrigine is effective for the maintenance treatment of bipolar disorder. It is more effective for depression relapse prevention than for mania relapse. Its primary limitation as an acute treatment is the time required for titration to an effective dosage. In addition to maintenance monotherapy, it is sometimes used in combination with lithium or divalproex, although combination with divalproex increases the risk of rash, and lamotrigine dosage adjustment is required.[37]

Mechanism of Action The mechanism of action of lamotrigine appears to involve blockage of ion channels and effects on glutamate transmission, although the precise mechanism in bipolar disorder is not clear.[33]

Dosing and Monitoring Lamotrigine is usually initiated at 25 mg daily for the first 1 to 2 weeks, then increasing in a dose-doubling fashion every 1 to 2 weeks to a target dosage of 200 to 400 mg per day. If lamotrigine is added to divalproex, the starting dosage is 25 mg every other day with a slower titration to reduce the risk of rash. If divalproex is added to lamotrigine, the lamotrigine dosage should be reduced by 50% for the same reason. If lamotrigine therapy is interrupted for more than a few days, it should be restarted at the initial dosage. Serum concentration monitoring is not routinely recommended for patients with bipolar disorder.[33]

Adverse Effects The lamotrigine adverse effect of greatest significance is a maculopapular rash, occurring in up to 10% of patients.[33] Although usually benign and temporary, some rashes can progress to life-threatening Stevens-Johnson syndrome. The risk of rash is greater with a rapid dosage titration and when given concurrently with divalproex. The risk is minimal when the dosage titration schedule is slow. Other side effects include dizziness, drowsiness, headache, blurred vision, and nausea. In contrast to other mood-stabilizing drugs such as lithium and divalproex, lamotrigine does not significantly influence body weight.

Drug Interactions Drug interactions involving lamotrigine are usually due to induction or inhibition of its metabolism by other drugs. It does not affect drug-metabolizing hepatic enzymes on its own, but other drugs that affect these pathways can have a significant effect on lamotrigine's clearance. In particular, divalproex slows the rate of elimination of lamotrigine by about half, necessitating dosage reduction. Conversely, carbamazepine increases the rate of lamotrigine metabolism. Upward adjustment in the lamotrigine dosage may be needed as a result.[35]

Oxcarbazepine

Oxcarbazepine is an analogue of carbamazepine, developed as an antiepileptic drug. An advantage over carbamazepine is that routine monitoring of hematology profiles and serum concentrations are not indicated, as the drug is less likely to cause hematologic abnormalities. Additionally, drug interactions are less significant, although it is at least a mild inducer of certain metabolic pathways, and vigilance for drug interactions is needed, especially with oral contraceptives. Oxcarbazepine appears in the most recent treatment algorithms for bipolar disorder,[17] but clinical trial data are limited and do not include randomized, prospective, controlled trials at the time of this writing. Data are limited to open-label and retrospective studies or add-on therapy with other mood-stabilizing agents.[38]

Adverse Effects Adverse effects due to oxcarbazepine include drowsiness, dizziness, gastrointestinal upset, and hyponatremia, the latter two of which may be more likely than with carbamazepine. It is less likely than carbamazepine to cause hematologic abnormalities.[34]

Others

High-potency benzodiazepine agents such as clonazepam have been used as adjunctive therapy, especially during acute mania episodes, to reduce anxiety and improve sleep.[39] Topiramate is commonly used for its putative mood-stabilizing effects, but unpublished, well-designed, randomized, controlled trials sponsored by the manufacturer showed no difference between topiramate and placebo for treatment of bipolar disorder. Uncontrolled, open-label data suggest possible use as an adjunctive agent.[38] Gabapentin has shown no efficacy over placebo and is not recommended for patients with bipolar disorder. Case reports or case series involving zonisamide, tiagabine, pregabalin, and levetiracetam have been published, but no controlled trials have been conducted to date.[38]

Antipsychotic Drugs

Conventional antipsychotic drugs such as chlorpromazine and haloperidol have long been used in the treatment of acute mania. More recently, atypical antipsychotic drugs including aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone have been approved for the treatment of bipolar mania or mixed mood episodes as monotherapy or in combination with mood-stabilizing drugs.[25] Aripiprazole and olanzapine are also approved for maintenance therapy. The combination of olanzapine and fluoxetine is approved for treatment of bipolar depression. Quetiapine is approved for treatment of

bipolar depression. Approval of antipsychotic drugs in bipolar disorder patients applies without regard to the presence of psychotic symptoms. In comparative studies, atypical antipsychotic drugs are equivalent in efficacy to lithium and divalproex for treatment of acute mania. Treatment guidelines include antipsychotic drugs as first-line therapy.[17] More limited studies in maintenance therapy indicate equivalent or possibly superior efficacy of atypical antipsychotic drugs compared to lithium, but these studies are sponsored and developed by manufacturers and have not been replicated widely.

The mechanisms of action, usual dosages, pharmacokinetics, adverse effects, and drug interactions involving antipsychotic drugs are discussed in detail in the chapter on schizophrenia. Dosages in bipolar disorder are similar to those used in schizophrenia. Higher dosages are often required to treat an acute episode than to prevent relapse. The recommended dosage of aripiprazole for bipolar disorder is 20 to 30 mg per day, somewhat higher than the average dosage used in schizophrenia.[40]

Atypical antipsychotic drugs are less likely than conventional agents to cause neurologic side effects, especially movement abnormalities. As a group, however, they are more likely to cause metabolic side effects such as weight gain, glucose dysregulation, and dyslipidemia.[36] Among the atypical antipsychotic drugs approved for treatment of bipolar disorder, olanzapine is more likely to cause metabolic side effects. Quetiapine and risperidone cause fewer metabolic effects than olanzapine. Aripiprazole and ziprasidone are neutral in effects on weight, glucose, and lipids. Adverse effects are discussed in detail in the chapter on schizophrenia.

Antidepressants

Treatment of depressive episodes in bipolar disorder patients presents a particular challenge because of the risk of a pharmacologic mood switch to mania, although there is not complete agreement about such risk. Treatment guidelines suggest lithium or lamotrigine as first-line therapy.[17,41] Olanzapine has also demonstrated efficacy in treatment of bipolar depression, and quetiapine is under review for approval of treatment of bipolar depression.[42] When these fail, efficacy data support use of antidepressants.

Guidelines agree that when antidepressants must be used, they should be combined with a mood-stabilizing drug to reduce the risk of mood switch to hypomania or mania.[17,41] The question of which antidepressant drugs are less likely to cause a mood switch is not resolved. Anecdotal reports suggested bupropion may be less likely to cause this effect, but systematic reviews have not supported this conclusion. Prevailing evidence recommends that tricyclic antidepressants be avoided.[41,43]

Duration of antidepressant therapy is also an unsettled question. It may be possible in some patients to prevent depressive relapse with a mood-stabilizing drug without maintenance antidepressant therapy following acute treatment with an antidepressant. If so, the risk of a mood switch with continued antidepressant therapy would be reduced.

Special Populations

Assessment and management by appropriate psychiatric specialists is important for special populations such as pediatrics, geriatrics, pregnancy, and others.

Pediatrics

Evidence regarding treatment of bipolar disorder in children and adolescents is more limited than in adults, reflecting the difficulty of conducting research in this population. Psychiatric comorbidity is common, which makes treatment and research more challenging. With these caveats, an increasing body of evidence supports the use of mood-stabilizing drugs and atypical antipsychotic drugs in children and adolescents with bipolar disorder.[44] The approach is similar to that used in adults, with monotherapy as first-line therapy, but only lithium is FDA-approved for children and adolescents as young as age 12. The guidelines additionally support divalproex, carbamazepine, olanzapine, quetiapine, and risperidone.[44] Aripiprazole and ziprasidone are not recommended at present because of a lack of published research, but evidence to support the other agents is mostly open-label trials or studies with small sample sizes. For patients with psychotic features, first-line therapy should include combined mood stabilizer and antipsychotic drugs. Patients who fail the initial choice of treatment can be switched to a different agent or augmented with the addition of a second agent.

Initial dosages of drug therapy in the pediatric population are lower than in adults. Metabolic elimination rates of many drugs are increased in children, however, so they may actually require higher dosages on a weight-adjusted basis. Dosages are titrated carefully according to response and tolerability. For lithium, divalproex, and carbamazepine, serum concentration monitoring is recommended as a guide to dosage adjustment and to minimize adverse effects.

Children and adolescent patients are often more sensitive to drug side effects than adults. In particular, they are more likely than adults to experience significant weight gain due to atypical antipsychotic drugs.[45] Cognitive toxicity, manifested as confusion, memory or concentration impairment, or impaired learning, is often difficult to detect and is a special consideration in the pediatric population so intellectual and educational development is not hindered by drug therapy.

Comorbid conditions must be addressed in order to maximize desired outcomes. For comorbid bipolar disorder and attention-deficit/hyperactivity disorder when stimulant therapy is indicated, treatment of mania is recommended before starting the stimulant in order to avoid exacerbation of mood symptoms by the stimulant.

Geriatrics

Treatment of elderly patients with bipolar disorder requires special care because of increased risks associated with concurrent non-psychiatric medical conditions and drug-drug interactions. General medical conditions including endocrine,

metabolic, or infectious diseases can mimic mood disorders. Patients should be evaluated for such medical illnesses that may cause or worsen mood symptoms. As physiologic systems change with aging, elimination of drugs is often slowed. Examples are slowed renal elimination of lithium and slowed hepatic metabolism of carbamazepine and valproic acid. As a result, dosages of drugs required for therapeutic effect are generally lower in geriatric patients. Also, changes in membrane permeability with aging increase risk of central nervous system side effects. Increased frequency of patient monitoring is often required, including serum drug concentration monitoring.

Vigilance for drug-drug interactions is required because of the greater number of medications prescribed to elderly patients and enhanced sensitivity to adverse effects. Pharmacokinetic interactions include metabolic enzyme induction or inhibition and protein binding displacement interactions (e.g., divalproex and warfarin). Pharmacodynamic interactions include additive sedation and cognitive toxicity, which increases risk of falls and other impairments.

Pregnancy

Treatment of bipolar disorder during pregnancy is fraught with controversy and conflicting recommendations. The key issue is the relative risk of teratogenicity with drug use during pregnancy versus risk of bipolar relapse without treatment with consequent potential harm to both the pregnant patient and the fetus. Judgment on an issue of such gravity depends on the history of the patient and whether the pregnancy is planned or unplanned. Treatment is best managed when the pregnancy is planned. Clinicians should discuss the issue with every patient with bipolar disorder who is of childbearing potential. A pregnancy test should be obtained prior to initiating drug therapy. For a patient with severe bipolar disorder, a history of multiple mood episodes, rapid cycling, or suicide attempt, discontinuing treatment, even for a planned pregnancy, is unwise. For a patient with a remote history of a single mood episode with subsequent long-term stability and who is contemplating pregnancy, the answer is less clear. Patients should be provided clear and reliable information about risks versus benefits of stopping or continuing therapy in order to make an informed decision. Patients who decide to discontinue drug therapy prior to pregnancy should taper medications slowly in order to reduce risk of relapse.[46]

Lithium is associated with Ebstein's anomaly, a downward displacement of the tricuspid valve into the right ventricle. Although more likely to occur in children of patients who took lithium during pregnancy, the absolute risk is considered small, around 0.1%. Pharmacokinetic handling of lithium changes as pregnancy progresses. Renal lithium clearance increases, which requires a dosage increase to maintain a therapeutic serum concentration. It may be advisable to decrease or discontinue lithium at term or the onset of labor to avoid toxicity postpartum when there is a large reduction in fluid volume.[46]

Lithium can cause hypotonicity and cyanosis in the neonate, usually termed the "floppy baby" syndrome. Most data indicate normal neurobehavioral development once these symptoms resolve. Lithium is readily transferred via breast milk. Breast-feeding is not advised for patients who are taking lithium.[30]

Valproic acid and carbamazepine are human teratogens. Neural tube defects such as spina bifida occur in up to 9% of infants exposed during the first trimester. The risk is related to exposure during the third and fourth weeks following conception. As such, women with unplanned pregnancies may not know they are pregnant until after the risk of exposure has occurred. Carbamazepine can cause fetal vitamin K deficiency. Vitamin K is important for facial growth and for clotting factors. Risk of facial abnormalities and neonatal bleeding is increased in infants of mothers who are treated with carbamazepine during pregnancy.[46]

Less data are available on other antiepileptic mood-stabilizing drugs. Birth defects in children of women who are prescribed lamotrigine during pregnancy appear to be no greater than in the general population, but based on an analysis of only several hundred cases.[47] The FDA has noted a possible, but inconclusive association between lamotrigine exposure during the first trimester and cleft lip and/or cleft palate.



Patient Encounter, Part 4: Outcome Evaluation

Following initial assessment, including evaluation of potential suicidality, support systems, and need for inpatient versus outpatient treatment, MW was hospitalized briefly, then followed in the community on medication along with psychotherapy. She has abstained from illicit substances and has returned to her job. She has responded well to treatment with sustained-release lithium carbonate 900 mg once daily at bedtime with a snack. Steady-state 12-hour serum lithium concentrations have stabilized at 0.9 mEq/L (0.9 mmol/L). She now returns to clinic for routine follow-up. She has tolerated the lithium except for a mild tremor and a gain of 7 pounds (3.2 kg). She is willing to accept these side effects for now, but asks about how long she must take medication since she is now feeling well.

- Assess therapeutic and adverse effects of treatment for this patient.
- Recommend strategies to maintain therapeutic efficacy while reducing or eliminating adverse effects.
- Educate the patient regarding need for continued maintenance treatment.

First-generation antipsychotic drugs have been available for many years, and more data are available on their use in pregnancy than for atypical antipsychotic drugs. Since experience with atypical antipsychotic drugs during pregnancy is limited, first-generation agents are often recommended for the treatment of acute mania during pregnancy.

Use of antidepressant drugs during pregnancy is discussed in the chapter on depression.

OUTCOME EVALUATION

Assessment of Therapeutic Effects

Effective interviewing skills and a therapeutic relationship with the patient are essential to assessing response to treatment. Understand the particular symptom profile and needs of individual patients. These become the primary therapeutic monitoring parameters. In addition to the clinical interview, some clinicians utilize symptom rating scales such as the Young Mania Rating Scale for mania and the Hamilton Depression Rating Scale (discussed in the chapter on depression). Check serum concentrations of mood-stabilizing drugs as a guide to dosage adjustment for optimal efficacy. The frequency of follow-up visits depends on response, tolerability, adherence, and other factors.

Adverse effects cause more non-adherence to prescribed therapy than any other factor. Monitor patients regularly for adverse effects and health status, especially since mood-stabilizing drugs and antipsychotic drugs commonly cause metabolic side effects such as weight gain. Repeat laboratory tests for renal and thyroid function for patients taking lithium, and hematology and liver function for patients taking carbamazepine or divalproex. Annual measurement of serum lipase may be advisable for patients taking divalproex. More specific discussion of metabolic side-effect monitoring of patients taking atypical antipsychotic drugs is discussed in the chapter on schizophrenia.

❽ *Patient education improves adherence to treatment, which reduces risk of relapse.* This is especially important since responsiveness to treatment declines as the number of mood episodes increases. Discuss the nature and chronic course of bipolar disorder and the risks of repeated relapses. Help patients understand that treatment of bipolar disorder is not a cure, but many patients can enjoy symptom-free or nearly symptom-free function. Make clear that long-term recovery is dependent on adherence to both pharmacologic and nonpharmacologic treatment. Explain the purpose of medication, common side effects to expect, and how to respond to them. Provide the patient and family with written information about medication indications, benefits, risks, and side effects. Discuss less frequent, but more dangerous side effects of drugs, and give written instructions on seeking medical attention immediately should they occur.



Patient Care and Monitoring

1. Assess the patient's symptoms and review the past history. Review the family history, including the history of response to treatment by family members.
2. Obtain an initial medical evaluation to rule out other causes of mood episodes.
3. Obtain a thorough medication use history, including present and past drugs; prescription and nonprescription drugs; the patient's self-assessment of response and side-effect problems; use of alcohol, tobacco, caffeine, and illicit substances; and use of herbal products and dietary supplements, as well as any allergies and adherence difficulties.
4. Assess potential drug-disease, drug-drug, and drug-food interactions.
5. Evaluate physiologic parameters that may influence pharmacokinetics.
6. Develop a plan for monitoring therapeutic outcomes, focusing on the individual symptom profile and level of function of each patient. Include a plan for dosage adjustments or alternate therapy if the patient fails to respond adequately. Include serum drug concentration monitoring as appropriate.
7. Develop a monitoring plan for drug side effects. Include measures to prevent side effects as well as management if they occur. Include appropriate laboratory measures.
8. Determine the role of nonpharmacologic therapy and how it is to be integrated with drug therapy.
9. Educate the patient on the nature of bipolar disorder and its treatment, what to expect with regard to response and side effects, and stress the need for adherence to treatment, even when feeling well.
10. Encourage a healthy lifestyle, including eliminating or stopping substance abuse and smoking, and encouraging proper nutrition and exercise.

ABBREVIATIONS

ACE-I:	angiotensin-converting enzyme inhibitor
CBT:	cognitive-behavioral therapy
DA	dopamine
DSM-IV-TR:	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
ECG:	electrocardiogram
ECT:	electroconvulsive therapy
FDA:	Food and Drug Administration
fMRI:	functional magnetic resonance imaging
FOI:	flight of ideas
GED:	general education diploma
5-HT:	serotonin

IOR:	ideas of reference
NE:	norepinephrine
NOS:	not otherwise specified
NSAID:	non-steroidal anti-inflammatory drug
PET:	positron emission tomography
THC:	tetrahydrocannabinol

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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37 Generalized Anxiety Disorder, Panic Disorder, and Social Anxiety Disorder

Sheila Botts, Tawny Bettinger, and Brian Greenlee



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Describe pathophysiologic findings in generalized anxiety, panic, and social anxiety disorder patients.
2. List common presenting symptoms of generalized anxiety, panic, and social anxiety disorders.
3. Identify the desired therapeutic outcomes for patients with generalized anxiety, panic, and social anxiety disorders.
4. Discuss appropriate lifestyle modifications and over-the-counter medication use.
5. Recommend psychotherapy and pharmacotherapy interventions for patients with generalized anxiety, panic, and social anxiety disorders.
6. Develop a monitoring plan for anxiety patients placed on specific medications.
7. Educate patients about their disease state and appropriate lifestyle modifications, as well as psychotherapy and pharmacotherapy for effective treatment.

Key Concepts

❶ The goals of therapy for generalized anxiety disorder are to acutely reduce the severity and duration of anxiety symptoms and restore overall functioning. The long-term goal in generalized anxiety disorder is to achieve and maintain remission.

❷ Antidepressants are considered first-line agents in the management of chronic generalized anxiety disorder.

❸ Benzodiazepines are recommended for acute treatment of generalized anxiety disorder when short-term relief is needed, as an adjunct during initiation of antidepressant therapy, or to improve sleep.

❹ The acute phase of panic disorder treatment lasts about 12 weeks and should result in marked reduction in panic attacks, ideally total elimination, and minimal anticipatory anxiety and social anxiety avoidance. Treatment should be continued to prevent relapse for an additional 12 to 18 months before attempting discontinuation.

❺ Panic disorder patients are more likely to experience stimulant-like side effects than patients with major depression and should be initiated on lower doses of antidepressant than those that are used for depression or other anxiety disorders.

❻ Antidepressants should be tapered when treatment is discontinued to avoid withdrawal symptoms, which include dysphoric mood, irritability, and agitation.

❼ The dose of benzodiazepine required for improvement in panic disorder generally is higher than that used in other anxiety disorders.

❽ Selective serotonin reuptake inhibitors (SSRIs) are considered the drugs of choice based on their tolerability and efficacy for social anxiety disorder as well as comorbid disorders.

❾ The onset of response to antidepressants in social anxiety disorder is delayed and may be as long as 8 to 12 weeks. Patients responding to medication should be continued on treatment for at least 1 year.

❿ Pharmacotherapy of social anxiety disorder should lead to improvement in physiologic symptoms of anxiety and fear, functionality, and overall well-being.

Anxiety is a normal response to stressful or fearful circumstances. Most people experience some degree of anxiety in reaction to stressful situations, such as final exams or giving a speech. This allows an individual to adapt to or manage the stressful/threatening situation. Anxiety symptoms generally

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Patient Encounter 1, Part 1

AX, a 27-year-old African-American woman, presents to your clinic with gastrointestinal complaints (e.g., constipation, bloating, and cramping) and fatigue. She is a single mother of three (ages 2, 3, and 6 years) and is a full-time college student. She states that she worries about everything: her grades, finances, the 6-year-old riding the school bus, etc. She states that "even if it's not important, I still worry." She has difficulty sleeping and says that she often feels like she might jump out of her skin. On one occasion she felt like she might be having a "heart attack or something."

- What manifestations described above are suggestive of an anxiety disorder?
- What additional information do you need to establish a diagnosis and develop a treatment plan?

are short-lived and do not necessarily impair function. Anxiety that becomes excessive, causes irrational thinking or behavior, and impairs a person's functioning is considered an anxiety disorder.

Anxiety disorders are among the most frequent mental disorders encountered by clinicians. Anxiety disorders often are missed or attributed incorrectly to other medical illnesses, with most patients being treated inadequately. The burden of detection and diagnosis most often falls to primary-care clinicians, to whom most patients present in the context of other complaints. Untreated anxiety disorders may result in increased healthcare utilization, morbidity and mortality, and poorer quality of life.

EPIDEMIOLOGY AND ETIOLOGY

Epidemiology

Prevalence

With a lifetime prevalence of 28.8%, anxiety disorders collectively represent the most prevalent *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition, Text Revision (DSM-IV-TR)[2] class of disorders, with specific phobia (12.5%) and social anxiety disorder (12.1%) being the most common.[3] Recent reports from the National Comorbidity Survey Revised (NCS-R) estimate the lifetime and 1-year prevalence of generalized anxiety disorder (GAD) for those 18 years of age and older to be 5.7% and 3.1%, respectively.[3,4] Rates for panic disorder (PD) are slightly lower, with an estimated 12-month prevalence of 2.7% and lifetime prevalence of 4.7%.

Most studies report higher rates of anxiety disorders among women (2:1 female:male) and older adults.[5] Data from the NCS-R show that while, in general, prevalence rates across the anxiety spectrum increase from the younger age group (18–29) to older age groups (30–44 and 45–59), rates are substantially lower for those older than age 59.[3]

Course of Illness

Anxiety disorders represent a diverse class of illnesses, with varied ages of onset. For example, according to the NCS-R epidemiologic study,[3] PD and GAD had a median age of onset of 24 and 31 years, respectively, whereas specific phobia and social anxiety disorder (SAD) tend to develop much earlier (median age of onset 7 and 13 years, respectively). Although GAD and PD may not manifest fully until adulthood, as many as half of adult anxiety patients report subthreshold symptoms during childhood.[6]

Anxiety disorders are characterized as chronic in nature with low rates of spontaneous symptom **remission** and high rates of relapse. Research illustrates that symptoms of anxiety disorders tend to wax and wane, with less than a third of patients remitting spontaneously.[7] In a 12-year follow-up study of anxiety disorder patients, recurrence rates were similar between PD with and without agoraphobia (56% and 58%, respectively) despite great differences seen in reported rates of remission (48% and 82% with treatment, respectively).[8] Fifty-eight percent of treated GAD patients experienced symptom remission, with 55% experiencing recurrence during the follow-up period. While individuals with SAD had the lowest remission rate with treatment (37%), those who did respond had the lowest rate of recurrence (39%) compared with patients with other anxiety disorders.

Remission, if achieved with treatment, is most likely to occur within the first 2 years of an index episode.[9] Similarly, the highest rates of relapse are seen within the first 2 years of the index episode. This suggests that many patients need ongoing maintenance treatment. Rates of remission do not appear to vary by sex.[9] Likewise, relapse rates do not appear to differ by sex for those who suffer from PD, GAD, or SAD. However, one study reported that women with PD without agoraphobia were three times more likely than men to experience a relapse of symptoms. Patients tend to spend a significant portion of time "being ill" during a particular episode. For example, in the 12-month follow-up study,[8] the average time spent "being ill" during an episode was 80% for SAD, 78% for PD, 74% for GAD, and 41% for PD without agoraphobia. With such a chronic course of illness and significant portion of time spent "being ill" during a particular episode, it is not surprising that patients afflicted with an anxiety disorder have been shown to display impaired psychosocial functioning and a compromised quality of life.[10,11] Appropriate treatment of an anxiety disorder has been shown to improve the patient's overall quality of life and psychosocial functioning.[11]

Comorbidity

Anxiety disorders rarely exist alone. More than 90% of individuals with an anxiety disorder have a lifetime history of one

or more other psychiatric disorders.[12] Depression is the most common lifetime comorbid illness, followed by alcohol- or substance-use disorders, as well as other co-occurring anxiety disorders, especially GAD and PD.[12] Generally speaking, the onset of SAD and GAD symptoms precedes major depressive disorder (MDD), whereas there is an equal chance of PD onset before, during, or after MDD. Regardless of when the comorbid psychiatric illness occurs, it can further complicate the anxiety picture and often is associated with even lower rates of remission and higher rates of relapse. It is essential that both disorders are addressed and treated appropriately.

Etiology

Both genetic and psychosocial factors appear to play a role in the initiation and expression of anxiety disorders.[13] Documentation of moderate genetic risk has been identified for all anxiety disorders, although some conflicting data do exist. Currently, no definitive gene or set of genes has been identified as being the causative factor for a specific anxiety disorder. Additionally, it is unclear if anxiety disorders share common genetic risk factors. Recent research suggests that genetic overlap may exist between GAD and PD and, to a lesser extent, SAD.[13]

It is possible that while genetics may create a vulnerable phenotype for an anxiety disorder, an individual's life stressors and means of coping with the stress also can play a significant role in precipitation and continued expression of the anxiety disorder.[14] In fact, some researchers believe that stressful life events may play a strong role in the onset of anxiety disorders, especially in GAD and PD.[13] It has been reported that those experiencing one or more negative life events have a three-fold increased chance of developing GAD.[5] Similar findings have been reported with PD.[14]

PATHOPHYSIOLOGY

The thalamus and amygdala are important in the generation of a normal fear response and play a central role in most anxiety disorders. They support the fundamental requirements of the nervous system's rapid detection and response system. Any such system requires a mechanism to detect a potential threat, evaluate the actual threat, and respond in a defensive or evasive manner. The thalamus plays a vital role in nearly every sensory modality, excluding olfaction and visceral sensation.[15] It provides the first real processing region to organize sensory data obtained from the environment. The thalamus passes information to higher cortical centers for finer processing and to the amygdala for rapid assessment of highly charged emotional information. The amygdala serves to provide emotional valence or the emotional importance of the information.[16] This helps the organism to act quickly on ambiguous but vital events. The cortex then performs a more detailed analysis, sending updates to the amygdala for comparison and any needed course corrections.[17] This finer evaluative process enables a decision on a course of action.

Anxiety becomes an anxiety disorder when activity of the fear-response network leads to maladaptive behavior or distress. Anxiety can become independent of stimuli as in PD, can be associated with benign stimuli as in phobias, or can continue beyond the necessary duration as in GAD. The precise mechanism by which these changes occur is unknown, but much has been discovered regarding how the amygdala effects changes throughout the brain and how this may be regulated by treatment[15] (Fig. 37–1).

Direct and indirect connections to the reticular activating system (RAS), a region spanning the medulla, pons, and midbrain, help to regulate arousal, vigilance, and fear. Modulation of these connections relies on the neurotransmitters serotonin

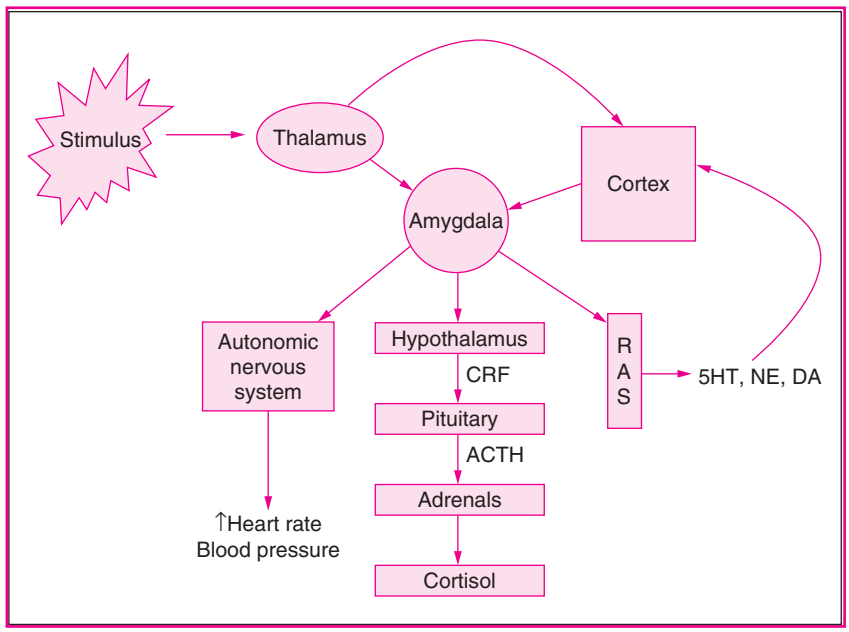


FIGURE 37–1. Neurocircuitry and key neurotransmitters involved in mediating anxiety disorders.

and norepinephrine, which have their primary origins in the RAS.[18] The amygdala sends projections to the hypothalamus influencing the autonomic nervous system to affect heart rate, blood pressure, and stress-associated changes. The amygdala also influences the **hypothalamic-pituitary-adrenal axis** (HPA axis), leading to a cascade of stress hormones.[19] One such hormone is cortisol, which, if elevated for prolonged periods, can have damaging effects on the brain and other organs. These are important targets in our understanding of how the amygdala regulates the fear response because they provide useful targets for current drug treatment and inform further research on anxiety disorders.

Noradrenergic System

Norepinephrine (NE)–producing cells reside primarily in a region of the brain called the **locus ceruleus (LC).** An increase in activity of cells in this region is associated with an increase in arousal, anxiety, and panic. Drugs such as yohimbine that increase activity of the LC can be anxiogenic, whereas drugs that decrease activity of the LC appear to improve anxiety symptoms. Furthermore, dysregulation of this region is implicated by elevated levels of NE or its metabolites in subjects with GAD, PD, and specific phobias.[19]

Serotonergic System

The **raphe nuclei** and the resident cell bodies of serotonin (5-HT)–producing neurons have an interesting yet complicated role in producing anxiety symptoms. One important role may be their ability to directly regulate the activity of cells in the LC. Activity of 5-HT cells in the raphe nuclei over time inhibits firing of noradrenergic cells in the LC. Other influences may be their ability to regulate cells in the prefrontal cortex and amygdala. Perhaps the strongest evidence for the involvement of the serotonergic system is the success of serotonin reuptake inhibitors in clinical treatment.[19]

GABA

Gamma-aminobutyric acid (GABA) plays an important role as an inhibitory neurotransmitter. The effects of GABA are nonspecific, and its role is complex. GABAergic drugs are used for acute anxiety reduction, but the lack of a specific target for their effect leads to multiple undesirable effects. Current research is focused on defining receptor subtypes that may allow for greater specificity in targeting anxiety symptoms.[20]

HPA Axis

The HPA axis provides a critical mechanism for regulation of the stress response and its effects on the brain and other organ systems. Several important hormones, including corticotropin-releasing hormone and cortisol, are involved in this pathway. These hormones regulate the effects of anxiety on the body and provide positive feedback to the brain.[19] A cycle of anxiety and sensitization by such feedback could, if unchecked, result in escalation of symptoms. Neuropeptides provide one mechanism to balance positive and negative feedback, helping to minimize such escalation.

Neuropeptides

Several neuropeptides are under current investigation for their role in anxiety disorders. Important neuropeptides include neuropeptide Y (NPY), substance P, and cholecystokinin. NPY appears to have a role in reducing the effect of stress hormones and inhibiting activity of the LC. Both mechanisms may contribute to the anxiolytic properties seen experimentally. Substance P may have anxiolytic and antidepressant properties. This may be due in part to its effects on corticotropin-releasing hormone.[21]

CLINICAL PRESENTATION AND DIAGNOSIS



Clinical Presentation and Diagnosis of GAD

General
Onset is typically in early adulthood. Anxiety emerges and dissipates more gradually than in PD. Laboratory evaluation usually is reserved for later onset, atypical presentation, or poor response to treatment.

Symptoms[2]
Excessive anxiety or worry involving multiple events or activities occurring more days than not for at least 6 months and associated with at least three of the following:

- Restlessness
- Easily fatigued
- Poor concentration
- Irritability
- Muscle tension
- Insomnia or unsatisfying sleep

Differential Diagnosis
Rule out underlying medical or psychiatric disorders and medications that may cause anxiety (Tables 37–1 and 37–2)

Laboratory Evaluation
- Basic metabolic panel
- Thyroid-stimulating hormone
- Polysomnogram



Clinical Presentation and Diagnosis of PD

General
Typically presents in late adolescence or early adulthood. Onset in older adults increases suspicion of relationship to medical disorders or substance use. Laboratory evaluation must be driven by history and physical examination.

Symptoms[2]
Recurrent, discrete episodes that typically develop rapidly and peak within 10 minutes involving at least four of the following symptoms:

- Palpitations or rapid heart rate
- Sweating
- Trembling or shaking
- Sensation of shortness of breath or smothering
- Feeling of choking
- Chest pain or discomfort
- Feeling dizzy or lightheaded
- Feeling of unreality or being detached from oneself
- Fear of dying
- Numbness or tingling sensation
- Chills or hot flushes

Differential Diagnosis
Rule out underlying medical or psychiatric disorders and medications that may cause anxiety (Tables 37–1 and 37–2).

Laboratory Evaluation
- Urine drug screen
- Basic metabolic panel
- Thyroid-stimulating hormone
- Electrocardiogram
- Holter monitor
- Electroencephalogram
- Urine vanillylmandelic acid (VMA)

TREATMENT: GENERALIZED ANXIETY DISORDER

Desired Outcomes

❶ *The goals of therapy for GAD are to acutely reduce the severity and duration of anxiety symptoms and restore overall functioning. The long-term goal in GAD is to achieve and maintain remission.* With a positive response to treatment, patients with GAD and comorbid depression should have minimal depressive symptoms.

General Approach to Treatment

Patients with GAD may be managed with psychotherapy, pharmacotherapy, or both. The treatment plan should be individualized based on the patient's symptom severity, comorbid illnesses, medical status, age, and preference. Patients with severe symptoms resulting in functional impairment should receive antianxiety medication.



Clinical Presentation and Diagnosis of SAD

General
Often occurs in context of other anxiety disorders. The feared social or performance situation can be limited to a specific social interaction (e.g., public speaking) or generalized to most any social interaction. Differs from specific phobia, in which the fear and anxiety are limited to a particular object or situation (e.g., insects, heights, public transportation).

Symptoms[2]
- Persistent fear of social interactions, during which time the individual is concerned about being embarrassed or being under scrutiny.
- Engaging in the feared activities can lead to extreme anxiety and panic.
- The fear leads to distress or avoidance of the situation sufficient enough to cause trouble in the patient's life.

Differential Diagnosis
Rule out underlying medical or psychiatric disorders and medications that may cause anxiety (Tables 37–1 and 37–2).

Laboratory Evaluation
Limited value. Laboratory investigation is of limited value and should be pursued only in context of other history or physical examination findings.



Patient Encounter 1, Part 2

AX returns to your clinic 4 months later stating that despite meeting with the school psychologist a few times, she continues to have problems. In addition to worrying and feeling nervous, she feels down a lot. "I don't have the energy to play with my children. I obsess over everything. My grades have really gone down hill. I cry a lot and feel hopeless."

PMH
Irritable bowel syndrome, GAD

FH
Mother treated for depression; father, ETOH dependence

SH
Drinks ETOH occasionally; cigarettes, 1 pack per day; lives independently with 3 children

Meds
Centrum multivitamin

- Given this information, what is your assessment of this patient?
- Develop a treatment plan, including nonpharmacologic and pharmacologic recommendations, duration of therapy, and monitoring plan.

TABLE 37–1. Medical Conditions That Can Cause Anxiety[2,22,23]

Psychiatric Disorders
Mood disorders, hypochondriasis, personality disorders, alcohol/substance abuse, alcohol/substance withdrawal, other anxiety disorders

Neurologic Disorders
CVA, seizure disorders, dementia, stroke, migraine, encephalitis, vestibular dysfunction

Cardiovascular Disorders
Angina, arrhythmias, congestive heart failure, mitral valve prolapse, myocardial infarction

Endocrine and Metabolic Disorders
Hypo/hyperthyroidism, hypoglycemia, Cushing's disease, Addison's disease, pheochromocytoma, hyperadrenocorticism, hyponatremia, hyperkalemia, vitamin B_{12} deficiency

Respiratory Disorders
Asthma, COPD, pulmonary embolism, pneumonia, hyperventilation

Other
Carcinoid syndrome, anemias, systemic lupus erythematosus

COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident.

Nonpharmacologic Therapy

Nonpharmacologic therapy includes psychoeducation, exercise, stress management, and psychotherapy. Psychoeducation should address pertinent information on GAD and its management. Patients should be instructed to avoid stimulating agents such as caffeine, decongestants, diet pills, and excessive alcohol use. Regular exercise is also recommended. Cognitive-behavioral therapy (CBT) is the most effective psychological therapy for GAD patients. CBT helps patients to recognize and alter patterns of distorted thinking and dysfunctional behavior. Some trials suggest that treatment gains with CBT may be maintained for up to 1 year.[25] It is unclear if the combination of CBT and medication is more effective than either treatment alone.

TABLE 37–2. Medications Associated with Anxiety Symptoms[2,22–24]

Category	Examples
Anticonvulsants	Carbamazepine, ethosuximide
Antidepressants	Bupropion, SSRIs, TCAs
Antihypertensives	Felodipine
Antimicrobials	Cephalosporins, ofloxacin, isoniazid
Antiparkinson drugs	Levodopa
Bronchodilators	Albuterol, isoproterenol, theophylline
Corticosteroids	Prednisone, methylprednisolone
Decongestants	Pseudoephedrine, phenylephrine
Herbals	Ma huang, St. John's wort, ginseng, guarana, belladonna
NSAIDs	Ibuprofen, indomethacin
Stimulants	Amphetamines, caffeine, cocaine, methylphenidate
Thyroid hormones	Levothyroxine
Toxicity	Anticholinergics, antihistamines, digoxin
Withdrawal of CNS depressants (abrupt)	Alcohol, barbiturates, benzodiazepines

SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; NSAIDs, non-steroidal anti-inflammatory drugs.

Pharmacologic Therapy

Antidepressants, benzodiazepines, buspirone, hydroxyzine, and pregabalin all have controlled clinical trial data supporting their use in GAD. Antidepressants have replaced benzodiazepines as the drugs of choice for chronic GAD owing to a tolerable side-effect profile, no risk for dependency, and efficacy in common comorbid conditions including depression, panic, obsessive-compulsive disorder (OCD), and SAD. Benzodiazepines remain the most effective and commonly used treatment for short-term management of anxiety where immediate relief of symptoms is desired. They are also recommended for intermittent or adjunctive use during GAD exacerbation or for sleep disturbance during the initiation of antidepressant treatment.[26] Buspirone and pregabalin are alternative agents for patients with GAD without depression. Hydroxyzine use is less desirable for long-term treatment owing to side effects.

Patients with GAD should be treated to remission of symptoms. While data are lacking on the optimal duration of pharmacotherapy, most guidelines recommend continuing treatment for an additional 3 to 10 months.[25–28] An algorithm for the pharmacologic management of GAD is shown in Fig. 37–2.

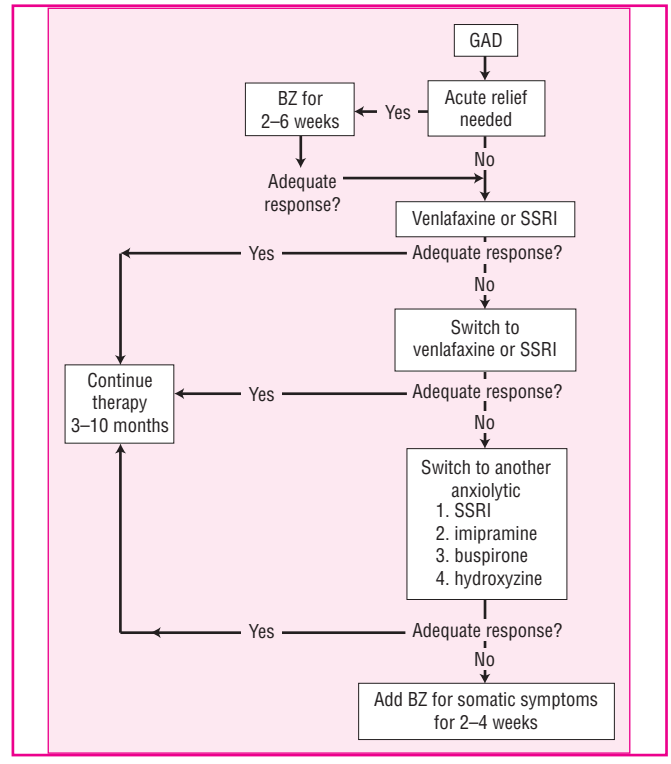


FIGURE 37–2. Treatment alogorithm for GAD. SSRI = selective serotonin reuptake inhibitor; BZ = benzodiazepine. (Reprinted, with permission, from reference 24.)

TABLE 37–3. Antidepressants Used in the Treatment of Generalized Anxiety Disorder[24,29,30]

Medication Class	Recommended Starting Dose (mg/day)	Usual Therapeutic Dosage Range (mg/day)
SSRIs		
Citalopram (Celexa)	20	20–50
Escitalopram[a] (Lexapro)	10	10–20
Fluoxetine (Prozac)	20	20–80
Fluvoxamine (Luvox)	50	100–300
Paroxetine	20	20–50
Paroxetine CR (Paxil, Paxil CR)	25	25–62.5
Sertraline (Zoloft)	50–100	50–200
SNRI		
Venlafaxine XR[a] (Effexor XR)	75	75–300
TCAs		
Imipramine (Tofranil)	50–75	75–200

[a]FDA approved for use in generalized anxiety disorder.
SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressant

Antidepressants

❷ *Antidepressants (Table 37–3) are considered first-line agents in the management of chronic GAD.* These agents reduce the psychic symptoms (e.g., worry and apprehension) of anxiety with a modest effect on autonomic or somatic symptoms (e.g., tremor, rapid heart rate, and/or sweating). All antidepressants evaluated have resulted in a similar degree of anxiety reduction. The onset of antianxiety effect is delayed 2 to 4 weeks. Venlafaxine and SSRIs usually are preferred over tricyclic antidepressants (TCAs) such as imipramine owing to improved safety and tolerability. Selection of a particular antidepressant agent generally is based on history of prior **response,** side-effect profile, drug-interaction profile (discussed Chap. 35), cost, or formulary availability.

Antidepressants modulate synaptic 5-HT, NE, and/or dopamine (DA) reuptake and receptor-activated neuronal signal transduction. These intracellular changes ultimately modify the expression of genes and proteins important in stress response (e.g., increase messenger RNA for glucocorticoid receptors and brain-derived neurotrophic factor and decrease mRNA expression for corticotropin-releasing factor).[31] Activation of these "stress adapting" pathways is thought to improve both somatic symptoms and psychic distress experienced in anxiety.[31]

SNRI (Venlafaxine)

Venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), alleviates anxiety in GAD patients with and without depression. Venlafaxine was shown to reduce anxiety effectively at doses 75 to 225 mg/day in 8-week trials, and response was maintained over an additional 6 months of treatment.[32,33] Venlafaxine has more favorable safety and side-effect profiles than TCAs. The most common side effects reported with venlafaxine by GAD patients are nausea, somnolence, dry mouth, dizziness, sweating, constipation, and anorexia.[34]

SSRIs

The SSRIs paroxetine, escitalopram, and sertraline have been shown to be significantly more effective than placebo in reducing anxiety symptoms. Paroxetine at doses of 20 and 40 mg/day achieved response in 62% and 68% of patients, respectively, over 8 weeks of treatment.[35] Remission occurred in 30% and 36%, respectively. In a 24-week relapse-prevention study, paroxetine was more effective than placebo at maintaining response, and patients were more likely to achieve remission with continued treatment (42.5% at 8 weeks versus 73% at 24 weeks).[36] In GAD trials, paroxetine was associated with a high rate of somnolence, nausea, abnormal ejaculation, dry mouth, decreased libido, and asthenia compared with placebo.[35] Escitalopram, in a dose range of 10 to 20 mg/day, was more effective than placebo in patients with GAD without depression. Fifty-eight percent of patients on escitalopram achieved response versus 38% on placebo over the 8 weeks of treatment.[37] Escitalopram was associated with headache, nausea, somnolence, upper respiratory tract infection, decreased libido, ejaculation disorder, and anorgasmia.[37] Sertraline was more efficacious than placebo in patients with GAD being treated for 12 weeks. Sertraline treatment resulted in 56% of patients achieving response, whereas 31% achieved remission.[38] Sertraline was associated with increased rates of nausea, insomnia, sweating, decreased libido, diarrhea, fatigue, and ejaculation disorder.[38] Limited comparative trial data suggest comparable outcomes between these SSRIs.[39,40] SSRI therapy is better tolerated than TCAs, and tolerability is similar to that with venlafaxine.

TCAs

Imipramine treatment resulted in a higher rate of remission of anxiety symptoms than trazodone, diazepam, or placebo (e.g., 73% versus 69% versus 66% versus 47%) in an 8-week controlled trial of DSM-III–diagnosed GAD patients. Antidepressants were more effective than diazepam or placebo in reducing psychic symptoms of anxiety. The use of TCAs generally is limited by bothersome adverse effects (e.g., sedation, orthostatic hypotension, anticholinergic effects, and weight gain).

Benzodiazepines

❸ *Benzodiazepines are recommended for acute treatment of GAD when short-term relief is needed, as an adjunct during initiation of antidepressant therapy, or to improve sleep.*[25,26] Benzodiazepine treatment results in a significant improvement in 65% to 75% of GAD patients, with most of the

improvement occurring in the initial 2 weeks of therapy.[41] They are more effective in reducing somatic symptoms of anxiety than psychic symptoms. The major disadvantages of benzodiazepines are their lack of effectiveness in treating depression and the risk for dependency and abuse. Benzodiazepines should be avoided in patients with chemical dependency.

Benzodiazepines exert their effects by enhancing transmission of the inhibitory neurotransmitter GABA through interaction with the $GABA_A$-receptor complex.[25] Although all benzodiazepines possess anxiolytic properties, only 7 of the 13 currently marketed agents are approved by the Food and Drug Administration (FDA) for the treatment of anxiety disorders (Table 37–4). All benzodiazepines are expected to provide equivalent benefit when given in comparable doses. Benzodiazpines differ substantially in their pharmacokinetic properties and potency for the $GABA_A$-receptor site.

Benzodiazepines are metabolized by hepatic oxidation (cytochrome P-450 3A4) and glucuronide conjugation. Lorazepam and oxazepam bypass hepatic oxidation and are conjugated only. They are preferred agents for patients with reduced hepatic function secondary to aging or disease. Many benzodiazepines are metabolized to long-acting metabolites (Table 37–4) that provide long-lasting anxiety relief. Drugs that either inhibit or induce CYP450 isozymes or glucuronidation are the major source of drug interactions (Table 37–5).

The most common side effects associated with benzodiazepine therapy include central nervous system (CNS) depressive effects (e.g., drowsiness, sedation, psychomotor impairment, and ataxia) and cognitive effects (e.g., poor recall memory and **anterograde amnesia**). Anterograde amnesia is more likely to occur with high-potency benzodiazepines such as lorazepam or alprazolam.[42] Some patients also may be disinhibited with benzodiazepine treatment and experience confusion, irritability, aggression, and excitement.[42]

Discontinuation of benzodiazepines may be associated with withdrawal, rebound anxiety, and a high rate of relapse. Higher doses of benzodiazepines and longer duration of therapy increase the severity of withdrawal and risk of seizures after abrupt or rapid discontinuation. Patients should be tapered rather than discontinued abruptly from benzodiazepine therapy to avoid withdrawal symptoms. The duration of the taper should increase with extended duration of benzodiazepine therapy.[27] For example, patients on benzodiazepine therapy over 2 to 6 months should be tapered over 2 to 8 weeks, whereas patients receiving 12 months of treatment should be tapered over 2 to 4 months. A general approach to the taper is to reduce the dose by 25% every 5 to 7 days until reaching half the original dose and then decreasing by 10% to 12% per week until discontinued. Patients should expect minor withdrawal symptoms and discomfort even when tapering. Rebound symptoms (e.g., return of original symptoms at increased intensity) are transient. The patient should be counseled so that rebound anxiety is not interpreted as a relapse. Relapse or recurrence of anxiety may occur in as many as 50% of patients discontinuing benzodiazepine treatment.[41,43] It is unclear if this relapse rate represents an inferiority of benzodiazepines or supports the chronic nature of GAD.

TABLE 37–4. Benzodiazepine Comparison Chart[24,30]

Drug Name (Brand Name) *Active Metabolites*	Time to Peak Concentration (hour)	Half-Life Range (hour)	Approved Dosage Range (mg/day)	Dose Equivalent (mg)
Alprazolam[a,b] (Xanax)	1–2	12–15	1–4 (GAD) 1–10 (PD)	0.5
Chlordiazepoxide[a] (Librium)	1–4	5–30	25–100	10
Desmethylchlordiazepoxide		18		
Demoxepam		14–95		
Desmethyldiazepam		40–120		
Oxazepam		5–15		
Clonazepam[b] (Klonopin)	1–4	18–50	1–4	0.25
Clorazepate[a] (Tranzene)	1–2		7.5–60	7.5
Desmethyldiazepam		40–120		
Oxazepam		5–15		
Diazepam[a] (Valium)	0.5–2	20–80	2–40	5
Desmethyldiazepam		40–120		
Temazepam		8–15		
Oxazepam		5–15		
Lorazepam[a] (Ativan)	2–4	10–20	0.5–10	0.75–1
Oxazepam[a] (Serax)	2–4	5–15	30–120	15

[a]FDA approved for use in generalized anxiety disorder.
[b]FDA approved for use in panic disorder.
GAD, generalized anxiety disorder; PD, panic disorder.

TABLE 37–5. Pharmacokinetic Drug Interactions with Benzodiazepines[44]

Drug	Effect
Alcohol (chronic)	Increased Cl of BZs
Carbamazepine	Increased Cl of alprazolam
Cimetidine	Decreased Cl of alprazolam, diazepam, chlordiazepoxide, and clorazepate and increased $t_{1/2}$
Disulfiram	Decreased Cl of alprazolam and diazepam
Erythromycin	Decreased Cl of alprazolam
Fluoxetine	Decreased Cl of alprazolam and diazepam
Fluvoxamine	Decreased Cl of alprazolam and prolonged $t_{1/2}$
Itraconazole	Potentially decreased Cl of alprazolam and diazepam
Ketaconazole	Potentially decreased Cl of alprazolam
Nefazodone	Decreased Cl of alprazolam, AUC doubled, and $t_{1/2}$ prolonged
Omeprazole	Decreased Cl of diazepam
Oral contraceptives	Increased free concentration of chlordiazepoxide and slightly decreased Cl; decreased Cl and increased $t_{1/2}$ of diazepam and alprazolam
Paroxetine	Decreased Cl of alprazolam
Phenobarbital	Increased Cl of clonazepam and reduced $t_{1/2}$
Phenytoin	Increased Cl of clonazepam and reduced $t_{1/2}$
Probenecid	Decreased Cl of lorazepam and prolonged $t_{1/2}$
Propranolol	Decreased Cl of diazepam and prolonged $t_{1/2}$
Ranitidine	Decreased absorption of diazepam
Rifampin	Increased metabolism of diazepam
Theophylline	Decreased alprazolam concentrations
Valproate	Decreased Cl of lorazepam

AUC, area under the plasma concentration curve; BZ, benzodiazepine; Cl, clearance; $t_{1/2}$, elimination half-life.
Compiled from reference 49.
Reprinted, with permission, from Kirkwood CK, Melton ST. Anxiety disorders: I. Generalized anxiety, panic, and social anxiety disorders. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw Hill; 2005: 1294.

Buspirone

Buspirone, a 5-HT_{1A} partial agonist, is thought to exert its anxiolytic effects by reducing presynaptic 5-HT firing.[44] Unlike benzodiazepines, it does not have abuse potential, cause withdrawal reactions, or potentiate alcohol and sedative-hypnotic effects. However, it has a gradual onset of action (i.e., 2 weeks) and does not provide immediate anxiety relief. Buspirone is considered a second-line agent for GAD owing to inconsistent data regarding its efficacy in chronic GAD or GAD with comorbid depression.[25,26] Some research suggests that buspirone is less effective in patients who have been treated previously (4 weeks to 5 years) with benzodiazepines.[45]

Buspirone should be initiated at a dose of 7.5 mg twice daily and titrated in 5 mg/day increments (every 2–3 days) to a usual target dose of 20 to 30 mg/day.[41] The maximum daily dose is considered to be 60 mg/day.

Buspirone generally is well tolerated and does not cause sedation. Most common side effects include dizziness, nausea, and headaches. Drugs that inhibit CYP3A4 (e.g., verapamil, diltiazem, itraconazole, fluvoxamine, nefazodone, and erythromycin) can increase buspirone levels. Likewise, enzyme inducers such as rifampin can reduce buspirone levels significantly. Bupirone may increase blood pressure when coadministered with an monoamine oxidase inhibitor (MAOI).

Alternative Agents

Hydroxyzine, kava kava, and pregabalin are alternative agents. Hydroxyzine may be effective for acute reduction of somatic symptoms of anxiety.[26] It does not improve psychic features of anxiety and does not treat depression or other common comorbid anxiety disorders. Kava kava, while potentially effective, is no longer recommended owing to reports of hepatotoxicity.[46] Pregabalin is mechanistically unique for an anxiolytic. It is a presynaptic modulator of excessive excitatory neurotransmitter release. It accomplishes this by selectively binding to the α_2-δ subunit of voltage-gated calcium channels. In a 4-week controlled trial versus alprazolam and placebo, pregabalin was effective for both somatic and psychic symptoms of anxiety with an onset of effect similar to alprazolam.[47] Pregabalin has an elimination half-life of approximately 6 hours and must be dosed two to three times daily. It is excreted renally and has a low risk of drug-drug interactions. Pregabalin is a schedule V controlled substance owing to a propensity to cause euphoria and risk of withdrawal symptoms when discontinued abruptly. Pregabalin should be used with caution in patients with a current or past history of substance abuse. Pregabalin is not beneficial for depression or other anxiety disorders, and long-term effectiveness in GAD is not yet established.

Outcome Evaluation

Assess patients for improvement of anxiety symptoms and for return to baseline occupational, social, and interpersonal functioning. With effective treatment, the patient should have no or minimal symptoms of anxiety or depression. While drug therapy is being initiated, evaluate patients more frequently to ensure tolerability and response. Increase the dose in patients exhibiting a partial response after 2 to 4 weeks on an antidepressant or 2 weeks on a benzodiazepine. Individualize the duration of treatment because some patients require up to one year of treatment.[27]

TREATMENT: PANIC DISORDER

Desired Outcomes

The main objectives of treatment are to reduce the severity and frequency of panic attacks, reduce anticipatory anxiety and agoraphobic behavior, and minimize symptoms of depression or other comorbid disorders.[48] The long-term goal is to achieve and sustain remission.

General Approach to Treatment

Treatment options include medication, psychotherapy (e.g., CBT preferred), or a combination of both. In some cases, pharmacotherapy will follow psychotherapy treatments when full response is not realized. Patients with panic symptoms without agoraphobia may respond to pharmacotherapy alone. Agoraphobic symptoms generally take longer to respond than panic symptoms. ❹ *The acute phase of PD treatment lasts about 12 weeks and should result in marked reduction in panic attacks, ideally total elimination, and minimal anticipatory anxiety and phobic avoidance. Treatment should be continued to prevent relapse for an additional 12 to 18 months before attempting discontinuation.*[48,49] Patients who relapse following discontinuation of medication should have therapy resumed.[49]

Nonpharmacologic Therapy

Patients with PD should be counseled to avoid stimulant agents (e.g., decongestants, diet pills, and caffeine) that may precipitate a panic attack. CBT consists of psychoeducation, continuous panic monitoring, breathing retraining, cognitive restructuring, and exposure to fear cues.[48] CBT is not a standardized treatment and may involve these features to varying degree. It is unclear if the individual components have differential benefits. Exposure therapy is useful for patients with phobic avoidance. CBT is considered a first-line treatment of PD, with efficacy similar to that of pharmacotherapy. In a large placebo-controlled trial comparing CBT with imipramine or combination (CBT + imipramine), CBT was as effective as the antidepressant after 12 weeks. Patients receiving CBT were less likely to relapse during the 6 months after treatment discontinuation.[50,51]

Pharmacologic Therapy

PD may be treated successfully with TCAs, SSRIs, SNRIs, or MAOIs, as well as benzodiazepines[51,52] (Table 37–6). While all these agents are similarly effective, SSRIs have become the treatment of choice in PD. Benzodiazepines often are used concomitantly with antidepressants, especially early in treatment,

TABLE 37–6. Antidepressants Used in the Treatment of Panic Disorder[24,30,51]

Medication Class	Recommended Starting Dose (mg/day)	Usual Therapeutic Dosage Range (mg/day)	Advantages	Disadvantages
SSRIs/SNRI			*SSRIs (in general)*	*SSRIs (in general)*
Citalopram	10	20–60	Antidepressant activity; antianxiety activity; single daily dosing (all but fluvoxamine); low toxicity; some available in generic	Activation; delayed onset of action; may precipitate mania; sexual side effects; GI side effects
Escitalopram	5–10	10–20		
Fluoxetine[a]	5–10	20–60		
Fluvoxamine	25	100–300		
Paroxetine[a]	10	20–60		
Sertraline[a]	25	50–200		
Venlafaxine XR[a]	37.5	75–225		
TCAs			*TCAs (in general)*	*TCAs (in general)*
Clomipramine	25 mg (twice a day)	75–250	Established efficacy; available in generic	Activation; sedation; anticholinergic effects; cardiovascular effects; delayed onset of action; may precipitate mania; sexual side effects; toxic in overdose; weight gain
Imipramine[a]	10–25	75–250		
MAOI				
Phenelzine	15	45–90	Antidepressant effects; available in generic	Dietary restrictions; drug interactions; weight gain; orthostasis; may precipitate mania

[a]FDA approved for use in panic disorder.
SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; MAOI, monoamine oxidase inhibitor.

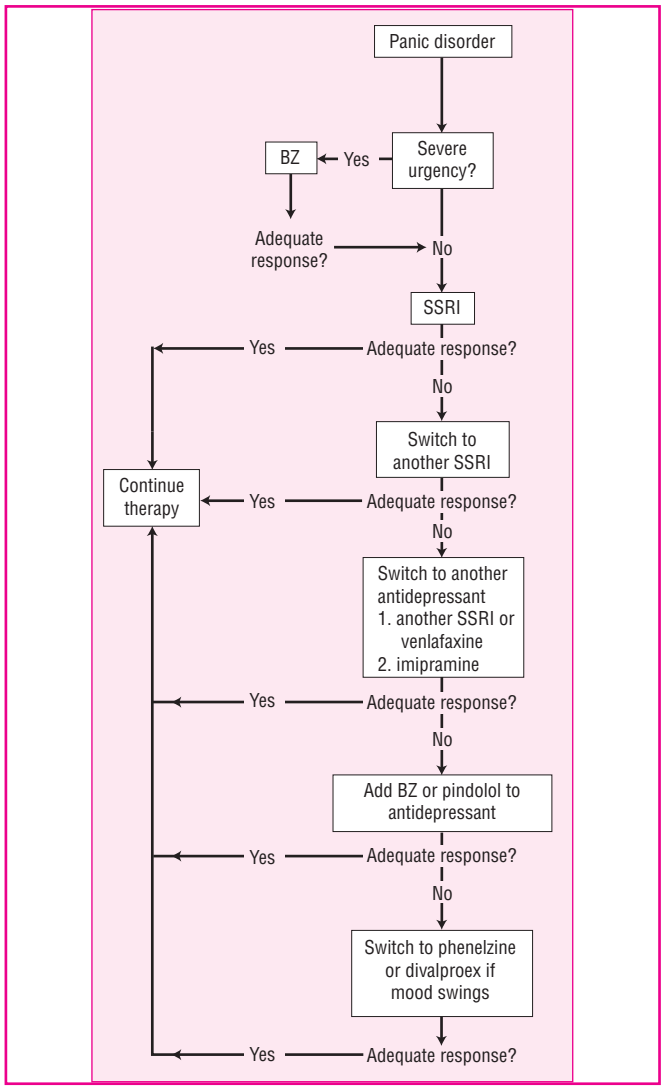


FIGURE 37–3. Algorithm for the pharmacotherapy of panic disorder. (Reprinted, with permission, from reference 24.)

or as monotherapy to acutely reduce panic symptoms. They are not preferred for long-term treatment but may be used when patients fail several antidepressant trials.[49] PD patients with comorbid depression should be treated with an antidepressant. An algorithm for pharmacologic management of PD appears in Fig. 37–3.

Antidepressants

Antidepressants have a delayed onset of antipanic effect, typically 4 weeks, with optimal response at 6 to 12 weeks. Reduction of anticipatory anxiety and phobic avoidance generally follows improvement in panic symptoms. ❺ *PD patients are more likely to experience stimulant-like side effects than patients with depression, and they should be initiated on lower doses (Table 37–6) of antidepressant than those that are used for depression or other anxiety disorders.* Target doses are similar to those used in depression. ❻ *Antidepressants should be tapered when treatment is discontinued to avoid withdrawal symptoms.*

TCAs

Treatment with imipramine, the most studied TCA, leaves 45% to 70% of patients panic free. Both desipramine and clomipramine have demonstrated effectiveness in PD as well. Despite their efficacy, TCAs are considered second- or third-line pharmacotherapy due to poorer tolerability and toxicity on overdose.[48,49] TCAs are associated with a greater rate of discontinuation from treatment than SSRIs.[53] PD patients taking TCAs may experience anticholinergic effects, orthostatic hypotension, sweating, sleep disturbances, dizziness, fatigue, sexual dysfunction, and weight gain. Stimulant-like side effects occur in up to 40% of patients.[49]

SSRIs

SSRIs are the drugs of choice for PD. All SSRIs have demonstrated effectiveness in controlled trials, with 60% to 80% of patients achieving a panic-free state.[28,48,49] With similar efficacy reported and no trials comparing SSRIs with other SSRIs, selection generally is based on pharmacokinetics, drug interactions, side effects, and cost differences (see Chap. 35 for more discussion). The most common side effects of SSRIs include headaches, irritability, nausea and other gastrointestinal complaints, insomnia, sexual dysfunction, increased anxiety, drowsiness, and tremor.[49] SSRIs should not be discontinued abruptly to avoid a withdrawal syndrome characterized by dysphoric mood, irritability, and agitation.

SNRIs

Venlafaxine was approved by the FDA recently for the treatment of PD. Venlafaxine in doses of 75 to 225 mg/day reduced panic and anticipatory anxiety in short-term controlled trials. The most common side effects include anorexia, dry mouth, constipation, somnolence, tremor, abnormal ejaculation, and sweating.[52]

MAOIs

MAOIs have not been evaluated systematically for treatment of PD under the current diagnostic classification and generally are reserved for patients who are refractory to other treatments.[48,49] MAOIs have significant side effects that limit adherence. Additionally, patients must adhere to dietary restriction of tyramine and avoid sympathomimetic drugs to avoid hypertensive crisis.

The reversible inhibitors of monoamine oxidase (RIMAs) brofaramine and meclobemide have been studied with mixed results.[48] Neither is approved for use in the United States, but they are available in Canada.

Others

Bupropion, trazodone, and nefazodone are not recommended for treatment of PD.

Benzodiazepines

Benzodiazpines are effective antipanic agents with significant effects on anticipatory anxiety and phobic behaviors. Alprazolam, the one studied most extensively, is associated with significant panic reduction after 1 week of therapy (e.g., 55%–75% panic free).[49] Benzodiazepines achieve similar outcomes to antidepressants over extended treatment, but benzodiazepine-treated patients are more likely to relapse when the drug is discontinued.[49] The risk for dependence and withdrawal and lack of efficacy for depression are significant concerns for long-term treatment of PD.[49] There is no evidence, however, that patients require dose escalation during extended treatment. This suggests that tolerance to therapeutic effect does not occur. Patients with PD do experience greater rebound anxiety and relapse when discontinuing benzodiazepines than do GAD patients. Tapering should be done at a slower rate and over a more extended period of time than with other anxiety disorders.[28,49]

❼ *The dose of benzodiazepine required for improvement generally is higher than that used in other anxiety disorders,* and this may explain why high-potency agents such as alprazolam and clonazepam generally are preferred. Lorazepam and diazepam, when given in equivalent doses, produce similar treatment benefits.[48,49] Doses should be titrated to response (Table 37–4). The use of extended-release alprazolam or clonazepam will minimize breakthrough panic symptoms that are sometimes observed with immediate-release alprazolam.[55]

Side effects associated with benzodiazepines in PD patients are similar to those observed in other disorders. Sedation, fatigue, and cognitive impairment are the most commonly reported side effects.[49] Benzodiazepines should be avoided in patients with current substance abuse, a history of such, dependence, or sleep apnea. Additionally, caution should be used in older adults because they have more pronounced psychomotor and cognitive effects.

Outcome Evaluation

Evaluate patients for symptom improvement frequently (e.g., weekly) during the first 4 weeks of therapy. The goal is to alleviate panic attacks and reduce anticipatory anxiety and phobic avoidance with resumption of normal activities. Alter the therapy of patients who do not achieve a significant reduction in panic symptoms after 6 to 8 weeks of an adequate dose of antidepressant or 3 weeks of a benzodiazepine. Regularly evaluate patients for adverse effects, and educate them about appropriate expectations of drug therapy.

Once the patient has achieved a significant response, continue therapy for at least 1 year. Evaluate for symptom relapse as well as adverse effects that may emerge with continued treatment (e.g., weight gain and sexual dysfunction). During drug discontinuation, monitor frequently for withdrawal, rebound anxiety, and relapse.

TREATMENT: SOCIAL ANXIETY DISORDER

Desired Outcomes

SAD is a chronic disorder that begins in adolescence and occurs with significant functional impairment and high rates of comorbidity. The goal of acute treatment is to reduce physiologic symptoms of anxiety, fear of social situations, and phobic behaviors. Patients with comordid depression should have a significant reduction in depressive symptoms. The long-term goal is to restore social functioning and improve the patient's quality of life.

General Approach to Treatment

Patients with SAD may be managed with pharmacotherapy or psychotherapy. There is insufficient evidence to recommend one treatment over the other, and data are lacking on the benefits of combining treatment modalities. Pharmacotherapy often is the first choice of treatment owing to relative greater access and reduced cost compared with psychotherapy.[56] Patients with SAD generally respond slowly to treatment, and many will not achieve a full response. Relapse is common when patients are discontinued after effective short-term treatment. Patients generally are continued on treatment for at least 1 year before attempting discontinuation.



Patient Encounter 2

BB, a 34-year-old white woman with generalized social anxiety disorder, is transferring her care to your clinic. She has been maintained on diazepam 10 mg twice daily for the past 4 years for her SAD. She states that her current therapy has her anxiety under control, and she is performing her duties as an office manager without problems. She has joined a gym recently and is attending a church social for single women once monthly. She has noticed she has difficulty thinking "sharply" and is more forgetful. She occasionally feels sad and becomes tearful but is usually able to "pick herself up." She is moderately overweight (BMI 29) with no other current medical problems. Denies ETOH or other substance use.

- Develop a treatment plan for this patient. Include (1) goals of therapy, (2) a detailed therapeutic plan, and (3) a monitoring plan for recommended therapy.

Nonpharmacologic Therapy

Patient education on disease course, treatment options, and expectations is essential given the chronic nature and functional impairment of SAD. Support groups may be beneficial for some patients. CBT targets avoidance-learning and negative-thinking patterns associated with social anxiety by exposing the patient to a feared situation. CBT is effective for reducing anxiety and phobic behaviors and leads to a greater likelihood of maintaining response after treatment discontinuation than does pharmacotherapy.[56]

Pharmacologic Therapy

Several pharmacologic agents have demonstrated effectiveness in SAD, including SSRIs, venlafaxine, phenelzine, RIMAs, benzodiazepines, gabapentin, and pregabalin. ❽ *SSRIs are considered the drugs of choice based on their tolerability and efficacy for SAD as well as comorbid disorders.* ❾ *The onset of response for antidepressants is delayed and may be as long as 8 to 12 weeks.*[28,57] *Patients responding to medication should be continued on treatment for at least 1 year.* Many will relapse on discontinuation, and there are no clear predictive factors of who will maintain response.[58] Some patients may elect more long-term treatment owing to fear of relapse. The clinician may use the suggested treatment algorithm (Fig. 37–4) to develop a treatment plan.

SSRIs and Venlafaxine

The efficacy of paroxetine, sertraline, and escitalopram was established in large controlled trials.[58–60] SSRIs improve social anxiety and phobic avoidance and reduce overall disability. Approximately 50% of patients achieve response during acute treatment. Limited data suggest that both fluvoxamine and citalopram are effective in SAD. Fluoxetine is not effective.[57,58]

The initial dose of SSRI is similar to that used in depression. Patients should be titrated as tolerated to response. Many patients will require maximum recommended daily doses. Patients with comorbid panic disorder should be started on lower doses (Table 37–4). When discontinuing SSRIs, the dose should be tapered slowly to avoid withdrawal symptoms, with the possible exception of fluoxetine. Relapse rates may be as high as 50%, and patients should be monitored closely for several weeks.[58] Side effects of SSRIs in SAD patients are similar to those seen in depression and most commonly include nausea, sexual dysfunction, somnolence, and sweating.

Venlafaxine extended release, in doses of 75 to 225 mg/day, improves social anxiety, performance, and avoidance behavior with a reduction in disability.[61] Treatment with venlafaxine results in response rates similar to those seen with paroxetine.[60] Venlafaxine may be effective in SSRI non-responders.[62] As with SSRIs, doses should be tapered slowly when discontinuing therapy. Tolerability is similar to that observed in depression trials with venlafaxine extended release. Common side effects are anorexia, dry mouth, nausea, insomnia, and sexual dysfunction.

MAOIs/RIMAs

The MAOI phenelzine and the RIMAs brofaramine and meclobemide are effective in SAD. Phenelzine is effective in 64% to 69% of SAD patients.[58] It is generally reserved for treatment-refractory patients owing to dietary restrictions,

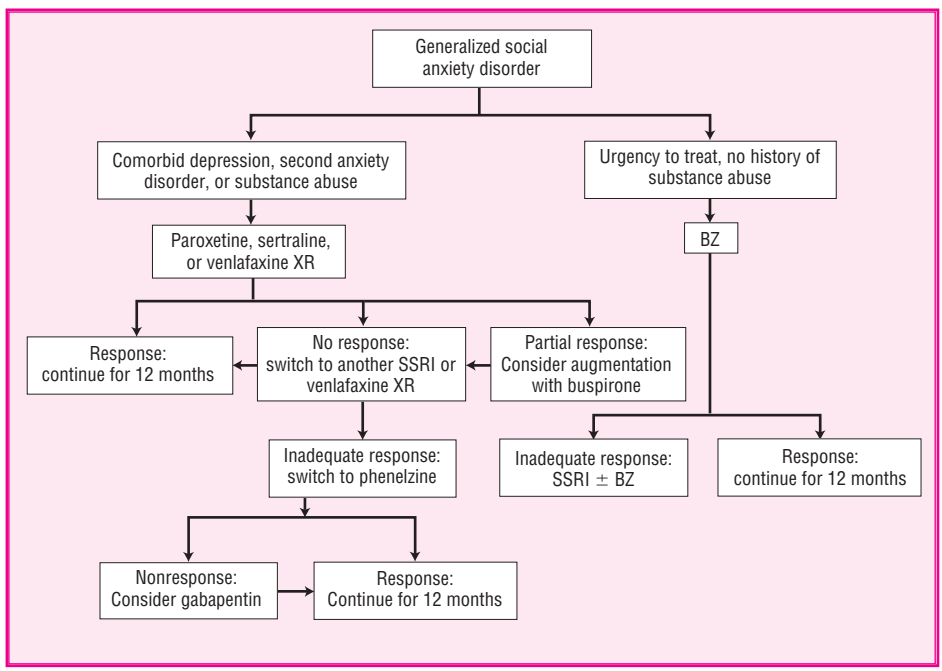


FIGURE 37–4. Algorithm for the pharmacotherapy of SAD. (Reprinted, with permission, from reference 24.)

drug interactions, and side effects. Neither brofaramine nor meclobemide is currently available in the United States, but they are available in Canada.

Alternative Agents

Benzodiazepines

Benzodiazepines are used commonly in SAD; however, there are limited data supporting their use. Clonazepam has been effective for social anxiety, fear, and phobic avoidance, and it reduced social and work disability during acute treatment.[58] Long-term treatment is not desirable for many SAD patients owing to the risk of withdrawal and difficulty with discontinuation, cognitive side effects, and lack of effect on depressive symptoms. Benzodiazepines may be useful for acute relief of physiologic symptoms of anxiety when used concomitantly with antidepressants or psychotherapy. Benzodiazepines are contraindicated in SAD patients with alcohol or substance abuse or history of such.

Anticonvulsants (Gabapentin, Pregabalin)

Gabapentin, a non-benzodiazapine GABA analog, was modestly effective in a 14-week controlled trial in SAD. Most patients were titrated to a maximal dose of 3600 mg/day.[58] Pregabalin 600 mg/day was effective for social anxiety, fear, and avoidance behavior in a 10-week controlled trial.[63] Pregabalin was well tolerated, and the most common side effects were somnolence and dizziness.

β-Blockers

β-Blockers decrease physiologic symptoms of anxiety and are useful for reducing performance anxiety. Propranolol or atenolol should be administered 1 hour before a performance situation. β-Blockers are not useful in generalized SAD.[58]

Outcome Evaluation

⑩ *Pharmacotherapy of SAD should lead to improvement in physiologic symptoms of anxiety and fear, functionality, and overall well-being.*[26] Many patients may not achieve full remission of symptoms but should have significant improvement. Monitor patients weekly during acute treatment (e.g., initiation and titration of pharmacotherapy). Once patients are stabilized, monitor monthly. Inquire about adverse effects and SAD symptoms at each visit. To aid in assessing improvement, ask patients to keep a diary to record fears, anxiety levels, and behaviors in social situations.[26] You may administer the Leibowitz Social Anxiety Scale (LSAS) to rate SAD severity and change, and the Social Phobia Inventory can be used as a "self-assessment" tool for SAD patients.

Counsel patients on appropriate expectations of pharmacotherapy in SAD, including the gradual onset of effect and the need for extended treatment of at least 1 year.



Patient Care and Monitoring

1. Review medical and laboratory data to rule out contributing causes of anxiety.
2. Assess the patient's symptoms and level of functional impairment to determine if pharmacotherapy is appropriate for the anxiety disorder.
3. Obtain a thorough history of prescription, non-prescription, and natural product use.
4. Determine what treatments have been tried or were useful in the past. Is the patient taking medication that may cause anxiety?
5. Educate the patient about lifestyle changes that will improve symptoms of anxiety. These include adequate sleep and exercise, stress management, meditation, and coping skills.
6. Inform patients of treatment options for anxiety disorders and the expected benefits of each (e.g., pharmacotherapy, psychotherapy, and combination treatment).
7. Develop a plan to assess the effectiveness of drug therapy during the first 12 weeks.
8. Determine an appropriate duration of treatment. Is long-term maintenance treatment needed?
9. Assess improvement in academic, social, interpersonal, and occupational functioning; quality of life; and well-being.
10. Evaluate the patient for the presence of adverse drug effects, drug-drug interactions, and drug allergies.
11. Stress the importance of adherence to medications to achieve and maintain response.
12. Provide patient education regarding disease state, lifestyle modifications, and pharmacotherapy.

- What differentiates anxiety from an anxiety disorder? How should it be treated?
- Potential complications of an untreated anxiety disorder.
- What potential adverse effects may occur? Is there a risk of dependence?
- Which drugs may interact with therapy?
- How to record symptoms (e.g., fears, panic attacks, avoidance behaviors) and report back to their clinician.

ABBREVIATIONS

CBT:	cognitive behavioral therapy
DA:	dopamine
DSM-IV-TR:	*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision
FDA:	Food and Drug Administration
GABA:	gamma-aminobutyric acid
GAD:	generalized anxiety disorder

5-HT:	serotonin
LC:	locus ceruleus
LSAS:	Liebowitz Social Anxiety Scale
NCS-R:	National Comorbidity Survey, Revised
NE:	norepinephrine
NPY:	neuropeptide Y
PD:	panic disorder
PDA:	panic disorder with agoraphobia
RAS:	reticular activating system
RIMA:	reversible inhibitors of monoamine oxidase A
SAD:	social anxiety disorder
SNRI:	serotonin-norepinephrine reuptake inhibitor
SSRI:	selective serotonin reuptake inhibitor
TCA:	tricyclic antidepressant

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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38 Sleep Disorders

John M. Dopp and Bradley G. Phillips



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Articulate the incidence and prevalence of sleep disorders, list the sequelae of undiagnosed or untreated sleep disorders, and appreciate the importance of successful treatment of sleep disorders.
2. Describe the mechanisms of the sleep disorders covered in this chapter, including insomnia, narcolepsy, restless-legs syndrome, obstructive sleep apnea, and parasomnias.
3. Assess patient sleep complaints, conduct sleep histories, and evaluate sleep studies to recognize day- and nighttime symptoms and characteristics of common sleep disorders.
4. Recommend and optimize appropriate sleep hygiene and nonpharmacologic therapies for the management and prevention of sleep disorders.
5. Recommend and optimize appropriate pharmacotherapy for sleep disorders.
6. Describe the components of a monitoring plan to assess safety and efficacy of pharmacotherapy for common sleep disorders.
7. Educate patients about preventive behavior, appropriate lifestyle modifications, and drug therapy required for effective treatment and control of sleep disorders.

Key Concepts

❶ Insomnia is most frequently a symptom or manifestation of an underlying disorder (secondary insomnia) but may occur in the absence of contributing factors (primary insomnia). Early treatment of insomnia may prevent the development of psychopathologic complications.

❷ Patients with sleep complaints should have a careful sleep history performed to assess for possible sleep disorders and to guide diagnostic and therapeutic decisions.

❸ Although clinical history guides diagnosis and therapy, only overnight polysomnography and multiple sleep latency tests (MSLTs) can definitively diagnose and/or guide therapy for obstructive sleep apnea, narcolepsy, and periodic limb movements of sleep.

❹ Treatment goals vary between different sleep disorders but generally include restoration of normal sleep patterns, elimination of daytime sequelae, improvement in quality of life, and prevention of complications and adverse effects from therapy.

❺ Benzodiazepine receptor agonists, including traditional benzodiazepines, zolpidem, zaleplon, and eszopiclone, are approved by the Food and Drug Administration (FDA) for the treatment of insomnia and are first-line therapies.

❻ Treatment of excessive daytime sleepiness in narcolepsy and other sleep disorders may require the use of sustained- and immediate-release stimulants to effectively promote wakefulness throughout the day and at key times that require alertness.

❼ Restless-legs syndrome treatment involves suppression of abnormal sensations and leg movements and consolidation of sleep. Dopaminergic and sedative-hypnotic medications are prescribed commonly.

❽ The main therapy for obstructive sleep apnea is nasal continuous positive airway pressure (CPAP) therapy because of its effectiveness.

❾ It is important to review patient medication profiles for drugs that may aggravate sleep disorders. Patients should be monitored for adverse drug reactions, potential drug-drug interactions, and adherence to their therapeutic regimens.

Normal humans sleep up to one-third of their lives and spend more time sleeping compared with any other single activity. Despite this, our understanding of the full purpose of sleep

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and the mechanisms regulating sleep homeostasis remains incomplete. Sleep is necessary to maintain wakefulness, health, and welfare. Unfortunately, disruption of normal sleep is prevalent and represents a major cause of societal morbidity, lost productivity, and reduced quality of life.[1] The link between adequate sleep and optimal health is becoming increasingly apparent, and sleep disturbances may contribute to the development and progression of comorbid medical conditions.

Sleep is governed and paced by the suprachiasmic nucleus in the brain that regulates **circadian rhythm.** Environmental cues and amount of previous sleep also influence sleep on a daily basis. There are two main types of sleep: **rapid-eye-movement (REM) sleep,** where eye movements and dreaming occur but the body is mostly paralyzed, and **non-REM sleep,** which consists of four substages (stages 1 to 4). Stage 1 serves as a transition between wake and sleep. Most of the time asleep is spent in stage 2 non-REM sleep. Stage 3 and stage 4 sleep often are grouped together and referred to as *deep sleep,* or *delta sleep,* because prominent delta waves are seen on the electroencephalogram (EEG) during these sleep stages.

EPIDEMIOLOGY AND ETIOLOGY

Sleep disorders are common. Approximately 50% of adults will report a sleep complaint over the course of their lives.[2] In general, sleep disturbances increase with age, and each disorder may have gender differences. The full extent and impact of disordered sleep on our society are not known because many patients' sleep disorders remain undiagnosed. Normal sleep, by definition, is "a reversible behavioral state of perceptual disengagement from and unresponsiveness to the environment."[3] As a result, individuals with sleep disorders will exhibit or complain about consequent symptoms (e.g., daytime sleepiness), or a bed partner will observe hallmark characteristics of the sleep disorder. Insomnia, restless-legs syndrome (RLS), and sleep-related breathing disorders are the most common sleep disorders.



Patient Encounter, Part 1

CH, a 53-year-old man with a history of hypertension, comes to your clinic complaining of sleepiness in the daytime, "crawly legs" at bedtime, and frequent awakenings at night. After further questioning, he explains that for the last hour or so before bedtime he cannot keep his legs still. He reports that he falls asleep relatively easily during the day. The symptoms have been worsening gradually over the past year and occur nightly. His wife reports that he kicks his legs the first part of the night, snores, and occasionally gasps for air after a breathing pause. His body mass index (BMI) is 30 kg/m^2, and he has experienced recent weight gain and complains about morning headaches.

- What sleep disorders do his symptoms suggest?
- What sleep disorders could you diagnose subjectively? What is your initial recommendation?
- What additional information do you need to know before creating a treatment plan for this patient?

Insomnia

The prevalence of insomnia increases with age and is nearly 1.5 times greater in females than in males. Approximately one-third of patients older than age 65 have persistent insomnia.[4,5] In the adult population, about 10% will experience chronic insomnia and slightly more will experience short-term insomnia. ❶*Insomnia is most frequently a symptom or manifestation of an underlying disorder (secondary insomnia) but may occur in the absence of contributing factors (primary insomnia). Early treatment of insomnia may prevent the development of psychopathologic complications.* Forty percent of patients with psychiatric conditions will have accompanying insomnia.[6] Secondary insomnia is triggered by acute stress and disappears when the stress resolves. Numerous co-existing medical conditions, such as pain, thyroid abnormalities, asthma, reflux, and medications, including selective serotonin reuptake inhibitors (SSRIs), steroids, stimulants, and β-agonists, can interfere with sleep and cause secondary insomnia. In cases of secondary insomnia, the clinician should treat the underlying primary cause along with insomnia symptoms.

Narcolepsy

Although difficult to estimate, the prevalence of narcolepsy is between 0.03% and 0.06%.[7] Significant differences have been reported for various ethnic groups. Narcolepsy has a higher prevalence in the Japanese and a lower prevalence in the Israeli populations.[8,9] **Cataplexy** is not required for diagnosis; however, between 50% and 80% of patients with narcolepsy have accompanying cataplexy.[10]

Restless-Legs Syndrome

Restless-legs syndrome occurs in 5% to 15% of the population, making it a common sleep disorder.[11,12] The prevalence of RLS increases with age and in various medical conditions such as end-stage renal disease (ESRD), pregnancy, and iron deficiency.[13] RLS appears to be more common in women than in men and has a genetic link. The majority of RLS patients (63% to 92%) report a positive family history.[14]

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a common disorder that is often unrecognized, affecting 4% of middle-aged white men and 2% of middle-aged white women.[15] In women, the frequency of OSA increases after menopause. OSA is as common or more common in African Americans and less common in Asian

populations. The risk of OSA increases with age and obesity. Individuals with OSA experience repetitive upper airway collapse during sleep, which decreases or stops airflow, with subsequent arousal from sleep to resume breathing. The severity is determined by overnight **nocturnal polysomnography** and is graded by the number of episodes of apnea (total cessation of airflow) and hypopnea (partial airway closure with blood oxygen desaturation) experienced during sleep. The severity is expressed as the **respiratory disturbance index (RDI),** quantified in events per hour. Mild sleep apneics have an RDI of between 5 and 15 episodes per hour; moderate, 15 to 30; and individuals with severe OSA can exhibit more than 30 episodes per hour.

Parasomnias

Non-REM **parasomnias** have variable prevalence rates depending on patient age and different diagnoses. Sleep talking, bruxism, sleepwalking, sleep terrors, and enuresis occur more frequently in childhood than in adulthood. Nightmares appear to occur with similar frequency in adults and children. REM behavior disorder (RBD), an REM-sleep parasomnia, has a reported prevalence of 0.5% and frequently is associated with concomitant neurologic conditions.[16] Chronic RBD is more common in elderly men and may have a familial disposition.

PATHOPHYSIOLOGY

Complicated processes govern wakefulness, sleep, and the transitions leading to sleep initiation and maintenance. Although the neurophysiology of sleep is complex, certain neurotransmitters promote sleep and wakefulness in different areas of the central nervous system (CNS). Serotonin is thought to control non-REM sleep, whereas cholinergic and adrenergic transmitters mediate REM sleep. Dopamine, norepinephrine, **hypocretin,** substance P, and histamine all play a role in wakefulness. Perturbations of various neurotransmitters are responsible for some sleep disorders and explain why various treatment modalities are beneficial.

Insomnia

Since insomnia is a complex and multifaceted disorder, there is no single pathophysiologic explanation for its various manifestations. Current hypotheses focus on a combination of possible models that incorporate physiologic, cognitive, and cortical arousal. Most insomnia models focus on hyperarousal and its interference with the initiation or maintenance of sleep.

Narcolepsy

The onset of narcolepsy-cataplexy is typically in adolescence and not at birth, suggesting that the disease may require environmental influence to develop. Currently, it is believed that narcolepsy results from autoimmune insult to the CNS because it is associated with HLA (major histocompatibility complex) DQB1*0602 and DQ1A1*0102.[17,18] Concentrations of hypocretin (a wake-promoting neuropeptide) in the cerebrospinal fluid (CSF) of narcolepsy patients are reduced significantly, suggesting that the autoimmune attack is against hypocretin-producing cells in the hypothalamus.[19] Intact hypocretin neurons normally stimulate arousal and wake-promoting neurons to stimulate cortical activation and behavioral arousal.

Restless-Legs Syndrome and Periodic Limb Movements of Sleep (PLMS)

RLS is a neurologic medical condition characterized by an irresistible desire to move the limbs. It is thought that these abnormal sensations are a result of iron deficiency in the brain and iron-handling abnormalities in the CNS. Iron and H-ferritin concentrations, along with transferrin receptor and iron transporter numbers, are reduced in the substantia nigra of patients with RLS.[20] These iron abnormalities lead to dysfunction of dopaminergic transmission in the substantia nigra.

Obstructive Sleep Apnea

At least 20 muscles and soft-tissue structures control patency of the upper airway. Patients with OSA may have differences in upper airway muscle activity during sleep and may have smaller airways, predisposing them to upper airway collapse and consequent apneic episodes during sleep. The inability of the upper airway to contend with factors that promote collapse, including fat deposition in the neck, negative pressure in the airway during inspiration, and a smaller lower jawbone, also may play a role in the pathogenesis of OSA. Hallmarks of OSA include witnessed apneas, gasping, or both.

Poor sleep architecture and fragmented sleep secondary to OSA can cause excessive daytime sleepiness (EDS) and neurocognitive deficits. These sequelae can affect quality of life and work performance and may be linked to occupational and motor vehicle accidents. OSA is also associated with systemic disease such as hypertension, heart failure, and stroke.[21–23] OSA is likely an independent risk factor for the development of hypertension.[24] Further, when hypertension is present, it is often resistant to antihypertensive therapy. Fatal and non-fatal cardiovascular events are two- to threefold higher in male patients with severe OSA.[25] OSA is associated with or aggravates biomarkers for cardiovascular disease, including C-reactive protein and leptin.[26,27] Patients with sleep apnea often are obese and may be predisposed to weight gain. Hence, obesity may further contribute to cardiovascular disease in this patient population.

Several factors suggest an association between OSA and systemic disease. Breathing against a closed upper airway during

sleep causes intermittent and repetitive episodes of hypoxemia and hypercapnia, dramatic changes in intrathoracic pressure, and activation of the sympathetic nervous system. These responses can produce acute hemodynamic and humoral responses. Blood pressure can increase to 220/120 mm Hg with each apneic episode.[28] Concentrations of circulating vasoconstrictors, such as endothelin-1 and norepinephrine, are increased during OSA.[29] These acute responses to OSA may predispose to and enhance the progression of vascular disease in the longer term. This is supported by studies showing impaired endothelium-dependent vasodilation, an early marker for vascular disease, in patients with untreated moderate to severe OSA.[30]

Parasomnias

The pathogenesis of parasomnias (e.g., sleepwalking, enuresis, sleep talking) is variable and not well described and involves state dissociation, whereby two states of being overlap simultaneously. For example, abnormal activation of the central pattern generator of the spinal cord that produces motor movements is hypothesized to underlie sleepwalking behavior. In RBD, active inhibition of motor activity in the perilocus coeruleus region is lost, resulting in loss of paralysis and dream enactment.



Clinical Presentation

Patients with sleep disorders may complain about daytime symptoms. A bed partner may witness hallmark characteristics of the sleep disorder. ❷*Patients with sleep complaints should have a careful sleep history performed to assess their possible sleep disorder in order to guide diagnostic and therapeutic decisions.*

Daytime Symptoms and Associated Characteristics

EDS is the primary symptom described by patients with sleep disorders. It is usually described as not waking up refreshed in the morning or falling asleep or fighting the urge to sleep during the day despite a night of sleep. Other daytime characteristics of sleep disorders include:

- Irritability, fatigue, or depression
- Confusion or impaired performance at work or school
- Cataplexy
- Hypertension

Nighttime Sleep Complaints

Depending on the sleep disorder, patients may exhibit or experience various nocturnal complaints during sleep hours. Some of these complaints can be uncovered by clinical history alone (e.g., hallucinations, RLS, and snoring), whereas others can be diagnosed only during sleep studies (e.g., OSA, nighttime awakenings, somnambulism, PLMS, etc.). Frequent complaints include:

- Inability to fall asleep, nighttime awakenings
- Sleepwalking (somnambulism), sleep talking (somniloquy)
- Cessation of breathing (apnea), snoring
- Sleep paralysis and/or hallucinations when waking or falling asleep
- Restlessness (PLMS or RLS)

CLINICAL PRESENTATION AND DIAGNOSIS

❸*Although clinical history guides diagnosis and therapy, only overnight polysomnography and/or multiple sleep latency tests (MSLTs) can definitively diagnose and guide therapy for OSA, narcolepsy, and periodic limb movements of sleep.*

Insomnia (Difficulty Initiating or Maintaining Sleep)

Insomnia is often characterized by difficulty falling asleep, frequent nocturnal awakenings, and early-morning awakenings. Difficulty initiating or maintaining sleep may result in daytime impairments in concentration and school or work performance. In secondary insomnia, social factors (e.g., family difficulties, bereavement), medications, and co-existing medical conditions (e.g., depression, bipolar disorder) may help to explain difficulties in initiating and maintaining sleep. Insomnia may be described as transient (a few days), short term (less than 3 weeks), or chronic (greater than 1 month) in duration.

Narcolepsy

The hallmark of narcolepsy is EDS and the need for unwanted episodes of sleep during the day during favorable and unfavorable conditions. Patients with narcolepsy may experience repeated nighttime awakenings and terrifying dreams, along with difficulty falling asleep. Narcoleptics frequently experience abnormal manifestations of REM sleep, including hallucinations and sleep paralysis that occur on falling asleep and/or awakening. Cataplexy is a weakness or loss of skeletal muscle tone in the jaw, legs, or arms that is elicited by emotion (e.g., anger, surprise, laughter, or sadness).

Obstructive Sleep Apnea

Common characteristics of OSA include snoring, choking, gasping for air, nocturnal reflux symptoms, and morning headaches. A bed partner or roommate may observe these characteristics and witness episodes where the patient stops breathing during sleep. Obesity predisposes to and can worsen OSA. Patients with large neck sizes (greater than 45 cm or 17.7" neck circumference) and a BMI of 30 kg/m^2 or greater are at higher risk for OSA. Hypertension, depression, and hypothyroidism are found frequently in patients with OSA.

Periodic Limb Movements of Sleep or Restless-Legs Syndrome

Although RLS symptoms can vary, patients commonly report creepy-crawly, burning, tingling, or achy feelings in the legs or arms. These sensations create a desire to move the limbs and may produce motor restlessness. Symptoms are worse in the evening and are worse or exclusively present at rest, with temporary relief with movement. Symptoms also can occur during sleep and often lead to semirhythmic (periodic) limb movements during sleep (PLMS). PLMS are objective findings during overnight polysomnography recorded by leg electrodes. PLMS are present in most patients with RLS but can occur independently. PLMS frequently are described by a bed partner as restlessness or repeated kicking of legs or thrashing of arms during sleep.

Parasomnias

Parasomnias are characterized by undesirable physical or behavioral phenomena that occur during sleep [e.g., sleepwalking, sleep talking, bruxism (grinding of teeth), enuresis, night terrors, and RBD]. RBD patients act out their dreams during sleep, often in a violent manner.

Circadian Rhythm Disorders (CRDs)

The most common CRDs include jet lag, shift-work sleep disruption, delayed sleep-phase disorder, and advanced sleep-phase disorder. Jet lag occurs when a person travels across time zones, and the external environmental time is mismatched with the internal circadian clock. Delayed and advanced sleep-phase disorders occur when bed and wake times are delayed or advanced (by 3 or more hours) compared with socially prescribed bed and wake times.

Sleep Diagnostics

Complete overnight polysomnography is the "gold standard" for diagnosing and identifying sleep-disordered breathing, PLMS, parasomnias, and nocturnal sleep irregularities related to narcolepsy. Sleep is observed and monitored in a controlled setting using an EEG, electro-oculogram, electromyogram, electrocardiogram, air thermistors, abdominal and thoracic strain belts, and an oxygen saturation monitor. This setup assesses and records sleep onset, arousals, sleep stages, eye movements, leg and jaw movements, heart rhythm, arrhythmias, airflow during sleep, respiratory effort, and oxygen desaturations.

Evaluations of Daytime Sleepiness

The two most commonly performed objective evaluations to assess daytime sleepiness are the multiple sleep latency test (MSLT) and the maintenance of wakefulness test (MWT). The MSLT is a series of four to six 20-minute naps every 2 hours during the day beginning 2 hours after morning awakening (following a normal night's sleep) to evaluate physiologic sleepiness. The patient is instructed not to resist the urge to fall asleep. **Sleep latency** of less than 5 or 6 minutes is considered pathologically sleepy. The occurrence of an REM onset period during two naps is indicative of a diagnosis of narcolepsy. The MWT is performed to assess a patient's ability to avoid succumbing to sleepiness (manifest sleepiness). Similar nap opportunities are set up for the MWT, with the exception that the patient is instructed to lie down in bed and attempt to stay awake. A subjective assessment of sleepiness can be completed using the Epworth Sleepiness Scale (ESS). The ESS is a validated questionnaire that is easy to use and reliably predicts subjective sleepiness. The maximum score is 24, and any patient with a score greater than 10 is considered sleepy.



Patient Encounter, Part 2: The Medical History, Physical Examination, and Diagnostic Test

CH undergoes nocturnal polysomnography and returns to your clinic for follow-up.

PMH
Hypertension poorly controlled since 1999.

FH
Father died at age 70 from stroke. Mother is still alive with history of restless legs and hypothyroidism.

SH
Married, works as an accountant, never has smoked, 2 drinks per night on the weekends.

Meds
- Hydrochlorothiazide 25 mg PO once daily
- Amlodipine 10 mg PO once daily

ROS
(+) daytime sleepiness (ESS: 18/24).

PE
VS: BP 154/84, P 78, RR 16, T 37.0°C (98.6°F).
Mouth: Airway crowded, large tonsils and uvula.

Labs
Within normal limits.

Overnight polysomnogram: Frequent obstructive apneas, hypopneas, and leg movements.

- RDI: 12 events/hour
- 310 leg movements, mostly occurring in first half of the night
- Successful alleviation of apneas and hypopneas with nasal continuous positive airway pressure

- Given this additional information, summarize the patient's diagnosis.
- Identify your treatment goals and recommendations for the patient.
- What nonpharmacologic and pharmacologic alternatives are available for this patient if prescribed therapy is not successful or not tolerated?

TREATMENT

❹*Treatment goals vary between different sleep disorders but generally include restoration of normal sleep patterns, elimination of daytime sequelae, improved quality of life, and prevention of complications and adverse effects from therapy.* All patients presenting with sleep complaints should have a thorough inventory of their sleep habits and sleep hygiene investigated during the interview and history taking. Nonpharmacologic interventions for insomnia are outlined in Table 38–1. Sleep hygiene should be reinforced in all patients, and behavioral, cognitive, and stimulus-control interventions are used mainly for patients with insomnia-type complaints. Both pharmacologic and nonpharmacologic therapies are effective at improving sleep and reducing insomnia complaints. An algorithm for the initial assessment and first treatment step is provided in Fig. 38–1.

Insomnia

The ideal hypnotic drug would be effective at reducing sleep latency and increasing total sleep time and be free of unwanted side effects. ❺*Benzodiazepine receptor agonists, including traditional benzodiazepines, zolpidem, zaleplon, and eszopiclone, are approved by the Food and Drug Administration (FDA) for the treatment of insomnia and are first-line therapies.*[31,32] Not all products are available in all countries. Pharmacologic treatment of insomnia is recommended for transient and short-term insomnia. Long-term use of hypnotics is not contraindicated unless the patient has another contraindication to their use. Eszopiclone is approved by the FDA for chronic use up to 6 months.[33] Although not first line-agents for insomnia, sedating antihistamines are prescribed commonly, and the number of prescriptions has increased dramatically over the last 20 years.[34] These and other therapies, detailed below, are used to treat insomnia.

TABLE 38–1. Nonpharmacologic Therapies for Sleep

Sleep Hygiene
- Keep a regular sleep schedule.
- Exercise frequently but not immediately before bedtime.
- Avoid alcohol and stimulants (caffeine, nicotine) in the late afternoon and evening.
- Maintain a comfortable sleeping environment that is dark, quiet, and free of intrusions.
- Avoid consuming large quantities of food or liquids immediately before bedtime.

Stimulus Control
- Go to bed only when sleepy.
- Avoid daytime naps.
- If you cannot sleep, get out of bed and go to another room—only return to your bed when you feel the need to sleep.
- Bed is for sleep and intimacy only (no eating or watching TV in bed).
- Always wake up at the same time each day.

Relaxation Training
- Reduce somatic arousal (muscle relaxation).
- Reduce mental arousal (attention focusing procedures, imagery training, meditation, etc.).
- Biofeedback (use of visual or auditory feedback to reduce tension).

Cognitive Therapy
- Alter beliefs, attitudes, and expectations about sleep.

Benzodiazepine Receptor Agonists (BZDRAs)

There are currently eight BZDRAs approved for insomnia, and the pharmacokinetic differences between these agents help to guide selection depending on patient considerations and specific sleep complaints (Table 38–2). These agents occupy the benzodiazepine receptors on the gamma-aminobutyric acid (GABA) type A receptor complex, resulting in opening of chloride channels that facilitate GABA inhibition and promote sleepiness.[35] BZDRAs have become the first-line agents for treating insomnia and sleep-maintenance problems because they are all efficacious, have wide therapeutic indices, and in clinical use have a low incidence of abuse.[31,35]

Patients should be instructed to take BZDRAs at bedtime and to avoid engaging in activities requiring alertness after ingestion. The BZDRAs come closer to the "ideal hypnotic" compared with other agents because they reduce sleep latency and increase total sleep time (except for zaleplon) with fewer adverse effects. Although BZDRAs generally are well tolerated and have good safety profiles, mild to moderate side effects can occur, and precautions are warranted, especially in high-risk populations.

Precautions and Safety

The most common side effects associated with BZDRAs include residual sedation (a prolongation of the sedative effects into the waking hours after sleep), grogginess, and psychomotor impairment.[36] Careful selection of a hypnotic agent with a duration of action matching the patient's budgeted sleep time can help minimize the risk of residual sedation. BZDRAs should be initiated at low doses, and agents with active metabolites (Table 38–2) should be avoided in elderly patients. BZDRAs may cause anterograde amnesia, defined as memory loss of activities and interactions after ingestion of the drug. All hypnotics can cause anterograde amnesia, and higher doses increase the extent of amnesia.[37,38]

On discontinuation of hypnotic BZDRAs, patients can experience rebound effects, specifically rebound insomnia that may last for one to two nights. Rebound insomnia occurs more frequently after discontinuation of shorter-duration BZDRAs compared with long-duration BZDRAs. Intermittent hypnotic therapy with the lowest dose possible reduces the likelihood of tolerance, dependence, and withdrawal when therapy is stopped. Patients should be counseled that rebound insomnia is not necessarily a return of their original symptoms, and it may take a few nights for rebound symptoms to subside.

Sedating Antidepressants

The increasing popularity of sedating antidepressants for the treatment of insomnia resulted in trazodone being the most prescribed drug in 2002.[39] Other common antidepressants also

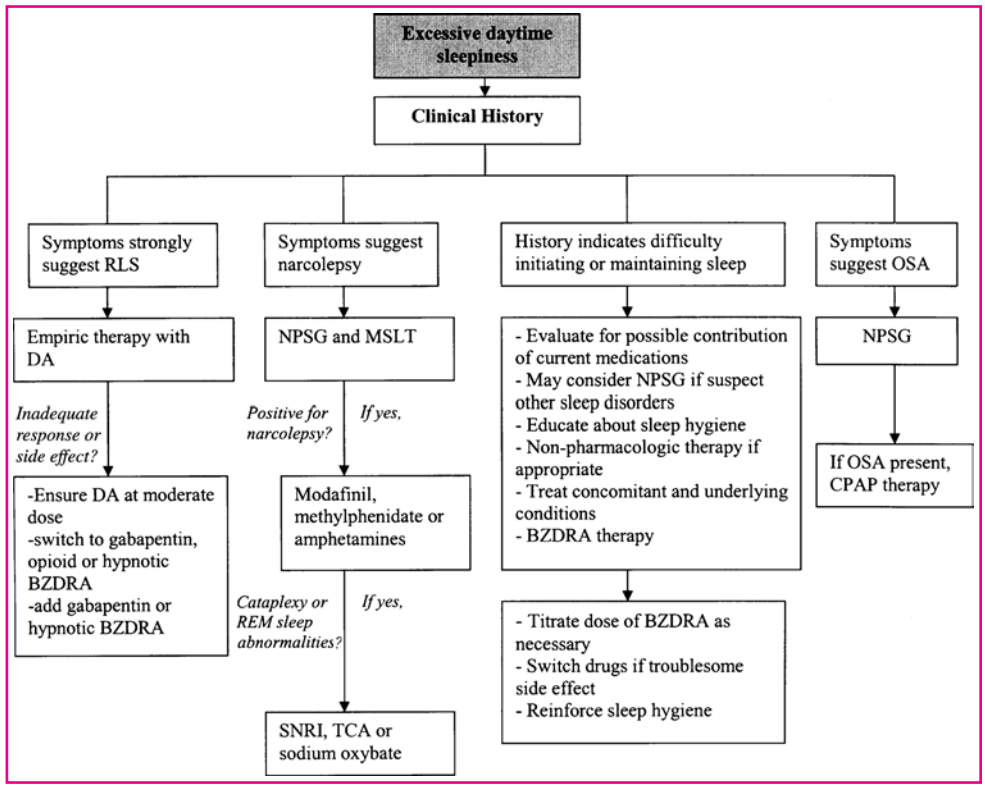


FIGURE 38–1. Primary assessment and initial treatment for complaint of excessive daytime sleepiness. RLS, restless-legs syndrome; NPSG, nocturnal polysomnography; OSA, obstructive sleep apnea; DA, dopamine agonist; MSLT, multiple sleep latency test; BZDRA, benzodiazepine receptor agonist; SNRI, serotonin and norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant; CPAP, continuous positive airway pressure.

TABLE 38–2. Pharmacokinetics of Prescription Medications Used to Treat Insomnia

Generic Name	Parent $t_{1/2}$ (hour)	Duration of Action (hour)	Daily Dose Range (mg)	Metabolic Pathway	Clinically Significant Metabolites	Advantages and/or Disadvantages
Estazolam (Prosom®)	2	12–15	1–2	Oxidation	—	Moderate duration
Eszopiclone (Lunesta®)	6	8	2–3	Oxidation Demethylation	—	Can be used up to 6 months for chronic insomnia
Flurazepam (Dalmane®)	8	10–30	15–30	Oxidation N-dealkylation	Hydroxyethylflurazepam Flurazepam aldehyde N-DAF[b]	High risk of hangover and residual effects
Quazepam (Doral®)	2	25–41	7.5–15	Oxidation N-dealkylation	2-Oxo-quazepam N-DAF[a]	High risk of hangover and residual effects
Ramelteon (Rozerem®)	1–2.6	Unpublished[b]	8	Oxidation Glucuronidation	M-II[c]	Non-controlled substance, may be useful in patients with history of substance abuse
Temazepam (Restoril®)	10–15	7	7.5–30	Conjugation	—	Moderate duration, well-tolerated, inexpensive
Triazolam (Halcion®)	2	6–7	0.125–0.25	Oxidation	—	Short-acting, little residual hangover
Zaleplon (Sonata®)	1	6	5–10	Oxidation	—	Short-acting, only for difficulty falling asleep
Zolpidem (Ambien®)	2–2.6	6–8	5–10	Oxidation	—	Short–moderate duration, no effects on sleep architecture
Zolpidem CR (AmbienCR®)		Perhaps longer	6.25–12.5			

[a]N-desalkyl flurazepam.
[b]Data not available.
[c]M-II is the major active metabolite of ramelteon.
Adapted, with permission, from *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. Table 71–4, p. 1325.

prescribed for insomnia include amitriptyline, mirtazapine, nefazadone, and doxepin. Antidepressants may be an appealing option for insomnia in patients with concomitant depression. However, at the doses frequently used for sleep, none of the agents exhibit significant antidepressant activity. Further, quality clinical studies demonstrating efficacy for treating insomnia are lacking. Side effects from antidepressants can be frequent and often are unpleasant, including carryover sedation, grogginess, anticholinergic effects, and weight gain. Tricyclic antidepressants (TCAs) should be used with caution in the elderly and patients with cardiovascular and hepatic impairment. Mirtazapine can cause daytime sedation, dizziness, and weight gain, a side effect that may worsen concomitant OSA.[40] Trazodone can cause hypotension and dizziness and should be used with caution in patients with heart disease or hypertension and those taking cardiovascular agents.[41,42]

Over-the-Counter and Miscellaneous Agents

Antihistamines such as diphenhydramine are known for their sedating properties and are frequently used over-the-counter medications (usual doses 25–50 mg) for difficulty sleeping. Diphenhydramine is approved by the FDA for the treatment of insomnia and can be effective at reducing sleep latency and increasing sleep time.[43] However, diphenhydramine produces undesirable anticholinergic effects and carryover sedation that limit its use. As with TCAs and BZDRAs, diphenhydramine should be used with caution in the elderly. Valerian root is an herbal sleep remedy that has inconsistent effects on sleep but may reduce sleep latency and efficiency at commonly used doses of 400 to 900 mg valerian extract. Ramelteon, a new melatonin receptor agonist, is indicated for insomnia characterized by difficulty with sleep onset. The recommended dose is 8 mg at bedtime. Ramelteon is not a controlled substance and thus may be a viable option for patients with a history of substance abuse.

Narcolepsy

Therapy for narcolepsy involves two key principles: (1) treatment of EDS with scheduled naps and CNS stimulants and (2) suppression of cataplexy and REM-sleep abnormalities with aminergic signaling drugs. Modafinil, methylphenidate, and amphetamines are effective FDA-approved drugs for the treatment of EDS with narcolepsy.[44] Modafinil is potentially advantageous in part because it is a schedule IV medication in contrast to CNS stimulants, which are schedule II. Modafinil is renewable for 6 months at a time and may have fewer peripheral and cardiovascular effects than traditional stimulants. Selegiline, a selective monoamine oxidase B enzyme inhibitor, is metabolized to amphetamines and can be successful at reducing daytime sleepiness. In an individual patient, one wake-promoting agent may work better than another, and if the first drug selected is not successful at adequate doses, a trial with another agent should be attempted. ❻ *Treatment of EDS in narcolepsy and other sleep disorders may require the use of sustained- and immediate-release stimulants to effectively promote wakefulness throughout the day and at key times that require alertness.* One potential treatment regimen includes a sustained-release preparation first thing in the morning and again at noon, followed by an immediate-release preparation as needed in the late afternoon or prior to driving to maintain wakefulness. One advantage of traditional CNS stimulants over modafinil is their ability to suppress REM sleep, which also may help to control cataplexy and REM-sleep abnormalities.

Traditional CNS stimulants have the potential to increase blood pressure and heart rate when used long term. In addition, excessive CNS stimulation can cause tremors and tics and can carry over into evening hours, where initiation of normal nighttime sleep can be disrupted. Caution should be used in patients with underlying cardiovascular or cerebrovascular disease and in patients with a history of seizures because stimulants may lower the seizure threshold.

Cataplexy

Traditionally, aminergic signaling antidepressants have been used effectively to control symptoms of cataplexy, sleep paralysis, and other REM-sleep manifestations of narcolepsy. These include TCAs and certain selective serotonin and serotonin/norepinephrine reuptake inhibitors (SSRIs and SNRIs). Clomipramine, protriptyline, imipramine, venlafaxine, and fluoxetine are the agents that have been used most frequently. In addition, low-dose selegiline also has been effective at reducing cataplexy. Although these drugs are not approved by the FDA for treatment of cataplexy, they effectively suppress REM sleep and have been the mainstay of anticataplectic therapy for years. Recently, sodium oxybate, a potent sedative with a very short duration of action, gained FDA approval for the treatment of narcolepsy with cataplexy. The mechanism whereby it reduces cataplexy is unknown. Two doses per night are taken, one at bedtime and one follow-up dose taken 2½ to 4 hours later. Patients frequently need to set an alarm to wake up to take their second dose. Sodium oxybate is tightly regulated and is only available from one central pharmacy owing to the high abuse potential of its active ingredient (gamma-hydroxybutyrate).

Restless-Legs Syndrome

❼ *RLS treatment involves suppression of abnormal sensations and leg movements and consolidation of sleep. Dopaminergic and sedative hypnotic medications are prescribed commonly.* In the last few years, dopamine agonists (DAs) have become the therapy of choice for the treatment of RLS, replacing levodopa/carbidopa as first-line agents. The DAs offer many advantages over levodopa/carbidopa, including longer half-lives to cover overnight symptoms, flexible dosing, and a reduced incidence of symptom augmentation. Up to 80% of patients who take levodopa/carbidopa eventually will experience symptom augmentation: RLS symptoms appear earlier in the day, previously unaffected body parts become involved, and higher doses of medication are required to control symptoms.[45] Ropinirole (Requip®) recently gained FDA approval for the treatment of RLS. Pramipexole and pergolide are also prescribed and have demonstrated efficacy in

clinical trials.[46,47] Gabapentin is an effective treatment for RLS, particularly in patients with painful symptoms.[48] BZDRAs such as temazepam, clonazepam, zolpidem, and zaleplon effectively reduce arousals associated with PLMS in patients with RLS.[49] Their main benefit is derived from improving sleep continuity in patients with RLS, particularly as adjunct treatment with other pharmacologic therapies. Opioids are effective for some patients' RLS symptoms, with oxycodone, propoxyphene, hydrocodone, and codeine being used most frequently. For both BZDRAs and opioids, caution should be used in the elderly, in patients who snore and are at risk for sleep apnea, and in patients with a history of substance abuse. Low iron levels frequently exacerbate RLS symptoms. Iron supplementation should be prescribed in patients who are iron-deficient. Iron supplementation in patients with serum ferritin concentrations of less than 50 mcg/L improves RLS symptoms. Medications frequently used for RLS are shown in Table 38–3.

Obstructive Sleep Apnea

❸ *The main therapy for OSA is nasal* ***continuous positive airway pressure (CPAP)*** *therapy because of its effectiveness.* CPAP alleviates sleep-disordered breathing by producing a positive pressure column in the upper airway using room air. The CPAP machine is small enough to be transportable and sits at the bedside. A flexible tube connects the CPAP machine to a mask that covers the nose. During overnight polysomnography, the pressure setting is increased until sleep-disordered breathing is eliminated. CPAP therapy has been shown to have a favorable impact on blood pressure and to attenuate some of the potential hemodynamic and neurohumoral responses that may link OSA to systemic disease.

Not all individuals tolerate CPAP therapy in part because it requires wearing a mask during sleep, and therapy can dry and irritate the upper airway. In some individuals, these barriers for adherence may be lessened or eliminated by properly fitting the mask, adding humidity or heat to therapy, or using bi-level positive airway pressure (BiPAP) therapy. BiPAP therapy applies a variable pressure into the airway during the inspiratory phase of respiration but, unlike CPAP, reduces the applied pressure during the expiratory phase of respiration.

There are other non-invasive therapies for OSA. Obesity can worsen sleep apnea, and weight management should be implemented for all overweight patients with OSA. In obese patients with mild OSA, weight loss alone can be effective, and studies have reported improvement in severity of OSA with gastric stapling. Oral appliances can be used to advance the lower jawbone and to keep the tongue forward to enlarge the upper airway. For individuals who suffer OSA only during certain positions (e.g., when on their back) during sleep, positional therapies may be effective. Surgical therapy (uvulopalatopharyngoplasty) opens the upper airway by removing the tonsils, trimming and reorienting the posterior and anterior tonsillar pillars, and removing the uvula and posterior portion of the palate. This is not a first-line option because it is invasive. In very severe cases, tracheostomy may be necessary. This procedure

TABLE 38–3. Frequently Used Medications for Restless-Legs Syndrome[49]

Medication	Half-Life (hour)	Dose Range (mg/day)[d]	Potential Side Effect or Disadvantage
Dopaminergic Agents[a]			
Levodopa/carbidopa (Sinemet®)	1.5–2	100–200 of levodopa	Nausea/vomiting, high incidence of symptom augmentation
Pramipexole (Mirapex®)	8–12[b]	0.125–1.5	Nausea/vomiting
Ropinirole (Requip®	6[c]	0.25–3	Nausea/vomiting
Pergolide (Permax®)	27	0.025–0.5	Nausea/vomiting, rare but serious heart valvulopathy and pleural fibrosis
Anticonvulsants			
Gabapentin (Neurontin®)	5–7[b]	300–3600	Dizziness, ataxia
Hypnotic Agents			
Clonazepam (Klonopin®)	30–40	0.5–2	Tolerance, carryover sedation
Temazepam (Restoril®)	10–15	7.5–30	Tolerance, sedation
Zolpidem (Ambien®)	2–2.6[c]	5–10	Tolerance, sedation
Zaleplon (Sonata®)	1[c]	5–10	Tolerance, sedation
Opioids			
Hydrocodone	3.8–4.5[c]	5–10	Constipation, nausea, sedation
Codeine	2.5–3.5[c]	30–60	Constipation, nausea, sedation
Propoxyphene	6–12[c]	100–600	Constipation, nausea, sedation
Oxycodone	3.2–12[b]	5–30	Constipation, nausea, sedation

[a]Dopaminergic agents are frequently given at bedtime or 2 hours prior to bedtime or the anticipated onset of RLS symptoms.
[b]May be longer in patients with renal dysfunction.
[c]May be longer in patients with hepatic dysfunction.
[d]Usual range, dosed at bedtime.

may be indicated in selected individuals who are morbidly obese, have severe facial skeletal deformity, experience severe drops in oxygen saturation (e.g., Sao_2 less than 70%), or have significant cardiac arrhythmias associated with their OSA.

There is no drug therapy for OSA. Drug therapy for symptoms of OSA may be considered in selected patients. For example, modafinil (Provigil®) is a wake-promoting medication that is approved by the FDA to improve wakefulness in patients who have residual daytime sleepiness while treated with CPAP. Initiation of wake-promoting medications should be attempted only after patients are using optimal CPAP therapy to alleviate sleep-disordered breathing. Other therapies (e.g., medroxyprogesterone) are not effective and may worsen OSA. Untreated or inadequately treated sleep apnea may hinder achieving blood pressure control in hypertensive patients. OSA should be considered and evaluated in hypertensive patients who are resistant to therapy or have signs and symptoms of OSA.

Parasomnias

Non-REM parasomnias usually do not require treatment. If needed, low-dose benzodiazepines such as clonazepam can be prescribed for bothersome episodes. Clonazepam reduces the amount of sleep time spent in stages 3 and 4 of non-REM sleep, where most non-REM parasomnias occur. For treating RBD, clonazepam 0.5 to 2 mg at bedtime is the drug of choice, although melatonin 3 to 12 mg at bedtime also may be effective. Patients with RBD also should have dangerous objects removed from the bedroom and cushions placed on the floor to reduce the chance of injury from breakthrough episodes.

Circadian Rhythm Disorders

Melatonin at doses of 0.5 to 5 mg taken at appropriate target bedtimes for east or west travel is becoming the drug of choice for jet lag. Melatonin significantly reduces jet lag and shortens sleep latency in travelers.[50] Hypnotic agents with relatively short durations of action (3 to 5 hours) also may be used to sustain sleep during the initial adaptation to the new time zone.

Drug-Disease and Drug-Drug Interactions

❾*It is important to review patient medication profiles for drugs that may aggravate sleep disorders. Patients should be monitored for adverse drug reactions and potential drug-drug interactions. They should be assessed for adherence to their therapeutic regimens.* Pharmacotherapy for sleep disorders should be individualized. Medications can be used commonly to treat several concomitant sleep disorders. Conversely, drug therapy may be effective for one sleep disorder and exacerbate another. For example, antidepressants may alleviate depressive symptoms but exacerbate symptoms of RLS. Medications that block dopaminergic transmission may worsen RLS symptoms. Smoking can worsen OSA, presumably by increasing upper airway edema. Alcohol and CNS depressants, including opiate analgesics, sedatives, and muscle relaxants, can worsen OSA, even in small doses, by reducing respiratory drive and relaxing the upper airway muscles responsible for maintaining patency. CNS depressants should be avoided, and if they are necessary, they should not be administered before sleep. Drug therapy for sleep disorders should be patient-specific, and careful consideration should be given to co-existing diseases, concomitant medications, and potential drug-drug and drug-disease interactions to optimize patient care and treatment.



Patient Encounter, Part 3: Modifying Treatment Plan

CH returns to the clinic 3 months later. The physician previously diagnosed him with obstructive sleep apnea and RLS. He received a prescription for CPAP, for OSA and ropinirole 0.5 mg at bedtime for RLS at his last visit. Via phone calls, his ropinirole dose has been increased to 3 mg at bedtime. He has received moderate relief of his RLS symptoms, but on occasion, he still awakens and cannot fall back asleep. His sleepiness and RLS symptoms are improved: ESS: 13/24.

- Based on the information presented, recommend additional therapy for the patient.
- What medications would you consider adding to reduce RLS symptoms and reduce awakenings?
- How would you assess the patient's CPAP therapy and adherence?
- What precautions would you want to counsel the patient on about his therapy?

OUTCOME EVALUATION

To determine the success of treatment, evaluate whether the treatment plan restored normal sleep patterns, reduced daytime sequelae, and improved quality of life without causing adverse effects. Schedule patients for follow-up within 3 weeks for insomnia and within 3 months for other sleep disorders. Perform a detailed clinical history to determine the patient's perception of treatment progress and symptoms along with medication effectiveness and side effects.

Instruct patients to keep sleep diaries of nightly sleep (number of hours, number of awakenings, and worsening or improved sleep) and daytime symptoms, along with documentation of episodes such as cataplexy or RBD. Increase medication to effective doses, and if necessary, start additional therapy to control symptoms. Patients with sleep disorders should experience relief of symptoms the first night of drug therapy but may not receive maximal benefit (effect on daytime symptoms) for a few weeks. Perform a detailed history of prescription, non-prescription, and non-traditional medications, and review the patient's sleep diary, daytime symptoms, and non-pharmacologic therapies on a regular basis.



Patient Care and Monitoring

Insomnia

1. Ideally limit hypnotic therapy to short-term use, and reevaluate after 2 to 3 weeks of therapy.
2. Evaluate improvement in the specific sleep complaint (e.g., how has therapy affected sleep latency?).
3. Inquire about carryover sedation and other side effects associated with the selected agent. Use a lower dose or select a drug with a shorter duration of action if the patient experiences carryover sedation.
4. Address other medical conditions that frequently coexist with insomnia and can worsen a patient's symptoms (e.g., psychiatric disorders, benign prostatic hypertrophy).

Narcolepsy

1. Administer the ESS at each visit to monitor progress with modafinil or stimulant therapy. Unfortunately, EDS in narcolepsy patients rarely is fully reversed.
2. Evaluate how sleepiness changes throughout the day to best determine how to use sustained- and immediate-release stimulants to maintain wakefulness. If the patient complains of sleep disruption from stimulant therapy, move the dosing time a few hours earlier until sleep disruption is avoided.
3. Review patients' sleep diaries to track the number of cataplexy, sleep paralysis, and hallucinatory events and when they occur.

RLS

1. Carefully assess both the patients' and bed partners' reports of the patients' nighttime limb movements.
2. Measurement of sleepiness (via ESS) and RLS symptoms should be completed at each visit to track progress with therapy.
3. Evaluate potential side effects of therapy, including nausea, drowsiness, sleep attacks, and headaches for the DA agents.
4. Review the sleep diaries and timing of RLS symptoms to watch for possible symptom augmentation.
5. If symptoms are not resolved, increase the dose of DA agent or add another agent such as gabapentin or a hypnotic benzodiazepine.

OSA

1. Evaluate CPAP therapy annually or at any time individuals experience symptoms (e.g., daytime sleepiness) despite CPAP therapy. For example, change in pressure settings to alleviate OSA may be needed if weight gain occurs.
2. Monitor compliance with CPAP therapy. CPAP machines have a built-in compliance meter to measure the hours used at effective pressure. Patients should use CPAP therapy for at least 5 hours each night. In addition to alleviating sleep-disordered breathing, CPAP therapy may improve cardiovascular outcomes.

Parasomnias

1. Ask patients and family members about any bothersome or dangerous sleepwalking episodes since the last visit and if therapy has reduced the frequency of these events.
2. For RBD, review the sleep diaries and interview bed partners to determine the number and nature of episodes.
3. Inquire about carryover sedation and anterograde amnesia from therapy.

ABBREVIATIONS

BiPAP:	bi-level positive airway pressure
BMI:	body mass index
BZDRA:	benzodiazepine receptor agonist
CPAP:	continuous positive airway pressure
CRD:	circadian rhythm disorder
DA:	dopamine agonist
EDS:	excessive daytime sleepiness
ESRD:	end-stage renal disease
ESS:	Epworth Sleepiness Scale
GABA:	gamma-aminobutyric acid
HLA:	histocompatibility leukocyte antigen
MSLT:	multiple sleep latency test
MWT:	maintenance of wakefulness test
NPSG:	nocturnal polysomnography
NREM:	non–rapid eye movement
OSA:	obstructive sleep apnea
PLMS:	periodic limb movements of sleep
RBD:	REM-sleep behavior disorder
RDI:	respiratory disturbance index
REM:	rapid eye movement
RLS:	restless-legs syndrome
SNRI:	serotonin norepinephrine reuptake inhibitor
SSRI:	selective serotonin reuptake inhibitor
TCA:	tricyclic antidepressant

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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39 Attention-Deficit Hyperactivity Disorder

Kevin W. Cleveland and John Erramouspe



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Explain the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition, Text Revision criteria necessary for the diagnosis of attention-deficit hyperactivity disorder.
2. Recommend a therapeutic plan, including initial doses, dosage forms, and monitoring parameters, for a patient with attention-deficit hyperactivity disorder.
3. Differentiate between the available pharmacotherapy used for attention-deficit hyperactivity disorder with respect to pharmacology and pharmaceutical formulation.
4. Recommend second-line and/or adjunctive agents that can be effective alternatives in the treatment of attention-deficit hyperactivity disorder when stimulant therapy is less than adequate.
5. Address potential cost-benefit issues associated with pharmacotherapy of attention-deficit hyperactivity disorder.
6. Recommend strategies for minimizing adverse effects of attention-deficit hyperactivity disorder medications.

Key Concepts

❶ To meet present attention-deficit hyperactivity disorder diagnostic criteria, patients need to display either hyperactivity, impulsivity, and/or inattentiveness before 7 years of age.

❷ The exact cause of attention-deficit hyperactivity disorder is unknown, but dysfunction in neurotransmitters norepinephrine and dopamine has been implicated as a key component.

❸ Attention-deficit hyperactivity disorder is rarely encountered without comorbid conditions.

❹ Treatment goals for attention-deficit hyperactivity disorder are to improve behavior, increase attention/response inhibition (ability to stay on task), and minimize side effects associated with pharmacotherapy.

❺ Pharmacotherapy is superior to behavioral therapy in the treatment of attention-deficit hyperactivity disorder. Behavior modification provided by parents and teachers in conjunction with pharmacotherapy improves treatment outcomes more than behavior therapy alone.

❻ Stimulants are first-line agents for the treatment of attention-deficit hyperactivity disorder. If the initial trial of a stimulant therapy fails, then a second trial of an alternative stimulant should be tried. On failure of a second trial of stimulant pharmacotherapy, it is rational to attempt a third trial with another stimulant formulation or select a non-stimulant agent such as bupropion, imipramine, or atomoxetine.

Attention-deficit hyperactivity disorder (ADHD) is the most common mental disorder that occurs in the pediatric population.[1–3] This disorder must begin in childhood before 7 years of age and can continue into adulthood. ADHD is characterized by a core group of symptoms: hyperactivity, impulsivity, and inattention. Further, ADHD can be classified into three basic forms: inattentive, hyperactive/impulsive, and combined. It can have a severe impact on a patient's ability to function in both academic and social environments, leading to a significant burden on family and school personnel. The exact cause of ADHD is unknown, but twin studies strongly suggest a genetic etiology.[3–5] Early diagnosis and appropriate treatment are essential to compensate for areas of deficit and to allow the patient to cope in both family and social environments.

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Patient Encounter, Part 1

A single mother and her rambunctious 6-year-old boy, AD, come to your clinic. The mother is concerned because her neighbor, who watches AD after school for no charge, has complained about the problems he is causing among her own children (4½- and 6-year-old boys). AD refuses to wait for his own turn in games and frequently hits the younger boy. The neighbor has said that unless AD becomes more manageable, she will not watch him after school. This is very distressing to AD's mother, who barely provides for her son and herself by working at the local convenience store for minimum wage. She cannot afford a professional babysitter for AD. She does not qualify for medical assistance. Further, she explains that his performance at school is getting worse, and he is becoming unmanageable in the classroom.

- Which of the patient's symptoms are suggestive of ADHD?
- What other information do you need to assess for ADHD?
- What help/suggestions could you offer to AD's mother?

EPIDEMIOLOGY AND ETIOLOGY

❶*This disorder usually begins by 3 years of age but must occur prior to 7 years of age to meet diagnostic criteria.* In the United States, ADHD is the most common neurobehavioral disorder that affects children.[1–3,6] ADHD has been estimated to occur between 4.3% and 12% of school-aged children.[6,7] ADHD tends to occur at a greater incidence in males than in females by approximately 3:1 in school-aged children.[7] However, during adolescence, the incidence of ADHD is equal between males and females. As adults, females have a greater incidence of ADHD symptoms than males.

Although ADHD generally is considered a childhood disorder, symptoms can persist into adolescence and adulthood. The prevalence of adulthood ADHD is estimated to be 4%, with 60% of adults having manifested symptoms of ADHD from childhood.[8,9] Further, problems associated with ADHD (e.g., social, marital, academic, career, anxiety, depression, smoking, and substance-abuse problems) increase with the transition of patients into adulthood.

PATHOPHYSIOLOGY

❷*The exact pathologic cause of ADHD has not been identified.* ADHD is generally thought of as a disorder of self-regulation or response inhibition. Patients who meet the criteria for ADHD have difficulty maintaining self-control, resisting distractions, and concentrating on ideas.[4,6] Further, children with ADHD often alternate between inattentiveness to monotonous tasks and overexcitement. Multiple brain studies have failed to elucidate any pathophysiologic basis for ADHD, although they have associated ADHD with atypical brain development in early childhood. Cerebral volume, the prefrontal cortex, the basal ganglia, and the caudate tend to be significantly smaller in children with ADHD than in children without the disorder.[4]

❷*Dysfunction in the roles of the* ***neurotransmitters*** *dopamine and norepinephrine is thought to be key in the pathology of ADHD.* Norepinephrine is responsible for maintaining alertness and attention, whereas dopamine is responsible for regulating learning, motivation, goal setting, and memory. Both these neurotransmitters predominate in the frontal subcortical system, an area of the brain responsible for maintaining attention and memory. Also, the propensity for a genetic link with this disorder is high. There is a 50% chance that a child who has a parent with ADHD will develop ADHD. Further, studies of twins have demonstrated a concordance rate of 92% for ADHD. An association has been made between the development of ADHD and predisposing factors such as fetal alcohol syndrome, lead poisoning, maternal smoking, and hypoxia.[4]

CLINICAL PRESENTATION AND DIAGNOSIS



Clinical Presentation

General

Patients with ADHD can present with inattention and/or hyperactivity-impulsivity. ADHD is rarely encountered without comorbid conditions.

Symptoms

- *Inattention*—has difficulty paying attention to details in school, work, and social activities, difficulty completing tasks that require a lot of mental effort; is easily distracted, forgetful.
- *Hyperactivity/impulsivity*—has difficulty sitting still, fidgets, has trouble playing quietly and waiting turns, frequently interrupts.
- *Combined*—exhibit both inattention and hyperactivity/impulsivity.

Diagnostic Criteria

- Must exhibit symptoms before 7 years of age that persist for greater than 6 months.
- Symptoms must be present in two or more settings and adversely affect functioning in social situations, school, or work.
- Must meet the diagnostic criteria in DSM-IV-TR (Table 39–1).
- Symptoms cannot be better explained by another mental disorder (e.g., autism).

TABLE 39–1. DSM-IV Diagnostic Criteria for ADHD

I. Either A or B:
  A. ***Inattention***. Must have at least six or more of the following symptoms of inattention for at least 6 months:
    1. Does not pay close attention to details in schoolwork, work, or other activities.
    2. Has trouble maintaining attention to tasks or activities.
    3. Has trouble actively listening when directly spoken to.
    4. Has difficulty following instructions and fails to finish important daily tasks (i.e., homework, chores, responsibilities at work).
    5. Demonstrates difficulty in organizing tasks/activities.
    6. Tends to avoid or put off activities that require concentration.
    7. Tends to misplace items needed to complete tasks or activities.
    8. Is easily distracted from current tasks or activities.
    9. Forgetful.
  B. ***Hyperactivity/impulsivity.*** Must have at least six or more of the following symptoms of hyperactivity/impulsivity for at least 6 months:
    Hyperactivity
    1. Fidgets and is restless in a sitting position.
    2. Cannot sit still for extended periods.
    3. Runs around when it is not appropriate.
    4. Cannot play quietly.
    5. Often "on the move."
    6 Talks excessively.
    Impulsivity
    7. Answers questions prematurely.
    8. Difficulty waiting one's turn.
    9. Interruptive or intrudes on others.
II. Above symptoms were present before 7 years of age.
III. Above symptoms are present in two or more settings.
IV. Impairment is clearly evident in social, school, or work functioning.
V. Symptoms cannot be attributed to another mental disorder (e.g., anxiety, depression, autism, or a personality disorder).

Based on the above criteria, ADHD can be divided into three types:
1. ADHD combined type: Both 1A and 1B.
2. ADHD inattentive type: 1A criteria are met.
3. ADHD hyperactive-impulsive type: 1B criteria are met.

Reprinted, with permission, from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision, (Copyright 2000). American Psychiatric Association.[11]

❸ *ADHD is rarely encountered without comorbid conditions and often is underdiagnosed.* Between 40% and 75% of patients with ADHD will have one or more comorbidities (e.g., learning disabilities, oppositional defiant conduct, anxiety, or depressive disorders).[10] It is important to identify other coexisting conditions in patients with ADHD to assist in initial and ongoing selection of treatment.

When a patient presents with inattention, hyperactivity, academic underachievement, and/or behavior problems, he or she should be evaluated for ADHD. Initial evaluation of the patient primarily should be for the purpose of information gathering. Evidence of the patient's behavior should be obtained from various settings, including the family and school. Information is gathered from parent interviews, school reports, and an interview with and observation of the patient. This information should include the age of onset, frequency, severity, and duration of symptoms.[10]

The most useful diagnostic criteria for ADHD is the *Diagnostic and Statistical Manual of Mental Health Disorders,* 4th edition, Text Revision (DSM-IV-TR) (Table 39–1). The DSM-IV-TR defines three subtypes of ADHD: (1) predominately inattentive, (2) predominantly hyperactive/impulsive, and (3) combined, in which both inattentive and hyperactive symptoms are evident.[11]

Other diagnostic tests, such as brain imaging, electroencephalograms, and continuous performance examinations, should be regarded as investigational and not used clinically for diagnosis. While some brain studies have demonstrated differences in brain morphology between ADHD patients and control individuals, these differences are not diagnostic.[4]

Although ADHD is considered a childhood disorder, signs and symptoms persist into adolescence and adulthood in approximately 40% to 80% and 60% of cases, repectively.[1,9] Adult ADHD is difficult to assess, and diagnosis is always suspect in patients failing to display clear symptoms prior to 7 years of age.[4] Adults with ADHD have higher rates of psychopathology, substance abuse, social dysfunction, and occupational underachievement.



Patient Encounter, Part 2: Medical History, Physical Examination, and ADHD Evaluation

AD's baseline physical examination was unremarkable. Family history is positive for cardiovascular disease, and there is no documented history of ADHD in the family. Patient weight: 20 kg (44 lbs)

Allergies
None known

Patient height: 45 in (144 cm)
BP: 96/55 mm Hg
Pulse: 80 beats/minute
AD's mother does not qualify for medical assistance, and she can hardly afford the monthly expenses.

- What stimulant and/or non-stimulant regimen(s) is(are) available that might control AD's symptoms?
- Which medications will facilitate adherence, minimize potential side effects, and offer an acceptable cost for AD's mother?
- What other information do you need before starting certain pharmacotherapy options?
- What are important counseling points to discuss with AD's mother?

TREATMENT

Desired Outcomes

❹*The primary therapeutic objectives in ADHD are to improve behavior and increase attention; secondary goals of treatment are to*

- Improve relationships with family, teachers, and peers
- Decrease disruptive behavior in academic and social settings
- Improve academic performance
- Increase independence in activities
- Minimize undesirable adverse effects of therapy

Nonpharmacologic (Behavioral) Therapy

Behavioral therapy can be used to treat patients with ADHD; however, it is generally not recommended as first-line monotherapy.[8] ❺*Several studies have demonstrated that treatment with medication alone is superior to behavioral intervention alone in improving attention.*[12] *However, behavioral therapy in combination with stimulant therapy was better at improving oppositional and aggressive behaviors.*[12] Behavioral modification involves training parents, teachers, and caregivers to change the physical and social environment and establishment of a reward/consequence system.[13] Success of behavioral modifications depends on the cooperation and involvement of the patient's parents and teachers.

Pharmacologic Therapy

The proposed mechanism of ADHD pharmacotherapy is to modulate neurotransmitters in order to improve academic and social functioning. Pharmacologic therapy can be divided into two categories: stimulants and non-stimulants. Stimulant medications include methylphenidate, dexmethylphenidate, amphetamine salts, and dextroamphetamine, whereas non-stimulant medications include atomoxetine, tricyclic antidepressants (e.g., imipramine), clonidine, guanfacine, and bupropion.

Stimulants

❻*Psychostimulants (e.g., methylphenidate and dextroamphetamine with or without amphetamine) are the most effective agents in treating ADHD. Once the diagnosis of ADHD has been made, a stimulant medication should be used first line in treating ADHD* (Fig. 39–1). Stimulants are safe and effective, with a response rate of 70% to 90% in patients with ADHD.[3,13,14] Generally, a trial of at least 3 months on a stimulant is appropriate, and this includes dose titration to response

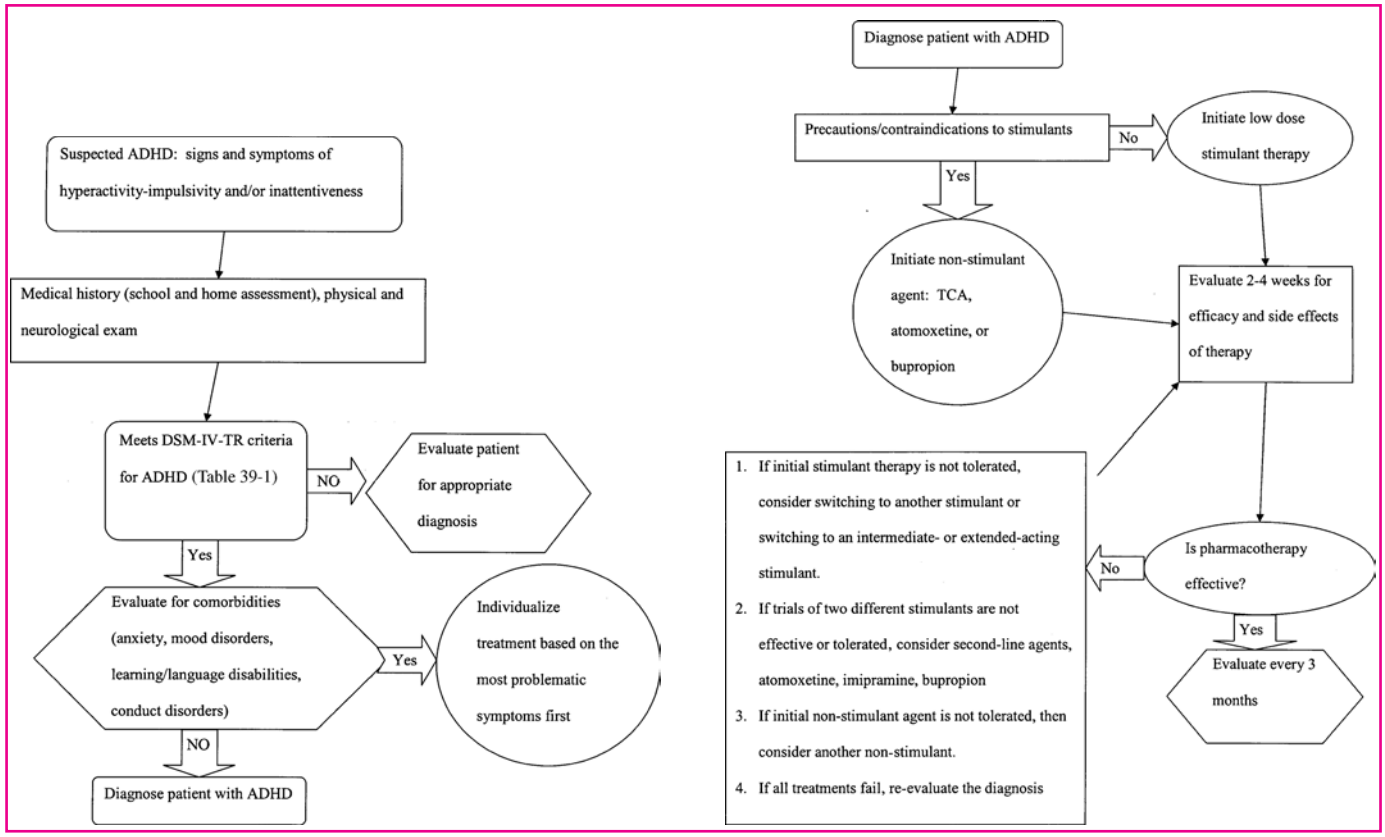


FIGURE 39–1. ADHD diagnosis and treatment algorithm.[8,13,16]

while balancing side effects.[8,13] ❻*If treatment with the first stimulant formulation fails, it is recommended to switch to a different stimulant formulation.*[13] For example, if the patient was started on methylphenidate but could not tolerate the side effects, switching to dextroamphetamine with or without amphetamine is rational. The majority of patients who fail one stimulant will respond to an alternative stimulant.[13] ❻ *If the patient fails two appropriate trials of different stimulant medications, a third stimulant formulation or second-line non-stimulant such as bupropion, imipramine, or atomoxetine can be considered.* The diagnosis of ADHD should be revalidated as well.

Stimulants theoretically exert their effect by blocking the reuptake of dopamine and norepinephrine, thus improving academic performance and decreasing motor activity in ADHD patients. Stimulants have been shown to decrease fidgeting and finger tapping, increase on-task classroom behavior and positive interactions at home and in social environments, and ameliorate conduct and anxiety disorders.[14]

Stimulants should be initiated at recommended starting doses and titrated up with a consistent dosing schedule to the appropriate response while minimizing side effects (Table 39–2). Generally, stimulants should not be used in patients who have glaucoma, severe hypertension or cardiovascular disease, hyperthyroidism, severe anxiety, or previous illicit or stimulant drug abuse. Further, stimulants can be used, albeit cautiously, in patients with seizure disorders, Tourette's syndrome, and **motor tics.**[14]

Initial response to short-acting stimulant formulations (e.g., methylphenidate and dextroamphetamine) is seen within 30 minutes and can last for 4 to 6 hours.[13,14] This short duration of effect frequently requires that short-acting stimulant formulations be dosed at least twice daily, thus increasing the chance of missed doses and non-compliance. Further, patients using any stimulant formulation but especially short-acting formulations can experience a **rebound effect** of ADHD symptoms as the stimulant wears off.[14]

To minimize rebound problems associated with short-acting formulations and still maintain early stimulant release, once-daily products (Adderall XR®, Concerta®, Metadate CD®, and Ritalin LA®) have been developed. Stimulant drug formulations can be divided into short-, intermediate-, and extended-acting preparations (Table 39–2). Most intermediate-acting agents release the medication in a slow, continuous fashion without any early release (except Dexedrine Spansules®). All extended-acting formulations have early release of medication and deliver a delayed release of stimulant in either a pulsed or continuous manner. Most of the extended-acting stimulants are capsules containing coated beads that can be opened and sprinkled on semisolid food. The exception, Concerta® tablets, uses an oral osmotic controlled-release delivery system (the empty tablet shell can be detected in the stool).

Adverse effects of stimulants can be generalized to the whole class (Table 39–3). Most of these side effects can be managed by changing dosing routine (i.e., giving with food, dividing daily dose, or giving the dose earlier in the day). Serious side effects such as hallucinations and abnormal movements require discontinuation of medication.[13,14]

Growth suppression or delay is a major concern for parents of children taking stimulants. However, the evidence of this side effect is not clear. At present, growth delay appears to be transient and to resolve by midadolescence, but more data are needed to firmly resolve this issue.[10] Another concern is the risk of substance abuse with stimulant use. A diagnosis of ADHD alone increases the risk of substance abuse in adolescents and adults. However, stimulant use has not been shown to further increase this risk but actually may decrease this risk, provided ADHD is treated adequately.[15]

The choice of ADHD medication should be made based on the patient's condition, the prescriber's familiarity with the medications, the ease of administration, and cost. Stimulants should be used first line in most ADHD patients, although there is no clear advantage of using one stimulant over another in managing symptoms of ADHD.[16]

Non-stimulants

Atomoxetine

Atomoxetine is the most recent addition to the ADHD armamentarium in both children and adults. In clinical studies, atomoxetine has demonstrated superior efficacy over placebo and equivalent efficacy when compared with a suboptimal immediate-release methylphenidate dose.[17–20] However, it is not clear whether atomoxetine is superior to typical methylphenidate doses or other stimulant formulations. ❻*Atomoxetine may be used as a second- or third-line medication for ADHD.*

Atomoxetine selectively inhibits the reuptake of adrenergic neurotransmitters, principally norepinepherine.[17–20] Atomoxetine is metabolized through the cytochrome P-450 CYP2D6 pathway. Approximately 5% to 10% of the population are CYP2D6 poor metabolizers, and atomoxetine's half-life is increased significantly in this population.[21] The recommended dosing for atomoxetine depends on the weight of the patient and is given daily in either a single or two divided doses[21] (Table 39–2). In poor metabolizers, atomoxetine should be dosed once daily at 25% to 50% of the dose typically used in normal metabolizers.[21] The maximum therapeutic effect of atomoxetine may take up to 4 weeks to be seen, which is significantly longer than what is required with stimulants. Common side effects of atomoxetine are similar to those of stimulants: dyspepsia, nausea, vomiting, somnolence, and decreased appetite. Some studies have reported an increase in blood pressure and heart rate.[18–20] There is evidence that atomoxetine can slow growth rate and cause weight loss; thus, height and weight should be monitored routinely in pediatric patients[18–20] (Table 39–3). Further, atomoxetine labeling includes strong warnings about severe hepatotoxicity and increased association with suicidal thinking.

TABLE 39–2. Selected Medications in Treating ADHD[a]

Drug, Generic (Brand)	Initial Dose	Titration Schedule	Typical Dosing Range (Maximum Dose)
Stimulants			
Short-acting			
Methylphenidate[b] (Methylin, Ritalin)	5 mg two times daily	↑ 5–10 mg/day in weekly intervals	5–20 mg two to three times daily (60 mg/day)
Dexmethylphenidate[b] (Focalin)	2.5 mg two times daily	↑ 2.5–5 mg/day in weekly intervals	5–10 mg twice daily (20 mg/day)
Dextroamphetamine[b] (Dexedrine)	2.5–5 mg every morning	↑ 2.5–5 mg/day in weekly intervals	5–20 mg twice daily (40 mg/day)
Intermediate-acting			
Methylphenidate[b] (Ritalin SR, Metadate ER, Methylin ER)	10 mg once daily	↑ 10 mg/day in weekly intervals	20–40 mg daily in the morning (60 mg/day)
Dextroamphetamine/ amphetamine[b] (Adderall)	2.5–5 mg once to twice daily	↑ 2.5–5 mg in weekly intervals	10–30 mg every morning or 5–20 mg twice daily (40 mg/day)
Dextroamphetamine[b] (Dexedrine Spansule)	5 mg every morning	↑ 5 mg/day in weekly intervals	5–30 mg daily or 5–15 mg twice daily (40 mg/day)
Extended-acting			
Methylphenidate[b] (Concerta)	18 mg every morning	↑ 9–18 mg/day in weekly intervals	18–54 mg every morning (54 mg/day)
(Metadate CD)	20 mg every morning	↑ 10–20 mg/day in weekly intervals	20–40 mg daily in the morning (60 mg/day)
(Ritalin LA)	20 mg every morning	↑ 10 mg/day in weekly intervals	20–40 mg daily in the morning (60 mg/day)
Dextroamphetamine/ amphetamine[b] (Adderall XR)	5–10 mg every morning (children) 20 mg once daily (adults)	↑ 5–10 mg/day in weekly intervals	10–30 mg every morning or 5–15 mg twice daily (30 mg/day, children) (60 mg/day, adult)
Dexmethylphenidate[b] (Focalin XR)	5 mg every morning (children) 10 mg every morning (adults)	↑ 5 mg/day in weekly intervals	10–20 mg daily in the morning (20 mg/day)
Non-stimulants			
Atomoxetine[b] (Strattera)	Less than or equal to 70 kg: 0.5 mg/kg per day divided once to twice daily	↑ to target dose of 1.2 mg/kg per day after 3 days	40–60 mg/day (1.4 mg/kg or 100 mg/day, whichever is less)
	Greater than 70 kg: 40 mg once daily	↑ 40 mg/day after 3 days (may ↑ to total of 100 mg/day after 2–3 weeks)	40–80 mg/day divided once to twice daily (100 mg/day)
Imipramine (Tofranil)	1.5 mg/kg per day in one or two divided doses	↑ 1 mg/kg per day every 3 to 4 days	1.5–3 mg/kg per day in one or two divided doses (5 mg/kg per day, child) 100–300 mg/day in one or two divided doses (300 mg/day, adult)
Clonidine (Catapres)	0.05 mg once daily	↑ 0.05 mg/day every 3 to 7 days	0.1 mg once to four times daily (0.4 mg/day)
Guanfacine (Tenex)	0.5 mg at bedtime	↑ 0.5 mg every 3 to 14 days	1.5–3 mg/day divided into two or three times daily (4 mg/day)
Bupropion (Wellbutrin, Wellbutrin SR, Wellbutrin XL)	3 mg/kg per day for 7 days (children); 150 mg once daily of SR or XL (adults)	↑ 3 mg/kg per day in weekly intervals (children); ↑ 150–300 mg/day in weekly intervals (adults)	6 mg/kg per day or 400 mg/day—whichever is smaller (children); 150–450 mg/day (400 mg/day SR; 450 mg/day XL - adults)

[a]Pediatric dosing except where adult dosing specified.
[b]FDA approved for treatment of ADHD.

Atomoxetine is similar to extended-acting stimulants in that it can be given once daily in many patients. Atomoxetine appears to lack any abuse potential and is not a controlled substance.[22] One big disadvantage of atomoxetine is cost compared with other ADHD medications (Table 39–4).

Due to the high cost and lack of long-term efficacy and comparison studies with stimulants, atomoxetine should be advocated only if the patient has failed or is intolerant to the standard stimulant therapy (Fig. 39–1).

Bupropion

Bupropion is a monocyclic antidepressant that inhibits the reuptake of norepinephrine and dopamine. Bupropion is effective for relieving symptoms of ADHD in children but is

TABLE 39–3. ADHD Medication Side-Effect Profiles, Management, and Monitoring

Drug	Side Effects	Management	Monitoring
Stimulants			
Methylphenidate, dextroamphetamine, mixed-salts amphetamine	GI upset, nausea, decreased appetite, potential growth delay	Administer after meals Encourage high-calorie meals Divide dose Give snacks in the evening Change to shorter-acting stimulant Use drug holiday or different medication if severe growth delay	Height, weight, blood pressure, pulse Eating and sleeping patterns Evaluate every 2 to 4 weeks until stable dose is achieved; then evaluate every 3 months
	Sleep disturbance	Give dose earlier in the day Give clonidine or guanfacine at bedtime Discontinue all doses given afternoon Change to a shorter-acting stimulant	
	Rebound symptoms	Change to longer-acting stimulant Overlap stimulant dosing	
	Moodiness	↓ Dose or change to longer-acting stimulant Verify diagnosis/comorbidity	
	Irritability	Evaluate time of occurrence Early onset: ↓ dose or change to longer-acting stimulant Late onset: Switch to longer-acting stimulant Evaluate for comorbidity	
	↑ Blood pressure and pulse	↓ Dose or change to longer-acting stimulant	
	Tics	Discountinue or change to a different stimulant Give clonidine or guanfacine	
Non-stimulants			
Atomoxetine	↑ Blood pressure and pulse, nausea, vomiting, fatigue, and insomnia	↓ Dose or change to another medication	Same as above but with baseline and routine liver function tests for hepatotoxicity
	Hepatotoxicity, suicidal thoughts	Discountinue or change to a another medication	
Tricyclic antidepressants (imipramine)	Sedation	Administer later in the day	Blood pressure, pulse, sleeping pattern
	Cardiac conduction delay, dizziness, ↑ pulse	↓ Dose or change medication	Evaluate every 3 days until stable dose is achieved; then evaluate every 3 months
	Anticholinergic effects (constipation, dry mouth, difficulty urinating, blurry vision)	↓ Dose or change medication	
Clonidine and guanfacine	Sedation, arrthymias, constipation, dizziness (↓ blood pressure)	Sedation: administer later in the day ↓ Dose or change medication	Same as above but with electrocardiogram (ECG)
Bupropion	GI upset, restlessness, sleep disturbances, rash, tics, risk of seizures	↓ Dose or change medication Tics, rash, and seizures: discontinue medication	Height, weight, blood pressure, pulse every month Eating and sleeping patterns

TABLE 39–4. 30-Day Cost[a] of Selected ADHD Medication Regimens

Generic	Regimen (Brand)	Cost[a]
Short-Acting Stimulants		
Methylphenidate		
Generic	5-, 10-, or 20-mg tab twice daily	$
Methylin®	5 mg/5 mL soln twice daily	$$
Dexmethylphenidate		
Focalin®	2.5-mg tab twice daily	$
	5- or 10-mg tab twice daily	$$
Dextroamphetamine		
Generic	5- or 10-mg tab twice daily	$
Intermediate-Acting Stimulants		
Methylphenidate		
Methylin ER®	10- or 20-mg ER tab daily	$
Dextroamphetamine[c]		
Dexedrine Spansule®	5-, 10-, or 15-mg cap daily	$$
Dextroamphetamine/amphetamine		
Generic	5-, 7.5-, 10-, 12.5-, 15-, 20-, or 30-mg tab daily	$
Extended-Acting Stimulants		
Methylphenidate		
Concerta®[c]	18-, 27-, 36-, or 54-mg tab daily	$$$
Metadate CD®[b]	10-, 20-, or 30-mg cap daily	$$$
Ritalin LA®[b]	10-, 20-, 30-, or 40-mg cap daily	$$$
Dextroamphetamine/amphetamine		
Adderall XR®[b]	5-, 10-, 15-, 20-, 25-, or 30-mg cap daily	$$$
Dexmethylphenidate		
Focalin XR®[b]	5-, 10-, or 20-mg cap daily	$$$
Non-stimulants		
Atomoxetine		
Strattera®	10-, 18-, 25-, 40-, 60-, 80-, or 100-mg cap daily	$$$$
Imipramine		
Generic	10-, 25-, or 50-mg tab twice daily	$
Clonidine		
Generic	0.1-, 0.2-, or 0.3-mg tab twice daily	$
Guanfacine		
Generic	1-mg tab twice daily	$
	2-mg tab twice daily	$$
Bupropion		
Generic	75- or 100-mg tab twice daily	$$
Wellbutrin SR®	100- or 150-mg SR tab twice daily	$$$
	200-mg SR tab twice daily	$$$$
Wellbutrin XL®	150- or 300-mg XL tab daily	$$$$

[a]Cost based on brand regimen specified without a dispensing fee or discount for a 1-month supply. Costs are current as of November 2006.
[b]Bimodal release (early then late; mimics twice daily dosing of shorter-acting stimulant counterpart).
[c]Ascending release (early then gradual/continuous).
$, less than $40; $$, $40 to $79; $$$, $80 to $120; $$$$, greater than $120.
tab, tablet; cap, capsule; chew tab, chewable tablet; soln, solution; SR, sustain release; ER, extended release; XL, extended release; LA, long-acting; CD, extended release (biphasic immediate release with extended release).

not as effective as stimulants.[23,24] Similar results have been shown in adults.[23] Specific dosing recommendations are outlined in Table 39–2. Bupropion is well tolerated with minimal side effects (e.g., insomnia, headache, and nausea). Side effects typically disappear with continuation of therapy and are minimized with slow titration of dose. Bupropion can worsen tics and movement disorders. Bupropion is a rational choice in an ADHD patient with comorbid depression.[23] However, seizures have been associated with bupropion doses greater than 6 mg/kg per day.[25] Seizures related to high doses can be minimized by reducing the dose or switching to a longer-acting formulation. Owing to the propensity of seizures with bupropion, its use is contraindicated in patients with seizure and eating disorders.

Tricyclic Antidepressants

The tricyclic antidepressants (TCAs), such as imipramine, can alleviate symptoms of ADHD. Like bupropion, TCAs likely will improve symptoms associated with comorbid anxiety and depression. The mechanism of action of TCAs is in blocking norepinephrine transporters, thus increasing norepinephrine concentrations in the synapse; the increase in norepinephrine is believed to alleviate the symptoms of ADHD. TCAs have been demonstrated to be an effective non-stimulant option for ADHD but less effective than stimulants. However, their use in ADHD has declined owing to case reports of sudden death and anticholinergic side effects[6,13] (Table 39–3). Further, TCAs may lower seizure threshold and increase the risk of cardiotoxicity, (e.g., arrythmias). Patients starting on TCAs should have a baseline and routine electrocardiograms.

Clonidine and Guanfacine

Clonidine and guanfacine are central α_2-adrenergic agonists that inhibit the release of norepinephrine presynaptically. Both these agents are less effective than stimulants in treating symptoms of ADHD but typically are used as adjuncts to stimulants to control disruptive or aggressive behavior and alleviate insomnia.[26] Guanfacine will last 3 to 4 hours longer than clonidine and requires less frequent dosing. Common side effects with clonidine and guanfacine are low blood pressure and sedation. Sedation is transient and should subside after 2 to 3 weeks of therapy.[26] Rarely, severe side effects such as bradycardia, rebound hypertension, irregular heart beats, and sudden death have been reported.

Pharmacoeconomic and Treatment Adherence Considerations

Proper ADHD treatment is a substantial financial burden.[27,28] Annual health care costs of patients with ADHD are more than double those of patients without ADHD ($1343 versus $503, respectively).[27] Further, the total cost of ADHD in the United States in 2000 was $31.6 billion.[28] The financial burden of ADHD can be attributed to the direct cost of pharmacotherapy, office visits, diagnostic measurements, therapy monitoring, and indirect costs (e.g., lost work time and productivity). It is estimated that children with ADHD are up to nine times more likely than other children to have prescriptions filled and incur office visits.

When selecting a treatment for an ADHD patient, the cost burden to the patient's family should be considered. Immediate-release stimulants may be more cost-effective in many patients compared with longer-acting stimulant formulations (Table 39–4), but in certain circumstances, longer-acting stimulant formulations may provide a cost benefit owing to increased adherence to the medication and prolonged control of symptoms of ADHD. Some non-stimulant ADHD medications (e.g., TCAs, α_2-adrenergic agonists, and bupropion) appear to be less costly than many stimulant formulations; however, these agents have not been proven to have superior efficacy over stimulants in treating ADHD. Decisions on selection of specific ADHD medications should not be based solely on cost, but efficacy and safety, along with adherence to the prescribed regimen, should be considered foremost.

OUTCOME EVALUATION

It is important to carefully document core ADHD symptoms at baseline to provide a reference point from which to evaluate effectiveness of treatment. Improvement in individualized patient outcomes are desired, such as (1) family and social relationships, (2) disruptive behavior, (3) completing required tasks, (4) self-motivation, (5) appearance, and (6) self-esteem. It is very important to elicit evaluations of the patient's behavior from family, school, and social environments in order to assess the preceding. Using standardized rating scales (e.g., Conners Rating Scales–Revised, Brown Attention-Deficit Disorder Scale, and IOWA Conners Scale) in both children and adults with ADHD helps to minimize variability in evaluation.[29] After initiation of therapy, evaluations should be done every 2 to 4 weeks to determine efficacy of treatment, height, weight, pulse, and blood pressure. Physical examination or liver function tests may be used to monitor for adverse effects.

Typically, therapeutic benefits will be seen within days of initiating stimulants and within a month or two with atomoxetine and bupropion. Once a maintenance dosing has been achieved, schedule follow-up visits every 3 months. At these visits, assess height and weight, and screen for possible adverse drug effects. If a patient has failed to respond to multiple agents, re-evaluate for other possible causes of behavior dysfunction. Counsel patients and their families that treatment is generally long term. Typically, appropriately treated patients learn to better control their ADHD symptoms as adults.



Patient Care and Monitoring

1. Assess the patient's symptoms and parent/teacher evaluations to determine whether they meet the DSM-IV-TR diagnostic criteria for ADHD. Evaluate whether the symptoms can be explained by another disorder.
2. Interview the patient and/or caregivers to obtain a complete medical history, which should include family medical history, current and past prescription and non-prescription medications, and dietary intake. Determine whether the patient is taking medication/supplements that could interfere with the therapy.
3. Educate the patient's parents and/or caregivers that behavioral therapy is not as effective as stimulant therapy. Educate parents regarding the issues of growth delay and substance abuse risks with stimulants.
4. Perform a baseline physical examination before starting stimulant therapy. Include blood pressure, pulse, and height and weight measurements. In patients taking stimulants, perform a general physical examination yearly, and monitor blood pressure quarterly in adults.
5. Start patients on a low initial dose of a stimulant and titrate up to the desired response in order to minimize side effects and costs.
6. If the patient is not responding to therapy after an adequate trial, assess compliance with the prescribed regimen. If the patient is not compliant, counsel the patient and caregivers and explore reasons for non-compliance. In some cases, switching to another stimulant formulation may improve compliance.
7. Important counseling points to convey to the patient and/or caregiver:
   - What is ADHD?
   - What are the complications of untreated ADHD?
   - When to take medications and what to expect with therapy.
   - What side effects to expect and what to do if these occur.
   - Controversy over substance abuse and growth delay with stimulant therapy.
   - What medications, prescription and non-prescription, to avoid.

ABBREVIATIONS

ADHD:	attention-deficit hyperactivity disorder
DSM-IV-TR:	*Diagnostic and Statistical Manual of Mental Disorders,* 4th edition, Text Revision

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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40 Diabetes Mellitus

Christopher L. Cook, John T. Johnson, and William E. Wade



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Discuss the incidence and economic impact of diabetes.
2. List screening and diagnostic criteria for diabetes.
3. Distinguish clinical differences in type 1, type 2, and gestational diabetes mellitus.
4. Discuss therapeutic goals for blood glucose, blood pressure, and lipids for a patient with diabetes.
5. Recommend nonpharmacologic therapies, including meal planning and physical activity, for patients with diabetes.
6. Compare oral agents used in treating diabetes by their mechanisms of action, time of action, side effects, contraindications, and effectiveness.
7. Select appropriate insulin therapy based on onset, peak, and duration of action.
8. Develop a comprehensive therapeutic patient monitoring plan for a patient with diabetes based on patient-specific factors.

Key Concepts

❶ Diabetes mellitus (DM) describes a group of chronic metabolic disorders that are characterized by hyperglycemia and are associated with long-term microvascular, macrovascular, and neuropathic complications.

❷ Glycemic control remains the primary objective in managing diabetes and its complications.

❸ Type 2 DM is the most prevalent form of diabetes and accounts for approximately 90% to 95% of all diagnosed cases. Type 2 DM is usually slow and progressive in its development and often is preceded by pre-diabetes. Rising blood glucose levels result from increasing insulin resistance and impaired insulin secretion leading to a situation of relative insulin deficiency.

❹ Although type 1 DM may appear at any age, it is encountered most commonly in individuals younger than 30 years of age. Type 1 DM is characterized by an absolute deficiency in insulin resulting from pancreatic β-cell destruction.

❺ Patients and clinicians can evaluate blood glucose control through a combination of self-monitoring of blood glucose data and hemoglobin HbA_{1c} testing.

❻ Several classes of oral agents are available to treat patients with type 2 DM who are unable to achieve glycemic control through diet and exercise.

❼ Insulin is the essential treatment for patients with type 1 DM and can overcome insulin resistance in patients with type 2 DM.

❶ ***Diabetes mellitus*** *(DM) describes a group of chronic metabolic disorders characterized by* ***hyperglycemia*** *that may result in long-term microvascular, macrovascular, and neuropathic complications.* These complications contribute to diabetes being the leading cause of (1) new cases of blindness among adults, (2) end-stage renal disease, and (3) non-traumatic lower limb amputations. In addition, the increased cardiovascular risk associated with DM contributes to it being the sixth leading cause of death in the United States. The financial impact of DM in 2002 was approximately $132 billion, or 1 of every 10 dollars spent on health care in the United States. This averages to an annual health care cost of $13,243 for patients with diabetes versus $2560 for those without diabetes.[1]

While prevention and treatment of DM remain a challenge, several landmark studies have shown that complications associated with DM can be delayed or prevented through proper

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blood glucose management.[2,3] ❷ Thus, *glycemic control remains the primary objective in diabetes management.*

EPIDEMIOLOGY AND ETIOLOGY

DM is characterized by a complete lack of insulin, a relative lack of insulin, or insulin resistance. These defects result in an inability to properly use glucose for energy. DM affects an estimated 20.8 million persons in the United States, or 7% of the population. While an estimated 14.6 million persons have been diagnosed, another 6.2 million people who have DM are unaware they have the disease. Worldwide, the number of people with DM is expected to rise to 35% by the year 2025.[1]

The increasing prevalence of DM is due in part to three influences: lifestyle, ethnicity, and age. Sedentary lifestyle coupled with greater consumption of high-fat foods and larger portion sizes has resulted in increasing rates of persons being overweight or obese. Current estimates indicate that 65% of the United States population is overweight and 30% is obese. Overweight is defined as **body mass index** (BMI) of greater than 25 kg/m^2, whereas a BMI of greater than 30 kg/m^2 constitutes obesity. The Centers for Disease Control and Prevention (CDC) estimates that 25% to 33% of Americans do not engage in an adequate amount of daily activity.[4] Compounding this lifestyle trend, certain ethnic groups are at a disproportionately high risk of DM. Individuals of Native American and Alaskan native, African-American, and Hispanic/Latino-American descent have a 1.7 to 2.2 times greater risk of developing DM compared with non-Hispanic whites.[1] In addition, African-American and Hispanic/Latino-American populations are growing at a faster rate than the general United States population. The third contributing factor is increasing age. The prevalence of DM increases with age from approximately 2% of individuals 20 to 39 years of age to 20.9% of individuals older than 60 years of age.[1] As the population ages, the incidence of DM is expected to increase.

❸ *Type 2 DM, previously referred to as* adult-onset *or* non-insulin-dependent DM, *is the most prevalent form of the disease and accounts for approximately 90% to 95% of all diagnosed cases.*[1] Type 2 DM is characterized by a relative insulin deficiency and insulin resistance.

❸ *Type 2 DM is usually slow and progressive in its development and often is preceded by* ***pre-diabetes****.* The development of pre-diabetes places the individual at high risk of eventually developing diabetes. It is currently estimated that 41 million persons in the United States have pre-diabetes. Pre-diabetes is defined as having either a fasting and/or a postprandial blood glucose level higher than normal but not high enough to be classified as DM. Because progression from pre-diabetes to diabetes is not inevitable, interventions during pre-diabetes are gaining popularity.

Risk factors for type 2 diabetes include:

- First-degree family history of DM (i.e., parents or siblings)
- Overweight or obese
- Habitual physical inactivity
- Race or ethnicity (Native American, Latino/Hispanic-American, Asian-American, African-American, and Pacific Islanders)
- Pre-diabetes (i.e., previously identified with impaired glucose tolerance or impaired fasting glucose)
- Hypertension (Greater than or equal to 140/90 mm Hg)
- High-density lipoprotein (HDL) less than 35 mg/dL (0.91 mmol/L) and/or a triglyceride level greater than 250 mg/dL (2.83 mmol/L)
- History of gestational diabetes or delivery of a baby weighing greater than 9 pounds (4.09 kg)
- History of vascular disease
- History of polycystic ovary disease
- Other conditions associated with insulin resistance (e.g., **acanthosis nigricans**)[5]

Type 1 DM, previously referred to as *insulin-dependent* or *juvenile-onset DM,* constitutes 5% to 10% of all diagnosed cases of DM. ❹ *Type 1 DM usually is diagnosed in children and adults younger than 30 years of age, although the disease can present at any age. This form of the disease is characterized by an absolute deficiency in insulin resulting from pancreatic β-cell destruction.* Latent autoimmune diabetes in adults (LADA), slow-onset type 1 or type 1.5 DM, is a form of autoimmune type 1 diabetes that occurs in individuals older than the usual age of onset. Patients often are mistakenly thought to have type 2 diabetes because the person is older and may respond initially to treatment with oral hypoglycemic agents. However, these patients do not have insulin resistance, but antibodies are present in the blood that are known to destroy pancreatic β-cells.

It has been suggested that the easiest way to differentiate between type 1 and type 2 DM is by measuring C-peptide levels. Type 1 diabetics have C-peptide levels below 1 ng/mL (0.33 nmol/L), whereas those with type 2 disease will have values greater than 1 ng/mL (0.33 nmol/L).

Glucose intolerance diagnosed in women during pregnancy is called gestational diabetes mellitus (GDM) and occurs in approximately 7% of all pregnancies. Women who have GDM have a 20% to 50% chance of developing diabetes within 5 to 10 years. Risk factors for GDM include obesity, **glycosuria,** strong family history of DM, age greater than 35 years of age, pre-diabetes detected before pregnancy, previous delivery of babies with birth weights greater than 9 pounds (4.09 kg), and ethnicity (African-American, Hispanic/Latino-American, or Native American). Clinical detection of and therapy for GDM are important because blood sugar control produces significant reductions in perinatal morbidity and mortality.

Rare forms of DM have been reported and account for 1% to 5% of all diagnosed cases. Causes of these rare forms of DM include specific genetic conditions, surgery, drugs, malnutrition,

TABLE 40–1. Medications That May Affect Glycemic Control[a]

Drug	Effect on Glucose	Mechanism/Comment
Angiotensin-converting enzyme inhibitors	Slight reduction	Improves insulin sensitivity
Alcohol	Reduction	Reduces hepatic glucose production
α-Interferon	Increase	Unclear
Diazoxide	Increase	Decreases insulin secretion, decreases peripheral glucose use
Diuretics	Increase	May increase insulin resistance
Glucocorticoids	Increase	Impairs insulin action
Nicotinic acid	Increase	Impairs insulin action, increases insulin resistance
Oral contraceptives	Increase	Unclear
Pentamidine	Decrease, then increase	Toxic to β-cells; initial release of stored insulin, then depletion
Phenytoin	Increase	Decreases insulin secretion
β-Blockers	May increase	Decreases insulin secretion
Salicylates	Decrease	Inhibition of I-kappa-B kinase-beta (IKK-beta) (only high doses, e.g., 4–6 g/day)
Sympathomimetics	Slight increase	Increased glycogenolysis and gluconeogenesis
Clozapine and olanzapine	Increase	Unclear; weight gain

[a]This list is not inclusive of all medications reported to cause glucose changes.
Reproduced, with permission, from DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiological Approach*. 6th ed. New York: McGraw-Hill; 2005, Table 72–10, p. 1346.

infections, and other illnesses. Table 40-1 contains a list of medications that may affect glycemic control. While the use of these medications is not contraindicated in persons with DM, caution and awareness of the effects on blood glucose should be taken into account when managing patient care.

PATHOPHYSIOLOGY

Normal Carbohydrate Metabolism

The body's main energy source is the metabolism of glucose. Cells metabolize glucose completely through glycolysis and the Kreb cycle, producing water and carbon dioxide as waste products. Glucose not immediately needed for energy is stored in the liver and muscles as glycogen. Later, when energy is needed, **glycogenolysis** converts stored glycogen back to glucose. Excess glucose also can be converted to triglycerides and stored in fat cells. Triglycerides subsequently undergo lipolysis, yielding glycerol and free fatty acids. While usually reserved for other functions, proteins also can be converted to glucose through a process called **gluconeogenesis.** Normal homeostasis is achieved through a balance of the metabolism of glucose, free fatty acids, and amino acids to maintain a blood glucose level sufficient to provide an uninterrupted supply of glucose to the brain.[6]

Insulin and glucagon are produced in the pancreas by cells known as islets of Langerhans. β-Cells make up 70% to 90% of the islets and produce insulin, whereas β-cells produce glucagon. The main function of insulin is to decrease blood glucose levels, whereas glucagon, along with other counterregulatory hormones, such as growth factor, cortisol, and epinephrine, increase blood glucose levels. While blood glucose levels vary, the opposing actions of insulin and glucagon, along with the counterregulatory hormones, maintain these values between 70 and 120 mg/dL (3.89 and 6.66 mmol/L).

Type 1 Diabetes

❹ *The primary defect in type 1 DM is an absolute insulin deficiency resulting from pancreatic β-cell destruction.* β-Cell destruction is most commonly the result of an autoimmune process usually precipitated through genetic susceptibility and/or an environmental trigger. Certain genetic markers can be measured to determine if a person is at risk of diabetes. The presence of human leukocyte antigens (HLAs), especially HLA-DR, is strongly associated with the development of type 1 diabetes. Over 95% of people with type 1 DM have HLA-DR3 and HLA-DR4 present. In addition, persons with DM often develop islet-cell antibodies, insulin autoantibodies, or glutamic acid decarboxylase autoantibodies. More than 90% of persons with type 1 DM have at least one diabetes-related antibody present. As more β-cells are destroyed, glucose metabolism becomes compromised due to reduced insulin release following a glucose load. At the time of diagnosis, most patients have a 90% loss of β-cell function. The remaining 10% of β-cell function at diagnosis creates a "honeymoon period" during which blood glucose levels are easier to control and smaller amounts of insulin are required. Once this remaining β-cell function is lost, patients become completely insulin-deficient and require more exogenous insulin. Figure 40–1 describes the progression of type 1 DM.

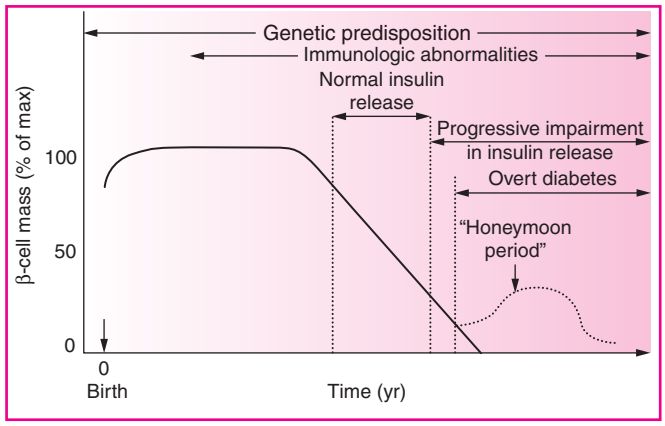


FIGURE 40–1 Scheme of the natural history of the β-cell defect in type 1 diabetes mellitus. (Used, with permission, from DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiological Approach*. 6th ed. New York: McGraw-Hill; 2005, Fig. 72–4, p. 1339.) yr, year.

Type 2 Diabetes

Type 2 DM is characterized by a slow, gradual onset of hyperglycemia that often is asymptomatic. The underlying metabolic dysfunction contributing to this disease is thought to be a combination of both genetic and environmental factors. ❸ *Rising blood glucose levels result from increasing insulin resistance and impaired insulin secretion leading to relative insulin deficiency.* Prior to describing these two insulin defects, it is necessary to understand normal insulin action and its role in glucose control.

Normal Insulin Action

During periods of fasting, most circulating glucose is produced in the liver by glycogenolysis. This **endogenous** production of glucose serves to ensure the brain a constant glucose supply. Insulin secretion during fasting periods is a low, steady basal rate of 0.5 to 1 units/hour.[6] On eating, blood glucose levels rise, and the insulin-secretion response occurs in two phases. An initial burst, known as *first phase insulin response,* lasts approximately 10 minutes and serves to suppress hepatic glucose production. This bolus of insulin minimizes hyperglycemia during meals and during the postprandial period. The loss of this first phase insulin response is an early event in the progression from glucose intolerance to DM. The *second phase of insulin response* is characterized by a gradual increase in insulin secretion, which stimulates glucose uptake by peripheral insulin-dependent tissues. Approximately 80% to 85% of glucose metabolism during this time occurs in muscle. The slower release of insulin allows the body to respond to the new glucose entering from digestion while maintaining blood glucose levels.

Impaired Insulin Secretion

A pancreas with normal β-cell function is able to adjust insulin production to maintain normal blood glucose levels. **Hyperinsulinemia,** or high blood levels of insulin, is an early finding in the development of type 2 DM. More insulin is secreted to maintain normal blood glucose levels until eventually the pancreas can no longer produce sufficient insulin. The resulting hyperglycemia is enhanced by extremely high insulin resistance, pancreatic burnout in which β-cells lose functional capacity, or both. Patients with type 2 DM typically have approximately 40% β-cell function at diagnosis. Decreasing β-cell function also results in a reduced ability to produce a first-phase insulin response sufficient to signal the liver to stop producing glucose during the fed state. As DM progresses, large numbers of patients with type 2 disease eventually lose all β-cell function and require **exogenous** insulin to maintain blood glucose control.

Insulin Resistance

Insulin resistance is the primary factor that differentiates type 2 DM from other forms of diabetes. Insulin resistance may be present up to 10 years prior to the diagnosis of DM and can continue to progress throughout the course of the disease. Resistance to insulin occurs most significantly in skeletal muscle and the liver. Insulin resistance in the liver poses a double threat because the liver becomes non-responsive to insulin for glucose uptake, and hepatic production of glucose during the fed state does not cease. Hyperglycemia results because ingested glucose and continued hepatic glucose production combine to raise blood glucose levels.

Metabolic Syndrome

Insulin resistance has been associated with a number of other cardiovascular risks, including abdominal obesity, hypertension, dyslipidemia, hypercoagulation, and hyperinsulinemia. The clustering of these risk factors has been termed metabolic syndrome. It is estimated that 50% of the United States population older than 60 years of age have metabolic syndrome. The most widely used criteria to define metabolic syndrome were established by the National Cholesterol Education Program Adult Treatment Panel III Guidelines (summarized in Table 40–2).

TABLE 40–2. Five Components of Metabolic Syndrome[20]

Risk Factor	Defining Level
1. Abdominal obesity	
• Men	Waist circumference greater than 102 centimeters (40 inches)
• Women	Waist circumference greater than 88 centimeters (35 inches)
2. Triglycerides	Greater than 150 mg/dL (1.70 mmol/L)
3. HDL cholesterol	
• Men	Less than 40 mg/dL (1.04 mmol/L)
• Women	Less than 50 mg/dL (1.3 mmol/L)
4. Blood pressure	Greater than or equal to 130/85 mm Hg
5. Fasting glucose	Greater than or equal to 100 mg/dL (5.55 mmol/L)

Note: Individuals having at least three of the five above meet the diagnostic criteria for metabolic syndrome.

Patients having this convergence of factors have been found to be at a much higher cardiovascular risk than would be expected from the individual components of the syndrome. Therefore, it is important to assume a more aggressive treatment plan for each of the individual abnormal components. Since pre-diabetes and DM are one of the component risk factors in the diagnostic criteria, a patient with pre-diabetes or DM having the convergence of factors may be treated more aggressively than a patient having pre-diabetes or DM alone.

CLINICAL PRESENTATION AND DIAGNOSIS

Screening

Currently, the American Diabetes Association (ADA) recommends routine screening for type 2 DM every 3 years in all adults starting at 45 years of age. Earlier and more frequent screening should be reserved for patients who are at higher risk. The ADA does not recommend screening for type 1 diabetes owing to the low incidence and acute presentation of symptoms.[7] See Table 40–3 for complete screening guidelines.

Gestational Diabetes

Risk assessment for GDM should be performed early in pregnancy with a random glucose test. If the normal diagnostic threshold for diabetes is exceeded during the first test and confirmed on a subsequent day, a diagnosis of GDM can be made. Otherwise, all women should be screened with an oral glucose tolerance test (OGTT) between weeks 24 and 28 of gestation unless they are in the low-risk category. The diagnostic



Patient Encounter, Part 1

MF is a large-framed 32-year-old Caucasian man who is 5 ft, 10 in (178 cm) tall and weighs 295 lb (134 kg). He has not been to the doctor in 5 years. He is diagnosed with irritable bowel syndrome today. He visits the local free clinic, and the following is discovered when labs and physical assessment are performed:

Fasting glucose: 189 mg/dL (10.49 mmol/L)
BUN: 13 mg/dL (4.64 mmol/L)
Creatinine: 1.2 mg/dL (106 µmol/L)
AST/SGOT: 26 IU/L (0.43 µKat/L)
ALT/SGPT: 26 IU/L (0.43 µKat/L)
TSH: 1.264 microunits/mL (1.26 mU/L)
Total cholesterol: 277 mg/dL (7.17 mmol/L)
LDL: 187 mg/dL (4.84 mmol/L)
HDL: 29 mg/dL (0.75 mmol/L)
Triglycerides: 305 mg/dL (3.45 mmol/L)
Hemoglobin A_{1c}: 11%
BP (blood pressure): 167/98 mm Hg

- What information is suggestive of diabetes?
- What criteria must be met before a diagnosis of diabetes can be made?
- What type of diabetes do you think MF has based on his clinical characteristics?
- What challenges can you identify for optimal clinical outcomes through the initial assessments for MF?
- What additional information do you need to know before creating a treatment plan for this patient?



Typical Clinical Presentation of Diabetes Mellitus

Characteristic	Type 1 DM	Type 2 DM
Age of onset	Childhood or adolescence	Greater than 40 years of age
Speed of onset	Abrupt	Gradual
Family history	Negative	Positive
Body type	Thin	Obese or history of obesity
Metabolic syndrome	No	Often
Autoantibodies	Present	Rare
Symptoms	**Polyuria**, **polydipsia**, **polyphagia**, rapid weight loss	Asymptomatic
Ketones at diagnosis	Present	Uncommon
Acute complications	**Diabetic ketoacidosis (DKA)**	Rare
Microvascular complications at diagnosis	Rare	Common
Macrovascular complications at or before diagnosis	Rare	Common

TABLE 40–3. American Diabetes Association Screening Recommendations for Diabetes Mellitus[5]

Asymptomatic Type 1

The American Diabetes Association does not recommend screening for type 1 diabetes due to the low incidence in the general population and to the acute presentation of symptoms.

Asymptomatic Type 2

1. The American Diabetes Association recommends screening for type 2 diabetes every 3 years in all adults beginning at 45 years of age, particularly in those with a body mass index greater than or equal to 25 kg/m^2.
2. Testing should be considered for persons younger than 45 years of age or more frequently in individuals who are overweight (body mass index greater than or equal to 25 kg/m^2) and have additional risk factors:

- Habitually inactive
- First-degree relative with diabetes
- Member of a high-risk ethnic population (e.g., African-American, Latino, Native American, Asian-American, Pacific Islander)
- Delivered a baby weighing greater than 9 lb (4.09 kg) or previous diagnosis of gestational diabetes mellitus
- Hypertensive (greater than or equal to 140/90 mm Hg)
- High density lipoprotein (HDL) cholesterol level less than 35 mg/dL (0.91 mmol/L) and/or a triglyceride level greater than 250 mg/dL (2.83 mmol/L)
- Polycystic ovary syndrome
- Previous impaired glucose tolerance or impaired fasting glucose
- Other clinical conditions associated with insulin resistance (e.g., acanthosis nigricans)
- History of vascular disease

Type 2 in Children and Adolescents

Criteria:

- Overweight (body mass index greater than 85th percentile for age and sex, weight for height greater than 85th percentile, or weight greater than 120% of ideal for height)

Plus any **two** of the following risk factors:

- Family history of type 2 diabetes in first- or second-degree relatives
- Race/ethnicity (Native American, African-American, Latino/Hispanic-American, Asian-American, Pacific Islander)
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, or polycystic ovary disease)

Age of initiation: Age 10 or at onset of puberty, if puberty occurs at a younger age
Frequency of testing: Every 2 years
Test method: Fasting plasma glucose preferred
Clinical judgment should be used to test for diabetes in high-risk patients who do not meet these criteria.

Gestational Diabetes

1. Risk assessment performed at first prenatal visit with random glucose screen.
2. All women should be screened with an oral glucose tolerance test between weeks 24 and 28 of gestation unless they are in the low-risk category.

criteria for OGTT are listed in Table 40–4. Women considered low risk include those of normal weight before pregnancy; younger than 25 years of age; without first-degree relatives with diabetes; non-Hispanic, African-American, or Native American ethnicity; and no prior history of glucose intolerance or poor obstetric outcome.[5]

Any woman diagnosed with GDM should be retested at 6 weeks postpartum. If the fasting plasma glucose (FPG) level is normal, then reassessment for DM should occur every 3 years. Family planning for subsequent pregnancies should be discussed, and monitoring for the development of symptoms of DM should be undertaken.

TABLE 40–4. Diagnosis of Gestational Diabetes with a 100 or 75 g Glucose Load[8]

	Plasma Glucose	
Time	**mg/dL**	**mmol/L**
100 g Glucose Load		
Fasting	95	5.3
1 hour	180	10.0
2 hours	155	8.6
3 hours	140	7.8
75 g Glucose Load		
Fasting	95	5.3
1 hour	180	10.0
2 hours	155	8.6

Note: Two or more venous plasma concentrations must be met or exceeded for a positive diagnosis of diabetes to be made. The test should be done in the morning after an 8- to 14-hour fast and after at least 3 days of unrestricted diet and unlimited physical activity. The patient should remain seated and should not smoke during the test.

Diagnostic Criteria

Diagnosis of DM includes glycemic outcomes exceeding threshold values with one of three testing options (Table 40–5). Confirmation of abnormal values must be made on a subsequent

TABLE 40–5. Criteria for the Diagnosis of Diabetes Mellitus[5]

1. Symptoms of diabetes plus a casual plasma glucose concentration greater than or equal to 200 mg/dL (11.1 mmol/L). *Casual* is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

or

2. Fasting plasma glucose greater than or equal to 126 mg/dL (7.0 mmol/L). *Fasting* is defined as no caloric intake for at least 8 hours.

or

3. Two-hour postload glucose greater than or equal to 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

Note: In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day. The oral glucose tolerance test is not recommended for routine clinical use.

day for diagnosis unless unequivocal symptoms of hyperglycemia exist, such as polydipsia, polyuria, and polyphagia. The ADA recommends FPG determination as the principal tool for diagnosis of DM in non-pregnant adults owing to ease of use, acceptability to patients, and lower cost.[7] While the OGTT is more sensitive and modestly more specific than FPG determination, it is difficult to reproduce the results and is rarely performed in practice today.

The ADA categorizes patients demonstrating impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) as having pre-diabetes.[8] The categorization thresholds of glucose status for FPG determination and the OGTT are listed in Table 40–6. These two conditions may co-exist or may be identified independently. FPG level represents hepatic glucose production during the fasting state, whereas postprandial glucose levels in the OGTT may reflect glucose uptake in peripheral tissues, insulin sensitivity, or a decreased first-phase insulin response.

TABLE 40–6. Categorization of Glucose Status[8]

	mg/dL	mmol/L
Fasting Plasma Glucose (FPG)		
• Normal	Less than 100	Less than 5.6
• Impaired fasting glucose (IFG)	100–125	5.6–6.9
• Diabetes mellitus[a]	Greater than or equal to 126	7.0
2-Hour Postload Plasma Glucose (Oral glucose tolerance test)		
• Normal	Less than 140	7.8
• Impaired glucose tolerance (IGT)	140–199	7.8–11.0
• Diabetes mellitus[a]	Greater than or equal to 200	11.1

[a]Provisional diagnosis of diabetes (diagnosis must be confirmed; see Table 40–5).

TREATMENT

Goals of Therapy

DM treatment goals include reducing long-term microvascular and macrovascular complications, preventing acute complications from high blood glucose levels, minimizing hypoglycemic episodes, and maintaining the patient's overall quality of life. To achieve these goals, near-normal blood glucose levels are fundamental. Two landmark trials, the Diabetes Control and Complications Trial[2] and the United Kingdom Prospective Diabetes Study,[3] showed that lowering blood glucose levels decreased the risk of developing chronic complications. A near-normal blood glucose level can be achieved with appropriate patient education. Proper care of DM requires goal setting and assessment for glycemic control, self-monitoring of blood glucose (SMBG) level, monitoring of blood pressure and lipid levels, regular monitoring for the development of complications, dietary and exercise lifestyle modification, and proper medication use. The complexity of proper DM self-care principles has a dramatic impact on a patient's lifestyle and requires a highly disciplined and dedicated person to maintain long-term control.

Setting and Assessing Glycemic Targets

❺ *Patients and clinicians can evaluate blood glucose control through the combination of the self-monitoring of blood glucose data and the hemoglobin A_{1c} (HbA_{1c}) test.* Self-monitoring of blood glucose enables patients to obtain their current blood glucose level at any time easily and relatively inexpensively. The HbA_{1c} test provides a weighted-mean blood glucose level from the previous 3 months.

Self-Monitoring of Blood Glucose

Self-monitoring of blood glucose is the standard method for routinely checking blood glucose levels. Each reading provides a point-in-time evaluation of glucose control that can vary widely depending on numerous factors, including food, exercise, stress, and time of day. By examining multiple individual points of data, patterns of control can be established. Therapy can be evaluated from these patterns, and adjustments can be made to improve overall blood glucose control. The ADA pre-meal plasma glucose goals are 90 to 130 mg/dL (5–7.22 mmol/L), and peak postprandial plasma glucose goals are less than 180 mg/dL (10 mmol/L).[5] The American Association of Clinical Endocrinologists (AACE) supports tighter SMBG controls, with pre-meal goals of less than 110 mg/dL (6.11 mmol/L) and peak

post-meal goals of less than 140 mg/dL (7.77 mmol/L).[9] For patients with type 1 DM, the ADA recommends that SMBG be performed at least three times daily. The frequency of testing in patients with type 2 DM is still controversial. The ADA recommends testing frequently enough to gain and maintain blood glucose control. While the majority of practitioners recommend SMBG to their patients with type 1 DM, the role of SMBG in improving glucose control in type 2 DM is unproven.[10]

Typically, in SMBG, a drop of blood is placed on a test strip that is then read by a glucometer. Recent technological advancements have decreased the blood sample size required to as small as 0.3 microliters, provided the capability of alternate site testing, and provided readings in as few as 5 seconds. Many SMBG devices can download or transfer information to a computer program that can summarize and produce graphs of the data. Identifying patterns in the patient's blood glucose data can aid practitioners in modifying treatment for better glucose control. Specific therapy adjustment can be made for patterns found at certain times of the day, on certain days, or with large day-to-day variances. While most testing occurs by lancing the fingertip to produce a blood droplet, alternate-site testing has been approved for testing the palm, arm, leg, and abdomen. Alternate-site testing was developed as a means to decrease the pain encountered with repeated fingersticks by using body locations that have a lower concentration of nerve endings.

In choosing a glucose meter for a patient, several additional factors may aid in the best selection for the patient. Larger display areas or units with audible instructions and results may be better suited for older individuals and those with visual impairment. Patients with arthritis or other conditions that decrease dexterity may prefer larger meters with little or no handling of glucose strips. Younger patients or busy professionals, on the other hand, may prefer the smaller meters with features such as faster results, larger memories, reminder alarms, and downloading capabilities that facilitate individuals checking their blood glucose levels.

Hemoglobin A_{1c}

Hemoglobin A_{1c} (HbA_{1c}) is the "gold standard" for evaluating long-term glycemic control.[11] Glucose interacts spontaneously with hemoglobin in red blood cells to form glycosylated derivatives. The most prevalent derivative is HbA_{1c}. Greater amounts of glycosylation occur when blood glucose levels increase. Because hemoglobin has a life span of approximately 120 days, levels of HbA_{1c} provide a marker reflecting the average glucose levels over this timeframe. The ADA goal for persons with DM is less than 7%, whereas the AACE supports a goal of less than 6.5%. Testing HbA_{1c} levels should occur at least twice a year for patients who are meeting treatment goals and four times per year for patients not meeting goals or those who have had recent changes in therapy.[5]

Blood Pressure, Lipids, and Monitoring for Complications

The ADA standards of medical care address many of the common comorbid conditions, as well as complications that result from the progression of DM. Table 40–7 presents goals for blood pressure measurements, lipids values, and monitoring parameters for complications associated with diabetes.

General Approach to Therapy

Type 1 DM

Treatment of type 1 DM requires providing exogenous insulin to replace the endogenous loss of insulin from the non-functional pancreas. Ideal insulin therapy mimics normal insulin physiology.



Patient Encounter, Part 2: The Follow-up Visit

MF comes back 1 week later for you to review the laboratory results with him and to determine if medications are necessary. When you check his FBG level today, the result is 210 mg/dL (11.7 mmol/L). A diagnosis of DM is made, but you have no other blood glucose records. The following information is gained from MF during the visit:

PMH
- Occasional sinus infections over the last several years
- Reports last eye examination about 6 years ago; believes he could use new glasses
- No other problems reported

FH
- Father: 64 years of age; history of alcohol abuse, hypertension, and myocardial infarction
- Mother: 62 years of age; history of type 2 DM, hypertension, and obesity
- Sister: 34 years of age; history of hypothyroid and obesity

SH
- Drinks 3 to 4 times per week and smokes cigarettes 1 to 2 packs per day for 20 years
- No steady employment

Meal history
Usually has a donut and large coffee in the mornings, fast-food "value meal" for lunch, and a diner meal for supper (meat and two vegetables)

Physical activity
No regular physical activity routine but does walk around about 30 minutes a day

- What are your treatment goals for MF regarding blood glucose, blood pressure, and lipids?
- What nonpharmacologic and pharmacologic approaches are available for MF?
- Are there any specialist care providers you would refer MF to?

TABLE 40–7. American Diabetes Association Recommended Goals of Therapy

Area	Goals
Glycemia	
HbA_{1c}	Less than 7% Every 3 months until in goal; then every 6 months
Preprandial plasma glucose	90–130 mg/dL (5.0–7.2 mmol/L)
Peak postprandial plasma glucose[a]	Less than 180 mg/dL (less than 10 mmol/L)
Blood Pressure	Less than 130/80 mm Hg Evaluate at every visit
Lipids	Evaluate at least yearly
Low-density lipoprotein (LDL)	Less than 100 mg/dL (2.59 mmol/L) or less than 70 mg/dL (1.81 mmol/L) if high risk
High-density lipoprotein (HDL)	Greater than 40 mg/dL (1.04 mmol/L) for males; greater than 50 mg/dL (1.3 mmol/L) for females
Triglycerides	Less than 150 mg/dL (1.70 mmol/L)
Monitoring for Complications	
Eyes	Dilated eye exam yearly
Feet	Feet should be examined at every visit
Urinary microalbumin	Yearly

[a]Peak postprandial glucose measurements should be made 1 to 2 hours after the beginning of the meal.

The basal-bolus approach attempts to reproduce basal insulin response through the use of intermediate- or long-acting insulin, whereas short- or rapid-acting insulin replicates bolus release of insulin physiologically seen around a meal in nondiabetics. A number of different regimens have been used through the years to more closely follow natural insulin patterns. As a general rule, basal insulin makes up approximately 50% of the total daily dose. The remaining half is provided with bolus doses around three daily meals. Exact doses are individualized to the patient and the amount of food consumed. Type 1 DM patients frequently are started on about 0.6 units/kg per day, and then doses are titrated until glycemic goals are reached. Most type 1 DM patients use between 0.6 and 1 unit/kg per day.

Currently, the most advanced form of insulin therapy is the insulin pump, also referred to as continuous subcutaneous insulin infusion (CSII). Using the short- or rapid-acting insulins only, these pumps are programmed to provide a slow release of small amounts of insulin as the basal portion of therapy, and then larger bolus doses are injected by the patient to account for the consumption of food.

Type 2 DM

Treatment of type 2 DM has changed dramatically over the past decade with the addition of a number of new drugs and the ADA recommendations to maintain tighter glycemic control. Figure 40–2 details an algorithm for type 2 diabetes. Lifestyle modifications, including education, nutrition, and exercise, are paramount to managing the disease successfully. Many patients assume that once pharmacologic therapy is initiated, lifestyle modifications are no longer necessary. Practitioners should educate patients regarding this misconception. Since type 2 diabetes is a progressive disease, blood glucose levels will eventually increase making insulin therapy and lifestyle modifications the eventual required therapy.

Gestational Diabetes

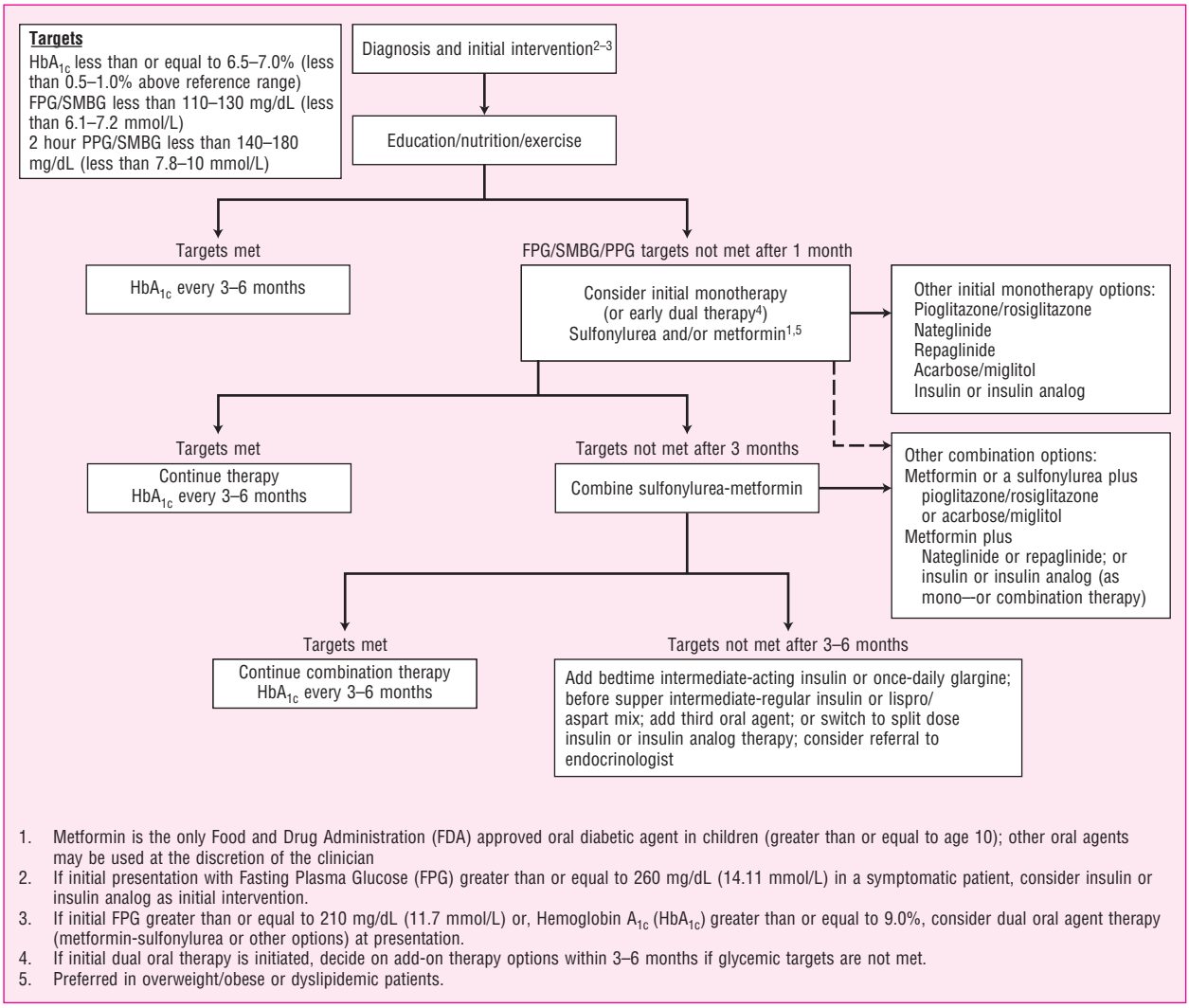
An individualized meal plan consisting of three meals and three snacks per day is recommended commonly in GDM. Preventing **ketosis,** promoting adequate growth of the fetus, maintaining satisfactory blood glucose levels, and preventing nausea and other undesired gastrointestinal side effects are desired goals in these patients. Controlling blood sugar levels is important to prevent harm to the baby. An abundance of glucose causes excessive insulin production by the fetus, which, if left uncontrolled, can lead to the development of an abnormally large fetus. Infant **hypoglycemia** at delivery, hyperbilirubinemia, and complications associated with delivery of a large baby also may occur when blood glucose levels are not controlled adequately.

Insulin should be used when blood glucose levels are not maintained adequately at target levels by diet and physical activity. Only human insulin should be used for treating GDM to prevent the transfer of anti-insulin antibodies. Oral glucose-lowering agents are not recommended during pregnancy. Additionally, women with pre-pregnancy hypertension and dyslipidemia should have their medications reevaluated at conception.

Nonpharmacologic Therapy

Diet

Despite the popular notion, there is not a "diabetic diet." The recommended diet for patients with diabetes is a meal plan low in fat, high in fiber, low to moderate in calories, and achieving a balance of the various components and nutrients needed.[12] Medical nutrition therapy (MNT) is considered an integral component of diabetes management and diabetes self-management education. People with DM should receive individualized MNT, preferably by a registered dietitian. As part of the diabetes management plan, MNT is not a single



1. Metformin is the only Food and Drug Administration (FDA) approved oral diabetic agent in children (greater than or equal to age 10); other oral agents may be used at the discretion of the clinician
2. If initial presentation with Fasting Plasma Glucose (FPG) greater than or equal to 260 mg/dL (14.11 mmol/L) in a symptomatic patient, consider insulin or insulin analog as initial intervention.
3. If initial FPG greater than or equal to 210 mg/dL (11.7 mmol/L) or, Hemoglobin A_{1c} (HbA_{1c}) greater than or equal to 9.0%, consider dual oral agent therapy (metformin-sulfonylurea or other options) at presentation.
4. If initial dual oral therapy is initiated, decide on add-on therapy options within 3–6 months if glycemic targets are not met.
5. Preferred in overweight/obese or dyslipidemic patients.

FIGURE 40–2 Glycemic control algorithm for type 2 DM in children and adults. (Adapted with permission, from DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiological Approach*. 6th ed. New York: McGraw-Hill; 2005, Fig. 72–8, p. 1356. Also refer to Nathan DM, Buse JB, Davidson MB, et al. Management of Hyperglycerin in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. Diabetes Care 2006; 29:1963–1972.) PPG, postprandial glucose; SMBG, self-monitoring of glucose.

visit to a dietitian but rather an ongoing continuing dialog to assist the patient to integrate healthier choices into his or her daily lifestyle decisions. As such, MNT should be customized to take into account cultural, lifestyle, and financial considerations. MNT plans should integrate a variety of foods that the patient enjoys and allow for flexibility to encourage patient empowerment and improve patient adherence.

During these MNT educational and planning sessions, patients receive instructions on appropriate food selection, preparation, and proper portion control. The primary focus of MNT for patients with type 1 DM is matching optimal insulin dosing to carbohydrate consumption. In type 2 DM, the primary focus is calorie reduction to achieve weight loss.

The ADA does not recommend low-carbohydrate diets in diabetes management. Although carbohydrates are a primary contributor to post-meal glucose levels, they are also an important source of energy, water-soluble vitamins, minerals, and fiber. Thus, the ADA recommends that carbohydrate intake consists of 45% to 65% of total calories.

Weight Management

Moderate weight loss has been shown to reduce cardiovascular risk, as well as delay or prevent the onset of DM in those with pre-diabetes. The recommended primary approach to weight loss is therapeutic lifestyle change (TLC), which integrates a 500 to 1000 kcal/day reduction in calorie intake and

an increase in physical activity.[12] A slow but progressive weight loss of 1 to 2 lb (0.45–0.91 kg) per week is preferred. While individual target caloric goals should be set, a general rule for weight-loss diets is that they should supply at least 1000 to 1200 kcal/day for women and 1200 to 1600 kcal/day for men. Since 80% of patients with type 2 diabetes are overweight, this strategy works best for these patients.

Physical Activity

Physical activity is also an important component of a comprehensive DM management program. Regular physical activity has been shown to improve blood glucose control and reduce cardiovascular risk factors, such as hypertension and elevated serum lipid levels. Physical activity is also a primary factor associated with long-term maintenance of weight loss and overall weight control. Regular physical activity also may prevent the onset of type 2 DM in high-risk persons.

Prior to initiating a physical activity program, several considerations should be made. Patients should undergo a detailed physical examination, including screening for microvascular or macrovascular complications that may be worsened by a particular activity. Initiation of physical activities in an individual with a history of a sedentary lifestyle should begin with a modest increase in activity. Walking, swimming, and cycling are examples of low-impact exercises that could be encouraged. At the same time, gardening and usual house-cleaning tasks are good exercises as well. Long-term goals are to perform at least 30 minutes of aerobic activity as many days a week as possible.[13]

Preventing Diabetes

The Diabetes Prevention Program was a 3-year study that showed that lifestyle modifications, including exercise (30 minutes/day, 5 days/week) and moderate (5%–10%) weight loss, reduce the probability of developing DM by 58% in patients with pre-diabetes. Results from this study suggest that diet, exercise, and behavior modification are effective in preventing type 2 DM in high-risk patients.[14]

Psychological Assessment and Care

Mental health and social state have been shown to have an impact on a patient's ability to carry out DM management care tasks. Approximately one in four patients with DM experience episodes of major depression. Therefore, clinicians should incorporate psychological assessment and treatment into routine care. The ADA guidelines recommend psychological screening, which includes determining the patient's attitudes regarding DM, expectations of medical management and outcomes, mood and affect, general and diabetes-related quality of life, and financial, social, and emotional resources. Patients demonstrating non-compliance, depression, an eating disorder, and/or cognitive functioning that impairs judgment should be referred to a mental health specialist familiar with DM.[5]



Patient Encounter, Part 3: Creating a Care Plan

Create a care plan for MF's DM, including:

- Statement of drug-related needs and/or problems
- Goals for therapy
- Detailed plan with nonpharmacologic and pharmacologic therapy
- Follow-up plan to evaluate whether MF's goals for therapy have been achieved and adverse effects avoided

Immunizations

Influenza and pneumonia are common preventable infectious diseases that increase mortality and morbidity in persons with chronic diseases including DM.[5] Yearly influenza vaccinations, commonly called flu shots, are recommended for patients with DM. Pneumococcal vaccination also is recommended for patients with DM as a one-time vaccination for most patients.

Pharmacologic Therapy

A number of therapeutic advancements and new options for managing patients with DM have become available over the past decade, including α-glucosidase inhibitors, biguanides, non-sulfonylurea secretagogues, and thiazolidinediones (TZD).[15] In addition, a number of new insulin formulations have been added to the armamentarium, including rapid-acting insulins, combination mixtures, and basal insulins.[16] Finally, a number of emerging therapies have been approved recently, including pramlintide, exanatide, inhaled insulin and the dipeptidyl peptidase-4 (DPP-IV) inhibitors. The following section describes the current oral agents available to treat type 2 DM. Later in this section, the insulins and other injectible medications for type 1 and type 2 DM will be addressed.[17, 18]

❻ *Oral agents currently available are indicated in patients with type 2 DM who are unable to achieve glycemic control through diet and exercise.* Oral agents commonly used in the management of type 2 DM typically are classified according to their mechanism of action. **Insulin secretagogues** include sulfonylureas and non-sulfonylurea secretagogues. These agents stimulate and enhance endogenous insulin release. **Insulin sensitizers** include the thiazolidinediones that decrease insulin resistance in the periphery. The biguanides decrease hepatic glucose output and the DPP-IV inhibitors enhance the incretin system. Each of these agents may be used as monotherapy (Table 40–8) or in combination with other medications for synergistic effects.

Sulfonylureas

Sulfonylureas represent the first class of oral antidiabetes agents approved for use in the United States. These drugs are classified as being either first- or second-generation agents. Both classes of sulfonylureas are equally effective when given at

TABLE 40–8. Oral Agents for the Treatment of Type 2 Diabetes Mellitus

Generic Name	Brand	Generic Available	Dosage Strengths (mg)	Starting Dosage (mg/day)	Doses/Day	Titration Intervals	Maximum Dose (mg)	Effect (hour)	Comments/Cautions
Sulfonylureas—First Generation									
Major adverse events: Hypoglycemia, weight gain									
Acetohexamide	Dymelor	Y	250, 500	250	1–2	5–7 days	1500	Up to 16	Metabolized in liver, excreted in kidneys
Chlorpropamide	Diabinese	Y	100, 250	250	1	3–5 days	500	Up to 72	Caution in elderly and kidney disease, disulfiram-like reaction with alcohol
Tolazamide	Tolinase	Y	100, 250, 500	100–250	1–2	Weekly	1000	Up to 24	Excreted via kidney, less side effects than tolbutamide
Tolbutamide	Orinase	Y	250, 500	1000–2000	2–3	3–5 days	3000	Up to 12	Excreted via kidney, but can be useful in kidney disease
Sulfonylureas—Second Generation									
Major adverse event: Hypopglycemia									
Glipizide	Glucotrol,	Y	5, 10	5	1–2	3–5 days	40	Up to 20	Take immediate release
Slow release	Glucotrol XL	N	2.5, 5, 10, 20	5	1	3–5 days	20	24	tablets on an empty stomach; caution in elderly
Glyburide	Diaβeta,	Y	1.25, 2.5, 5	5	1–2	Weekly	20	Up to 24	Metabolized in liver and excreted in kidneys and bile, caution in
	Micronase,	Y							
Micronized	Glynase	N	1.5, 3, 6	3	1–2	Weekly	12	Up to 24	elderly
Glimepiride	Amaryl	N	1, 2, 4	1–2	1	3–5 days	8	24	60% renal and 40% liver elimination, take with first main meal
Non-sulfonylurea Secretagogues									
Hypoglycemia and weight gain are at a reduced risk due to short duration of action									
Nateglinide	Starlix	N	60, 120	120	3 with meals	Not applicable	120 per meal	Up to 4	Frequency of dosing dependent on frequency of meals
Repaglinide	Prandin	N	0.5, 1, 2	0.5–1	3 with meals	Weekly	4 per meal; 16 daily	Up to 4	Frequency of dosing dependent on frequency of meals
Biguanides									
Major adverse events: GI symptoms, nausea, diarrhea, lactic acidosis									
Metformin	Glucophage	Y	500, 850, 1000	500	2	1–2 weeks	2550	Up to 24	Renally excreted unmetabolized
Extended release	Glucophage XR	N	500, 750	500–1000	1	Weekly	2000	Up to 24	Discontinue if serum creatinine greater than 1.4 mg/dL (females) or 1.5 mg/dL (males)

Thiazolidinediones									
Major adverse events: Edema, weight gain; discontinue use if alanine aminotranferase (ALT) greater than 3 times normal; monitor liver function tests at baseline and periodically thereafter									
Pioglitazone	Actos	N	15, 30, 45	15	1	8–12 weeks	45	24	Metabolism by cytochrome P-450 2C8 and 3A4 pathways, days for onset of action
Rosiglitazone	Avandia	N	2,4, 8	2–4	1–2	8–12 weeks	8 mg/day or 4 mg twice daily	Up to 24	Metabolism by cytochrome P-450 2C8 and 2C9 pathways, days for onset of action
α-Glucosidase Inhibitors									
Major adverse events: GI symptoms including flatulence, cramps, and abdominal distension									
Acarbose	Precose	N	25, 50, 100	25	1–3 with meals	4–8 weeks	100 mg 3 times daily	Up to 3	Eliminated in bile, take with first bite of meal, little absorption
Miglitol	Glyset	N	25, 50, 100	25	1–3 with meals	4–8 weeks	100 mg 3 times daily	Up to 3	Eliminated through kidney and feces, take with first bite of meal
Dipeptidyl peptidase-4 inhibitors									
Major adverse events: Nasopharyngitis, upper respiratory tract infection									
Sitegliptin	Januvia	N	25, 50, 100	100	1	Not applicable	100	24	Reduce dosage for renal insufficiency
Combination Products									
Glyburide/ Metformin	Glucovance	N	1.25/250 2.5/500 5/500	2.5–5/500	2 with meals	2 weeks	[a]	[a]	[a] [a]
Glipizide/ Metformin	Metaglip	N	2.5/250, 2.5/500, 5/500	2.5–5/500	2 with meals	2 weeks	[a]	[a]	
Rosiglitazone/ Metformin	Avandamet	N	1/500, 2/500, 4/500, 2/1000, 4/1000	1–2/500	2 with meals	[a]	[a]	[a]	[a]
Pioglitazone/ Metformin	Actosplus Met	N	15/500, 15/850	15/500 or 15/850	1–2	[a]	[a]	[a]	[a]

[a]Refer to information for individual products in the combination.
GI, gastrointestinal; N, no; Y, yes

equipotent doses. Today, the vast majority of patients receiving a sulfonylurea are prescribed a second-generation agent.

Sulfonylureas enhance insulin secretion by blocking ATP-sensitive potassium channels in the cell membranes of pancreatic β-cells. This action results in membrane depolarization, allowing an influx of calcium to cause the translocation of secretory granules of insulin to the cell surface, and enhances insulin secretion. The extent of insulin secretion depends on the blood glucose level. More insulin is released in response to higher blood glucose levels, whereas the additional insulin secretion from sulfonylureas is less at near-normal glucose levels. Insulin is then transported through the portal vein to the liver, suppressing hepatic glucose production.[6]

All sulfonylureas undergo hepatic biotransformation, with most agents being metabolized by the cytochrome P-450 2C9 pathway. First-generation sulfonylureas are more likely to cause drug interactions than second-generation agents. All sulfonylureas except tolbutamide require a dosage adjustment or are not recommended in renal impairment. In elderly patients or those with compromised renal or hepatic function, lower starting dosages are necessary.

Monotherapy with sulfonylureas generally produce a 1.5% to 2% decline in HbA_{1c} concentrations and a 60 to 70 mg/dL (3.33–3.89 mmol/L) reduction in FBG levels. Secondary failure with these drugs occurs at a rate of 5% to 7% per year as a result of continued pancreatic β-cell destruction. One limitation of sulfonylurea therapy is the inability of these products to stimulate insulin release from β-cells at extremely high glucose levels, a phenomenon called glucose toxicity.

Non-sulfonylurea Secretagogues

While producing the same effect as sulfonylureas, non-sulfonylurea secretagogues, also referred to as meglitinides, have a much shorter onset and duration of action. Non-sulfonylurea secretagogues also produce a pharmacologic effect by interacting with ATP-sensitive potassium channels on the β-cells; however, this binding is to a receptor adjacent to those to which sulfonylureas bind.

The primary benefit of non-sulfonylurea secretagogues is in reducing post-meal glucose levels by about 40 mg/dL (2.22 mmol/L). These agents have demonstrated a reduction in HbA_{1c} levels between 0.6% and 1%. Owing to the rapid onset and short duration of action of these agents, non-sulfonylurea secretagogues are to be taken within 15 minutes of a meal. They also may be used in combination therapy with other drugs to achieve synergistic effects. Combining a non-sulfonylurea secretagogue with a sulfonylurea usually improves glucose control.

Biguanides

The only biguanide approved by the Food and Drug Administration (FDA) and currently available in the United States is metformin. Metformin was approved in the United States in 1995, although it has been used extensively in Canada and Europe since 1959. This agent is thought to lower blood glucose by increasing insulin sensitivity in both hepatic and peripheral muscle tissues; however, the exact mechanism of action remains unknown. Metformin has been shown to reduce HbA_{1c} levels by 1.5% to 2% and FPG levels by 60 to 80 mg/dL (3.33–4.44 mmol/L) when used as monotherapy. The response to metformin can vary according to the starting point of the patient. Larger effects can be seen in patients with a higher initial HbA_{1c} level (e.g., greater than 10%) than in patients beginning therapy with a relatively lower value (e.g., less than 8%). It is effective in reducing fasting as well as post-meal blood glucose levels. Metformin does not affect insulin release from β-cells of the pancreas, so hypoglycemia is not a common side effect. While the onset of action begins within days, the maximum therapeutic effect of this agent may not be observed until after 2 weeks of therapy.

Metformin also has been shown to produce beneficial effects on serum lipid levels and thus has become a first-line agent for type 2 DM patients with metabolic syndrome. Triglyceride and low-density lipoprotein (LDL) cholesterol levels often are reduced by 8% to 15%, whereas high-density lipoprotein (HDL) cholesterol improves by approximately 2%. A modest weight loss of 2 to 3 kg (4.4–6.6 lb) also has been reported with metformin therapy. Metformin often is used in combination with a sulfonylurea or a thiazolidinedione for synergistic effects.

Metformin does not undergo significant protein binding and is eliminated from the body unchanged in the urine. Elderly patients with a calculated creatinine clearance of less than 70 to 80 mL/minute should not receive this product. It is contraindicated in patients with a serum creatinine level greater than or equal to 1.4 mg/dL (124 μmol/L) in women and 1.5 mg/dL (133 μmol/L) in men. Additionally, therapy with metformin should be withheld in patients undergoing radiographic procedures in which a nephrotoxic dye is used. Therapy should be withheld the day of the procedure, as well as for the following 2 to 3 days.

Primary side effects associated with metformin therapy are gastrointestinal in nature, including decreased appetite, nausea, and diarrhea. These side effects can be minimized through slow titration of the dose and often subside within 2 weeks. Discontinuation because of side effects occurs in only 3% to 5% of patients.

Biguanides such as metformin are thought to inhibit mitochondrial oxidation of lactic acid, thereby increasing the chance of lactic acidosis occurring. Fortunately, the incidence of lactic acidosis in clinical practice is rare. Patients at greatest risk for developing lactic acidosis include those with liver disease or heavy alcohol use, severe infection, heart failure, and shock. Thus, it is common practice to evaluate liver function prior to initiation of metformin.

Thiazolidinediones

Commonly referred to as TZDs or glitazones, thiazolidinediones have established a significant role in type 2 DM therapy. As monotherapy, both rosiglitazone and pioglitazone reduce

FPG levels by 30 to 50 mg/dL (1.67–2.78 mmol/L), and the overall effect on HbA_{1c} is a 1% to 1.5% reduction. Onset of action for thiazolidinediones is delayed for several weeks and may require up to 12 weeks before maximum effects are observed. Combining a sulfonylurea, non-sulfonylurea secretagogue, metformin, or insulin with a thiazolidinedione can improve HbA_{1c} reductions to 2% to 2.5%.

Additional effects of thiazolidinediones are seen in the lipid profile. Both pioglitazone and rosiglitazone increase HDL cholesterol by 3 to 9 mg/dL (0.08–0.23 mmol/L). Pioglitazone has been shown to decrease serum triglycerides by 10% to 20%, whereas no substantial effect is observed with rosiglitazone. LDL cholesterol concentrations increase by 5% to 15% with rosiglitazone, whereas no significant increase has been reported for pioglitazone.

Thiazolidinediones are known to increase insulin sensitivity by stimulating peroxisome proliferator-activated receptor gamma (PPAR-γ). Stimulation of PPAR-γ results in a number of intracellular and extracellular changes, including an increased number of insulin receptors, increased insulin receptor sensitivity, decreased plasma fatty acid levels, and an increase in a host of intracellular signaling proteins that enhance glucose uptake.

Thiazolidinediones may produce fluid retention and edema; however, the mechanism by which this occurs is not completely understood. It is known that blood volume increases approximately 10% with these agents, resulting in approximately 6% of patients developing edema. Thus, these drugs are contraindicated in situations in which an increased fluid volume is detrimental, such as heart failure. Fluid retention appears to be dose-related and increases when combined with insulin therapy.

A few cases of hepatotoxicity have been reported with rosiglitazone and pioglitazone, but no serious complications have been reported, and symptoms typically reverse within several weeks of discontinuing therapy. Therefore, periodic liver function tests should be performed at baseline and during thiazolidinedione therapy. Patients with a baseline alanine aminotransferase (ALT) level greater than 2.5 times the upper limit of normal should not receive a TZD. If ALT levels rise to greater than 3 times the upper limit of normal in patients receiving a TZD, the medication should be discontinued.

α-Glucosidase Inhibitors

Acarbose and miglitol are α-glucosidase inhibitors currently approved in the United States. As monotherapy, α-glucosidase inhibitors reduce FPG concentrations by between 40 and 50 mg/dL (2.22–2.78 mmol/L); however, HbA_{1c} reductions range only from 0.3% to 1%. While these agents have been popular in Europe and other parts of the world, they have failed to gain widespread use in the United States. High incidences of gastrointestinal side effects, including flatulence (41.5%), abdominal discomfort (11.7%), and diarrhea (28.7%), have limited their use. Low initial doses followed by gradual titration may minimize gastrointestinal side effects.



Patient Encounter, Part 4: Oral to Insulin Therapy

Several years have passed since you have been following MF's therapy. His weight is down to 230 lb (104.6 kg), and he tries to maintain his diet and exercise. His recent HbA_{1c} levels have increased up to 8.4% from 7.2% despite combination therapy with sulfonylureas and metformin. The physician believes that it is time to start insulin therapy for MF and asks you to initiate therapy and follow his regimen.

- What insulin therapy would you choose for MF?
- How would you transition MF to insulin?

α-Glucosidase is an enzyme along the brush border of intestinal cells that breaks down complex carbohydrates into simple sugars, resulting in absorption. α-Glucosidase inhibitors work by delaying the absorption of carbohydrates from the intestinal tract, which reduces the rise in postprandial blood glucose concentrations. Gastrointestinal side effects occur as the result of intestinal bacteria in the distal gut metabolizing undigested carbohydrates and producing carbon dioxide and methane gas. α-Glucosidase inhibitors are contraindicated in patients with short-bowel syndrome or inflammatory bowel disease. In addition, neither drug in this class is recommended for patients with a creatinine clearance of less than 25 mL/minute.

Dipeptidyl peptidase-4 inhibitors

The newest therapeutic class of oral agents for DM is the dipeptidyl peptidase-4 (DPP-IV) inhibitors. Sitagliptin is the first and only agent in this class to be FDA approved, but vildagliptin and saxagliptin are currently in clinical trials and may soon join this class as therapeutic options. Sitagliptin is indicated for patients with type 2 DM as monotherapy or in combination therapy with metformin or a thiazolidinedione. The DPP-IV inhibitors slow the inactivation of incretin hormones within the gut. The incretin hormones are released throughout the day by the intestines and increased levels are produced in response to a meal. Normal or elevated incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), increase insulin production and release by the pancreatic beta cells. In addition, GLP-1 has been shown to decrease glucagon secretion from the pancreatic alpha cells which leads to a decrease in hepatic glucose production. Since DPP-IV inhibitors increase and prolong only active incretin levels, the resulting increase in insulin release and glucagon reduction occur in a glucose dependent manner.

Reductions in HbA_{1c} of 0.7%–0.8% were found in clinical trials verses placebo in both monotherapy and combination therapy using the recommended dose of sitagliptin 100 mg daily taken with or without food. Dosage adjustments to 50 mg and 25 mg daily are recommended for patients with moderate

(CrCl greater than or equal to 30 to less than 50 mL/minute) and severe (CrCl less than 30 mL/minute) renal impairment respectively. Renal function monitoring is recommended prior to initiation and periodically thereafter. Adverse events in clinical trials included nasopharyngitis (5.2%), upper respiratory tract infection (6.3%), and headache (5.1%). Currently, no significant drug interactions are known.

Insulins

Insulin is the one agent that can be used in all forms of DM for blood sugar control. ❼ *Insulin is the essential treatment for patients with type 1 DM and can overcome insulin resistance in patients with type 2 DM.* Insulin is available commercially in various formulations that vary markedly in terms of onset and duration of action and the source from which a product is obtained. Insulins can be divided into four separate classes based on their length of action. Most formulations are available as U-100, indicating a concentration of 100 units/mL. Insulin is typically refrigerated, and most vials are good for 28 days at room temperature. Specific details of insulin products are listed in Table 40–9.

The most common route of administration for insulin is subcutaneous injection using a syringe or pen device. Insulin syringes are distinguished according to the syringe capacity, syringe markings, and needle gauge and length. The most common insulin syringe capacities are 30, 50, and 100 units. The 30- and 50-unit syringes are marked at 1-unit increments, whereas the 100-unit syringe is marked at 2-unit intervals. Syringe needles range from 28 to 31 gauge and $^{5}/_{16}$- to $^{1}/_{2}$-in length. The insulin pens are self-contained systems of insulin delivery. The primary advantage of the pen system is that the patient does not have to draw up the dose from the insulin vial.

Regular Insulin

Regular insulin is unmodified crystalline insulin commonly referred to as natural insulin. It is a clear solution that has a relatively rapid onset and short duration of action. On subcutaneous injection, regular insulin forms small aggregates called hexamers that undergo conversion to dimers followed by monomers before systemic absorption can occur. Therefore, patients should be counseled to inject regular insulin subcutaneously 30 minutes prior to consuming a meal. Regular insulin is the only insulin that can be administered intravenously.

Rapid-Acting Insulin

Three rapid-acting insulins have been approved in the United States: lispro, aspart, and glulisine. Substitution of one or two amino acids in regular insulin results in the unique pharmacokinetic properties characteristic of these agents. Onset of action of rapid-acting insulins varies from 15 to 30 minutes, with peak effects occurring 1 to 2 hours following administration.

Intermediate-Duration Insulin

Neutral Protamine Hagedorn, better known as NPH insulin, is prepared by a process in which protamine is conjugated with regular insulin, rendering a product with a delayed onset but extended duration of action. With the advent of the long-acting insulins, NPH insulin use has declined due to: (1) an inability to predict accurately when peak effects occur, and (2) a duration of action of less than 24 hours. Additionally, protamine is a foreign protein that may increase the possibility of an allergic reaction.

NPH insulin can be mixed with regular insulin and used immediately or stored for future use up to 1 month at room temperature or 3 months in refrigeration. NPH insulin can be mixed with either aspart or lispro insulins, but it must be injected immediately after mixing. Whenever mixing insulin products with NPH insulin, the shorter-acting insulin should be drawn into the syringe first.

Long-Duration Insulin

Two long-duration insulin preparations are approved for use in the United States. Glargine and detemir are designed as once-daily-dosing basal insulins. Insulin glargine differs from regular insulin by three amino acids, resulting in a low solubility at physiologic pH. The clear solution is supplied at a pH of 4, which precipitates on subcutaneous administration. Given this property, glargine cannot be administered intravenously or mixed with other insulin products. Both glargine and detemir do not produce peak serum concentrations and can be administered irrespective of meals or time of day.

Combination Insulin Products

A number of combination insulin products are available commercially. NPH is available in combinations of 70/30 and 50/50 with regular insulin. Two short-acting insulin analog mixtures are also available. Humalog Mix 75/25 contains 75% insulin lispro protamine suspension and 25% insulin lispro. Novolog Mix 70/30 contains 70% insulin aspart protamine suspension and 30% insulin aspart. The lispro and aspart insulin protamine suspensions were developed specifically for these mixture products and will not be commercially available separately.

Oral Inhalation Insulin

The first inhaled insulin product was approved in early 2006. Exubera, recombinant human insulin, is an alternative to mealtime injectible insulin available in the United States. It has an onset of action of between 10 to 20 minutes, which is similar to rapid-acting insulin, and a duration of action of around 6 hours, which is similar to regular insulin. Inhaled insulin will not totally replace injectible insulin because long-acting insulin injections are necessary for basal control. This product is available in 1 and 3 mg blister packs, which are equivalent to about 3 to 8 units of injectible insulin. Some patients may need multiple inhalations to attain their mealtime dose. Exubra is not recommended for patients with chronic lung disease such as asthma or chronic obstructive pulmonary disease, patients who smoke, or patients who have stopped smoking within the past 6 months. Monitoring of lung function should be performed at baseline and 6 months' post initiation of therapy.

TABLE 40–9. Insulin Agents for the Treatment of Type 1 and Type 2 Diabetes Mellitus

Generic Name (Insulin)	Brand	Manufacturer	Strength	Onset (minutes)	Peak (hours)	Duration (hours)	Administration Options
Rapid-Acting Insulin							
Lispro	Humalog	Eli Lilly	U-100	15–30	0.5–2.5	3–4	10 mL vial, 3 mL cartridge and disposable pen
Aspart	Novolog	Novo-Nordisk	U-100	15–30	1–3	3–5	10 mL vial, 3 mL cartridge and disposable pen
Glulisine	Apidra	Aventis	U-100	15–30	1–2	3–4	10 mL vial, 3 mL cartridge and disposable pen
Short-Acting Insulin							
Regular	Humulin R	Eli Lilly	U-100, U-500	30–60	2–3	3–6	U-100 10 mL vial; U-500 20 mL vial
	Novolin R	Novo-Nordisk	U-100				10 mL vial, 3 mL cartridge, 3 mL *Innolet*
Intermediate-Acting Insulin							
Neutral protamine Hagedorn	Humulin N	Eli Lilly	U-100	2–4 hours	4–6	8–12	10 mL vial, 3 mL cartridge
	Novolin N	Novo-Nordisk	U-100				10 mL vial, 3 mL cartridge, 3 mL *InnoLet*
Long-Acting Insulin							
Glargine	Lantus	Aventis	U-100	4–5 hours	Flat	22–24	10 mL vial, 3 mL cartridge for *Opticlik*
Detemir	Levmir	Novo-Nordisk	U-100	3–4 hours	Flat	Up to 24	10 mL vial, 3 mL cartridge, 3 mL *Innolet*, 3 mL disposable *FlexPen*
Combination Insulin Products							
Neutral protamine Hagedorn and regular	Humulin 70/30	Eli Lilly	U-100	30–60	1.5–16	10–16	10 mL vial, 3 mL disposable pen
	Novolin 70/30	Novo Nordisk	U-100	30–60	2–12	10–16	10 mL vial, 3 mL cartridge, 3 mL *Innolet*
	Humulin 50/50	Eli Lilly	U-100	30–60	2–5.5	10–16	10 mL vial
Neutral protamine lispro and lispro	Humalog Mix 75/25	Eli Lilly	U-100	15–30	1–6.5	15–18	10 mL vial, 3 mL disposable pen
Neutral protamine aspart and aspart	Novolog Mix 70/30	Novo Nordisk	U-100	15–30	1–4	Up to 24	10 mL vial, 3 mL cartridge, 3 mL disposable *FlexPen*
Oral Inhalation Insulin							
Recombinant human insulin	Exubera	Pfizer	1 mg = ~3 units injectible insulin	10–20	0.5–1.5	6	1 mg, 3 mg blister packs

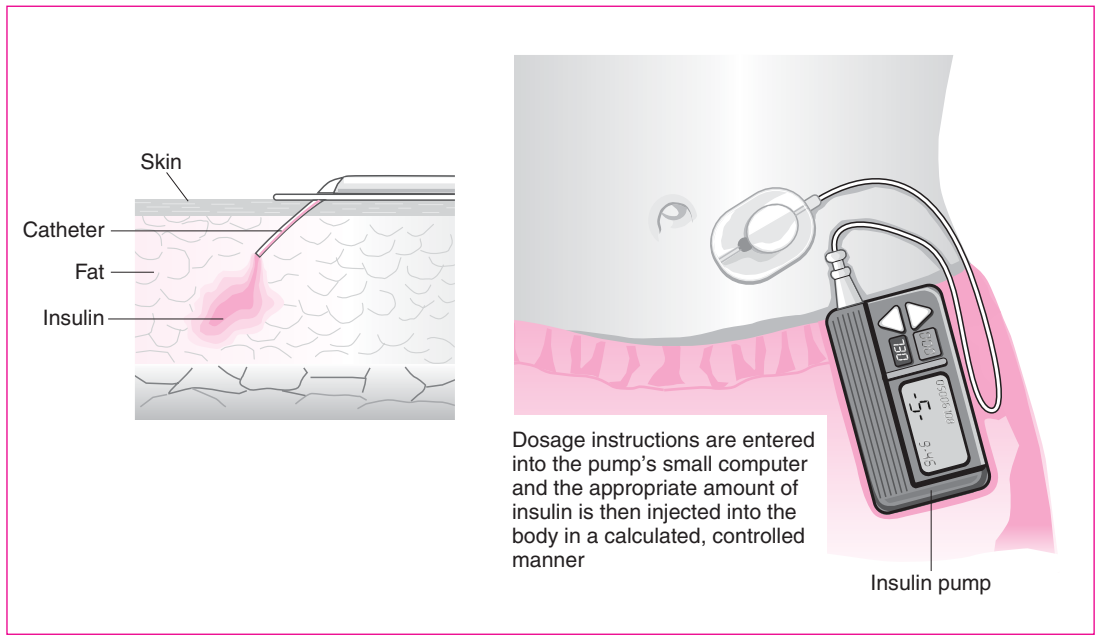


FIGURE 40–3 Insulin pump.

Insulin Pump Therapy

Insulin pump therapy consists of a programmable infusion device that allows for basal infusion of insulin 24 hours daily, as well as bolus administration following meals. As seen in Fig. 40–3, an insulin pump consists of a programmable infusion device with an insulin reservoir. This pump is attached to an infusion set with a small needle that is inserted in subcutaneous tissue in the patient's abdomen, thigh, or arm. Most patients prefer insertion in abdominal tissue because this site provides optimal insulin absorption. Patients should avoid insertion sites along belt lines or in other areas where clothing may cause undue irritation. Infusion sets should be changed every 2 to 3 days to reduce the possibility of infection.

Patients use a carbohydrate-to-insulin ratio to determine how many units of insulin are required. To determine an individual's ratio, the 450 rule is used for patients using regular insulin, whereas the 500 rule is used for lispro or aspart pump users. To calculate the ratio using the 500 rule, the patient would divide 500 by his or her total daily dose of insulin. For example, if a patient were using 25 units of insulin daily, his or her carbohydrate-to-insulin ratio would be 500:25, or 20:1. This ratio theoretically means that 1 unit of lispro or aspart insulin should cover 20 g of carbohydrate. If blood sugar levels are below or above the desired blood glucose target, the amount of insulin can be adjusted. Once this ratio is determined, patients can eat more or fewer carbohydrates at a given meal and adjust the bolus dose accordingly.

Insulin pump therapy may be used to lower blood glucose levels in any type of DM; however, patients with type 1 DM are the most likely candidates for this form of treatment. Use of an insulin pump may improve blood glucose control, reduce wide fluctuations in blood glucose levels, and allow individuals to have more flexibility in timing and content of meals and exercise schedules. Nonetheless, insulin pump therapy is not for everyone. The complexity associated with its use, cost, increased need for blood glucose monitoring, and psychological factors may prevent individuals from using this technology optimally.

Incretin Mimetics

Incretin mimetics are agents with biologic activities similar to incretin hormones but have longer durations of action. Incretin hormones are substances produced by the gastrointestinal tract in response to food that act to stimulate insulin secretion. Obese, insulin-resistant patients with type 2 diabetes have lower levels of incretin hormones. Exanatide is the first incretin mimetic approved by the FDA and is indicated as adjunct therapy in type 2 DM in which adequate blood glucose control has not been achieved with sulfonylureas, metformin, or both (Table 40–10). HbA_{1c} reductions ranging from 0.5% to 1% have been observed with this agent, whereas FPG concentrations decrease by 8 to 10 mg/dL (0.44–0.56 mmol/L). Postprandial glucose values decline by 60 to 70 mg/dL (3.33–3.89 mmol/L).

Exanatide lowers blood glucose levels by producing glucose-dependent insulin secretion; reducing post-meal glucagon secretion, which decreases post-meal glucose output; increasing satiety, which decreases food intake; and regulating gastric emptying, which allows nutrients to be absorbed into the circulation more smoothly. Serum levels peak approximately 2 hours after subcutaneous administration. Exanatide is eliminated renally and is not recommended in patients with a creatinine clearance of less than 30 mL/minute.

An increased risk of hypoglycemia occurs when exanatide is used in combination with a sulfonylurea; however, this is not encountered in exanatide monotherapy or in conjunction

with metformin and/or thiazolidinedione therapy. Side effects include nausea (44%), vomiting (13%), and diarrhea (13%). No major drug interactions have been found with exanatide. The extent and rate of absorption of orally administered drugs may be affected with concomitant use of exanatide; however, no clinical significance has been established to date.

Exanatide is available in 5 and 10 mcg injectible prefilled disposable pens. Initial therapy is 5 mcg twice daily, injected before the two largest meals of the day. Meals should be separated by at least 5 to 6 hours. Doses then are increased after a month to 10 mcg if the patient's blood glucose is improving and nausea is limited. Exanatide can be given up to 60 minutes before a meal, but practical use indicates that injection just before a meal may decrease nausea. An average weight loss of 3 to 5 pounds (1.36–2.27 kg) commonly occurs with the 5 mcg dose, whereas a weight loss of 5 to 10 pounds (2.27–4.55 kg) is observed with the 10 mcg dose.

Amylin

Pramlintide acetate was approved for use in the United States in March 2005 (Table 40-10). This agent is a synthetic analog of human amylin, which is a naturally occurring neuroendocrine peptide that is co-secreted by the β-cells of the pancreas in response to food. Amylin secretion is completely or relatively deficient in patients with diabetes. Pramlintide is given by subcutaneous injection before meals to lower postprandial blood glucose elevations. However, unlike insulin, it does not cause weight gain. Use of pramlintide actually results in an average weight loss of 2.2 to 4.4 lb (1–2 kg).

Pramlintide is indicated as combination therapy with insulin in patients with type 1 or 2 DM. It has been shown to decrease HbA_{1c} by an additional 0.4% to 0.5%. Pramlintide slows gastric emptying without altering absorption of nutrients, suppresses glucagon secretion, and leads to a reduction in food intake by increasing satiety. By slowing gastric emptying, the normal initial post-meal spike in blood glucose is reduced.

Hypoglycemia, nausea, and vomiting are the most common side effects encountered with pramlintide therapy, although pramlintide itself does not produce hypoglycemia. To decrease the risk of hypoglycemia, doses of short-acting, rapid-acting, or premixed insulins should be reduced by 50% before pramlintide is initiated. Pramlintide is metabolized primarily by the kidneys, but dosage adjustments in liver or kidney impairment are not required. Pramlintide has the potential to delay the absorption of orally administered medications. When rapid absorption is needed for efficacy of an agent, pramlintide should be administered 2 hours before or 1 hour after this drug. Pramlintide should not be used in patients receiving medications that alter gastrointestinal motility, such as anticholinergic agents, or drugs that slow the absorption of nutrients, such as α-glucosidase inhibitors.

Treatment of Concomitant Conditions

Coronary Heart Disease

Nearly two-thirds of patients with DM will die of coronary heart disease (CHD). Interventions targeting smoking cessation, glycemic control, blood pressure control, lipid management, antiplatelet therapy, and lifestyle changes, including diet and exercise, can reduce the risk of cardiovascular events. Patients with diabetes should receive at least an aspirin daily unless contraindicated. Refer to appropriate chapters in the text concerning CHD.

TABLE 40–10. Non-insulin Injectible Agents for the Treatment of Diabetes Mellitus

Generic Name (Brand)	Type of Diabetes Mellitus	Dosage Strengths (mcg)[b,c]	Starting Dosage	Doses/Day	Titration Interval	Maximum Dose (mcg)	Time to Effect (minute)	Comments/Cautions
Pramlintide[a] (Symlin)	1	15, 30, 45, 60	15	3	3–7 days	60	20	Take just before major meals; reduce insulin by 50% Maintenance dose 30–60 mcg
	2	60, 120	60	3	3–7 days	120	20	Side effects: Hypoglycemia, nausea, vomiting May delay oral drug absorption
Exanatide[a] (Byetta)	2	5, 10	5	2	1 month	10	15–30	Take just before morning and evening meal; prefilled disposable pen; may delay absorption of oral drugs; separate doses by 1 hour Side effects: Nausea, vomiting, diarrhea, increased hypoglycemia with sulfonylureas

[a]Generic not available in United States.
[b]Pramlintide supplied as 0.6 mg/mL in 5 mL vials.
[c]Exanatide supplied as 250 mcg/mL, 1.2 mL for the 5 mcg prefilled pen and 2.4 mL for the 10 mcg per dose prefilled pen.

Hyperlipidemia

The National Cholesterol Education Program Adult Treatment Panel III guidelines classify the presence of DM to be of the same risk equivalence as CHD. The primary target for lipid-lowering treatment of LDL cholesterol is less than 100 mg/dL (2.59 mmol/L). For patients at high cardiovascular risk, LDL target is 70 mg/dL (1.81 mmol/L). Treatment with an HMG-CoA reductase inhibitor, commonly called a *statin,* often is required to achieve these goals. After LDL cholesterol goals are reached, triglyceride and HDL goals also should be achieved. Treatments including niacin or fibrate therapy may be used to reach these secondary goals. However, caution should be used with statin-fibrate combination therapy because a higher risk of adverse events has been reported (see Chapter 9).

Hypertension

Uncontrolled blood pressure plays a major role in the development of macrovascular events and nephropathy in patients with DM. The ADA recommends that blood pressure goals for patients with DM be less than 130/80 mm Hg. In addition, there are several general principles regarding the treatment of hypertension in diabetes patients. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, and calcium channel blockers are recommended as initial therapy because of their beneficial effects on renal function. Low-dose thiazide diuretics also can be used as either first- or second-line therapy. The most common use of thiazide diuretics for patients with DM is in synergistic combination with other agents. β-Blockers also can be used as either first- or second-line therapies. While β-blockers may mask the symptoms of hypoglycemia, it is generally believed that the benefit of β-blockers outweighs the low risk of hypoglycemia in the patient with type 2 DM. In order to achieve blood pressure goals, most patients require combination therapy with two or three antihypertensive agents (see Chapter 2).

Treatment of Acute Complications

Hypoglycemia

Hypoglycemia, or low blood sugar, can be defined clinically as a blood glucose level of less than 50 mg/dL (2.78 mmol/L). Individuals with DM can experience symptoms of hypoglycemia at varying blood glucose levels. Patients who have regular blood glucose levels as high as 300 to 400 mg/dL (16.65–22.2 mmol/L) may experience symptoms of hypoglycemia once blood glucose levels are lowered to the middle to upper 100 mg/dL (5.55 mmol/L) range. Most people whose blood glucose levels are controlled adequately may experience symptoms when levels fall below 70 mg/dL (3.89 mmol/L). Symptoms of hypoglycemia include shakiness, sweating, fatigue, hunger, headaches, and confusion. Common causes of hypoglycemia include delayed or inadequate amounts of food intake, especially carbohydrates, excessive doses of medications (e.g., sulfonylureas and insulin), exercising when insulin doses are reaching peak effect, or inadequately adjusted drug therapy in renally or hepatically impaired patients. Patients experiencing symptoms of hypoglycemia should check their blood glucose level, consume 15 g of carbohydrate, and wait 10 to 15 minutes for symptom resolution. Examples of acceptable treatments may include a small box of raisins, 4 oz (approximately 120 mL) of orange juice, 8 oz (approximately 240 mL) of skim milk, or three to six glucose tablets. In patients receiving an α-glucosidase inhibitor in combination with a sulfonylurea or insulin, hypoglycemia should be treated with glucose tablets or skim milk owing to the mechanism of action of the α-glucosidase inhibitors. If the blood glucose level has dropped below 50 mg/dL (2.78 mmol/L), as much as 30 g of carbohydrate may be necessary to raise blood glucose levels adequately. For patients with hypoglycemia experiencing a loss of consciousness, a glucagon emergency kit should be administered by intramuscular or subcutaneous route, and emergency medical personnel should be contacted. The patient should be rolled onto his or her side to prevent aspiration since many patients receiving the glucagon injection will vomit.

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is a reversible but potentially life-threatening medical emergency that results from a relative or absolute deficiency in insulin. Without insulin, the body cannot use glucose as an energy source and must obtain energy via **lipolysis**. This process produces ketones and leads to acidosis. While DKA occurs frequently in young patients with type 1 DM on initial presentation, it can occur in adults as well as with patients who have type 2 DM. Often precipitating factors such as infection or errors in administration of insulin or oral diabetes medications can cause DKA. Signs and symptoms develop rapidly over a few hours and commonly include fruity or acetone breath, nausea, vomiting, dehydration, polydipsia, polyuria, and deep, rapid breathing. Non-specific symptoms include lethargy, headache, and weakness. Hallmark diagnostic criteria for DKA include hyperglycemia (greater than 250 mg/dL, 13.9 mmol/L), ketosis (anion gap greater than 10), and acidosis (arterial pH less than or equal to 7.25). Typical fluid deficit is 6 L or more, with major deficits of serum sodium and potassium common. The severity of DKA depends on the magnitude of the decrease in arterial pH, serum bicarbonate levels, and the mental state rather than the magnitude of the hyperglycemia.

Treatment goals of DKA consist of reversing the underlying metabolic abnormalities, rehydrating the patient, and normalizing the serum glucose. Fluid replacement with normal saline at 1 L/hour is recommended to rehydrate the patient and to ensure that the kidneys are perfused. Potassium and other electrolytes are supplemented as indicated by laboratory assessment. The use of sodium bicarbonate in DKA is controversial and generally is not recommended when the pH is greater than or equal to 7.1. Regular insulin at 0.1 to 0.2 unit/kg per hour by continuous intravenous infusion is the preferred treatment in DKA to regain metabolic control rapidly. Once plasma glucose values

TABLE 40–11. Management of Diabetic Ketoacidosis

1. Confirm diagnosis (↑ plasma glucose, positive serum ketones, metabolic acidosis).
2. Admit to hospital; intensive-care setting may be necessary for frequent monitoring or if pH less than 7.0 or unconscious.
3. Assess: Serum electrolytes (K^+, Na^+, Mg^{2+}, Cl^-, bicarbonate, phosphate)
   Acid-base status—pH, HCO_3^-, P_{CO_2}, β-hydroxybutyrate
   Renal function (creatinine, urine output)
4. Replace fluids: 2–3 L of 0.9% saline over first 1–3 hours (5–10 mL/kg per hour); subsequently, 0.45% saline at 150–300 mL/hour; change to 5% glucose and 0.45% saline at 100–200 mL/hour when plasma glucose reaches 250 mg/dL (14 mmol/L).
5. Administer regular insulin: IV (0.1 units/kg) or IM (0.4 units/kg), then 0.1 units/kg per hour by continuous IV infusion; increase 2- to 10-fold if no response by 2–4 hours. If initial serum potassium is less than 3.3 mmol/L (3.3 mEq/L), do not administer insulin until the potassium is corrected to greater than 3.3 mmol/L (3.3 meq/L).
6. Assess patient: What precipitated the episode (non-compliance, infection, trauma, infarction, cocaine)? Initiate appropriate work-up for precipitating event (cultures, CXR, ECG).
7. Measure capillary glucose every 1–2 hours; measure electrolytes (especially K^+, bicarbonate, phosphate) and anion gap every 4 hours for first 24 hours.
8. Monitor blood pressure, pulse, respirations, mental status, and fluid intake and output every 1–4 hours.
9. Replace K^+: 10 mEq/hour when plasma K^+ less than 5.5 mEq/L, ECG normal, urine flow and normal creatinine documented; administer 40–80 mEq/hour when plasma K^+ less than 3.5 mEq/L or if bicarbonate is given.
10. Continue above until patient is stable, glucose goal is 150–250 mg/dL, and acidosis is resolved. Insulin infusion may be decreased to 0.05–0.1 units/kg per hour.
11. Administer intermediate or long-acting insulin as soon as patient is eating. Allow for overlap in insulin infusion and subcutaneous insulin injection.

CXR, chest x-ray; ECG, electrocardiogram; IM, intramuscularly; IV, intravenous.
Source: Adapted from M Sperling, in *Therapy for Diabetes Mellitus and Related Disorders*, American Diabetes Association, Alexandria, VA, 1998; and AE Kitabchi et al: Diabetes Care 24:131, 2001.

drop below 250 mg/dL (13.9 mmol/L), the insulin infusion may be decreased, and dextrose 5% to 10% can be added to the intravenous fluids. During the recovery period, it is recommended to continue administering insulin and to allow patients to eat as soon as possible. Dietary carbohydrates combined with insulin assist in the clearance of ketones. Resolution of DKA is indicated by a blood glucose level of less than 200 mg/dL (11.1 mmol/L), a bicarbonate level of greater than or equal to 10 mEq/L (10 mmol/L), and a venous pH of greater than 7.3. See Table 40–11 for the management of DKA.[19]

Hyperosmolar Hyperglycemic State

Hyperosmolar hyperglycemic state (HHS) is a life-threatening condition similar to DKA that also arises from inadequate insulin, but HHS occurs primarily in older patients with type 2 DM. DKA and HHS also differ in that HHS lacks the lipolysis, ketonemia, and acidosis associated with DKA. Patients with hyperglycemia and dehydration lasting several days to weeks are at the greatest risk of developing HHS. Illness and infection are common precipitating causes of HHS. Two main diagnostic criteria for HHS are a plasma glucose value of greater than 600 mg/dL (33.3 mmol/L) and a serum osmolality of greater than 320 mOsm/kg. The extreme hyperglycemia and large fluid deficits resulting from osmotic diuresis are major challenges to overcome with this condition. Similar to DKA, the treatment of HHS consists of aggressive rehydration, correction of electrolyte imbalances, and continuous insulin infusion to normalize serum glucose. However, in patients with HHS, blood glucose levels should be reduced gradually to minimize the risk of cerebral edema.

Treatment of Long-Term Complications

Retinopathy

Diabetic retinopathy occurs when the microvasculature that supplies blood to the retina becomes damaged. This damage permits leakage of blood components through the vessel walls. Diabetic retinopathy is the leading cause of blindness in adults 20 to 74 years of age in the United States. Retinopathy is staged as either non-proliferative or proliferative. Non-proliferative retinopathy often causes no visual disturbances and may remain asymptomatic for years. Proliferative retinopathy occurs when new retinal vessels form as a result of retinal ischemia in a process called **neovascularization.** Vision loss from proliferative retinopathy may range from mild blurring, to obstruction of vision, to complete blindness. Blurred vision is the presenting symptom for many patients who are diagnosed with diabetes. The ADA recommends that patients with DM receive a dilated eye examination annually by an ophthalmologist or optometrist. Glycemic control is the best prevention for slowing the progression of retinopathy. Early retinopathy may be reversed with improved glucose control.

Neuropathy

Peripheral neuropathy is the most common complication reported in type 2 DM. This complication generally presents as pain, tingling, or numbness in the extremities. The feet are affected more often than the hands and fingers. A number of treatment options have been tried with mixed success. Current options include pregabalin, gabapentin, low-dose tricyclic antidepressants, duloxetine, venlafaxine, topiramate, non-steroidal anti-inflammatory drugs, and topical capsaicin.

Autonomic neuropathy is also a common complication as DM progresses. Clinical presentation of autonomic neuropathy may include **gastroparesis,** resting tachycardia, orthostatic hypotension, impotence, constipation, and hypoglycemic autonomic failure. Therapy for each individual autonomic complication is addressed separately.

Microalbuminuria and Nephropathy

DM is the leading contributor to end-stage renal disease. Early evidence of nephropathy is the presence of albumin in the urine. Therefore, as the disease progresses, larger amounts of protein spill into the urine. The ADA recommends urine protein tests annually in type 2 DM patients. For children with type 1 DM, annual urine protein testing should begin with the onset of puberty or 5 years after the diagnosis of diabetes. The most common form of screening for protein in the urine is a random spot collection for measurement of the urine albumin/creatinine ratio. The desirable value is less than 30 mcg of albumin per milligram of creatinine. Microalbuminuria is defined as between 30 and 300 mcg of albumin per milligram of creatinine. The presence of microalbuminuria is a strong risk factor for future kidney disease in type 1 DM patients. In type 2 DM patients, microalbuminuria has been found to be a strong risk factor for macrovascular disease. Glycemic control and blood pressure control are primary measures for the prevention of progression of nephropathy. ACE inhibitors and angiotensin II receptor blockers prevent the progression of renal disease in type 2 DM patients. Treatment of advanced nephropathy includes dialysis and kidney transplantation.

Foot Ulcers

Lower extremity amputations are one of the most feared and disabling sequelae of long-term uncontrolled DM. A foot ulcer is an open sore that develops and penetrates to the subcutaneous tissues. Complications of the feet develop primarily as a result of peripheral vascular disease, neuropathies, and foot deformations. Peripheral vascular disease causes ischemia to the lower limbs. This decreased blood flow deprives the tissues of oxygen and nutrients and impairs the ability of the immune system to function adequately. Symptoms of peripheral vascular disease include intermittent claudication, cold feet, pain at rest, and loss of hair on the feet and toes. Smoking cessation is the single most important treatment for peripheral vascular disease. In addition, exercising by walking to the point of pain and then resting and resuming can be a vital therapy to maintain or improve the symptoms of peripheral vascular disease. Pharmacologic intervention with pentoxifylline or cilostazol also may be useful to improve blood flow and reduce the symptoms of peripheral vascular disease.

Neuropathies play a large part in the development of foot ulcers. Loss of sensation in the feet allows trauma to go unnoticed. Autonomic neuropathy can cause changes in the blood flow, perspiration, skin hydration, and possibly bone composition of the foot. Motor neuropathy can lead to muscle atrophy, resulting in weakness and changes in the shape of the foot. To prevent foot complications, the ADA recommends daily visual examination of the feet and a foot check performed at every physician visit. Sensory testing with a 10-gauge monofilament can detect areas of neuropathy. Treatment consists of glycemic control, preventing infection, debriding dead tissues, applying dressings, treating edema, and limiting ambulation. Untreated foot problems may develop gangrene, necessitating surgical intervention.

Special Situations

Hospitalized Care

Aggressive treatment of hyperglycemia in hospitalized patients can prevent unnecessary cost to patients and health care systems. When patients are either physically or emotionally stressed, counterregulatory hormones are released, increasing blood glucose levels. Insulin drip therapy for patients with blood glucose levels greater than 140 mg/dL (7.77 mmol/L) is considered superior to sliding-scale insulin. Sliding-scale insulin therapy typically lags the blood glucose level instead of proactively addressing the increased blood glucose levels. Blood glucose levels can be measured by several methods. Arterial samples are usually 5 mg/dL (0.28 mmol/L) higher than capillary values and 10 mg/dL (0.56 mmol/L) greater than venous values.

When preparing an insulin infusion for a patient, several factors must be considered. Insulin will absorb to glass and plastic, reducing the amount of insulin actually delivered by 20% to 30%. Priming the tubing will decrease variability of insulin infused. Therefore, when patients can be converted safely from infusion to needle and syringe therapy, the total daily dose should be reduced by 20% to 50% of the daily infusion amount.

Sick Days

Patients should monitor their blood glucose levels more closely during sick days because it is common for illness to increase values. Additional insulin coverage may be necessary to prevent DKA. Patients should monitor for the presence of urine ketones by a urine dipstick test that changes color in the presence of ketones. Sugar and electrolyte solutions such as sports drinks may be used by type 1 DM patients to prevent dehydration, electrolyte depletion, and hypoglycemia. However, patients with type 2 DM may require sugar-free products if blood glucose levels are elevated consistently. With proper management, patients can decrease their chance of illness-induced hospitalization.

Outcome Evaluation

- The success of therapy for DM is measured by the ability of the patient to manage his or her disease appropriately between health care provider visits.
- Appropriate therapy necessitates adequate patient education about the disease, development of a meal plan to which patients can comply, and integration of a regular exercise program.
- Patient care plans should include a number of daily evaluations to be performed by the patient, such as examination of the feet for any sores, cuts, or abrasions; checking the skin for dryness to prevent cracking and chafing; and monitoring blood glucose values as directed. Weekly appraisals of weight and blood pressure are also advised.

- Until HbA_{1c} levels are at goal, quarterly visits with the patient's primary health care provider are recommended. Table 40–7 summarizes the specific ADA goals for therapy. The practitioner should review SMBG data and a current HbA_{1c} level for progress and address any therapeutic or educational issues.
- At minimum, yearly laboratory evaluation of serum lipids, urinary microalbumin, and serum creatinine should be performed. If the patient is on a thiazolidinedione, liver function tests should be performed at least once a year.



Patient Care and Monitoring

1. Assess the patient for development or progression of DM and DM-related complications.
2. Evaluate SMBG for glycemic control, including FPG and postprandial levels.
   - Are the blood glucose values too high or low?
   - Are there specific times of day or specific days not in control?
   - Is hypoglycemia occurring?
3. Assess the patient for changes in quality-of-life measures, such as physical, psychological, and social functioning and well-being.
4. Perform a thorough medication history of prescription, over-the-counter, and herbal product use.
   - Are there any medication problems, including presence of adverse drug reactions, drug allergies, and drug interactions?
   - Is the patient taking any medications that may affect blood glucose control?
5. Review all available laboratory data (some settings may have only patient-reported values) for attainment of ADA goals (Table 40–7). What therapy goals are not being met, and what tests or referrals to other members of the health care team are needed?
6. Recommend appropriate therapy, and develop a plan to assess effectiveness.
7. Stress adherence to prescribed lifestyle and medication regimen.
8. Provide patient education on diabetes, lifestyle modifications, appropriate monitoring, and drug therapy:
   - Causes of DM complications and how to prevent them.
   - How lifestyle changes including diet and exercise can affect diabetes.
   - How to perform SMBG and what to do with the results.
   - When to take medications and what to expect.
   - What adverse effects may occur?
   - What warning sign(s) should be reported to the physician?

ABBREVIATIONS

AACE:	American Association of Clinical Endocrinologists
ACE:	angiotensin-converting enzyme inhibitors
ADA:	American Diabetes Association
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
BMI:	body mass index
BP:	blood pressure
BUN:	blood urea nitrogen
CDC:	Centers for Disease Control and Prevention
CHD:	Coronary Heart Disease
CSII:	continuous subcutaneous insulin infusion
DKA:	diabetic ketoacidosis
DM:	diabetes mellitus
DPP-IV:	dipeptidyl peptidase-4
FDA:	Food and Drug Administration
FPG:	fasting plasma glucose
GDM:	gestational diabetes mellitus
GIP:	glucose-dependent insulinotropic polypeptide
GLP-1:	glucagon-like peptide-1
HbA_{1c}:	hemoglobin A_{1c}
HDL:	high-density lipoprotein cholesterol
HHS:	hyperosmolar hyperglycemic state
HLA:	human leukocyte antigen
IFG:	impaired fasting glucose
IGT:	impaired glucose tolerance
IKK-beta:	I-kappa-B kinase beta
LADA:	latent autoimmune diabetes in adults
LDL:	low-density lipoprotein cholesterol
MNT:	medical nutrition therapy
NPH:	neutral protamine Hagedorn
OGTT:	oral glucose tolerance test
PPAR-γ:	peroxisome proliferator activator receptor gamma
PPG:	postprandial glucose
SGOT:	serum glutamic oxolacetic transaminase
SGPT:	serum glutamic pyruvic transaminase
SMBG:	self-monitoring of blood glucose
TLC:	therapeutic lifestyle change
TSH:	thyroid-stimulating hormone
TZDs:	thiazolidinediones

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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41 Thyroid Disorders

Michael D. Katz



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Explain the major components of the hypothalamic-pituitary-thyroid axis and the interaction among these components.
2. Discuss the prevalence of thyroid disorders, including subclinical (mild) and overt (typical signs and/or symptoms present) hypothyroidism and hyperthyroidism.
3. Discuss the relationship between serum thyroid-stimulating hormone (TSH) levels and primary thyroid disease and the advantages for the use of TSH levels over other tests such as serum T_4 (thyroxine) and T_3 (triiodothyroinine) levels.
4. Identify the typical signs and symptoms of hypothyroidism and the consequences of inadequate treatment.
5. Describe the clinical use of levothyroxine in the treatment of hypothyroidism, including initial dose and dose titration, and patient monitoring.
6. Discuss the issues regarding levothyroxine product bioequivalence and the advantages of maintaining patients on the same product.
7. Identify the typical signs and symptoms of Graves' disease and the consequences of inadequate treatment.
8. Describe the management of hypothyroidism and hyperthyroidism in pregnant women.
9. Discuss the pharmacotherapy of Graves' disease, including the advantages and disadvantages of antithyroid drugs versus radioactive iodine, adverse effects, and patient monitoring.
10. Describe the potential effects of amiodarone, lithium, and interferon-α on thyroid function.

Key Concepts

❶ In most patients with thyroid hormone disorders, the measurement of a serum thyroid-stimulating hormone (TSH) level is adequate for the diagnosis of hypothyroidism and hyperthyroidism. The target TSH for most patients being treated for thyroid disorders should be the mean normal value of 1.4 milliunits/L or 1.4 microunits/mL (target range 0.5–2.5 milliunits/L or 0.5–2.5 microunits/mL).

❷ Hypothyroidism can affect virtually any tissue or organ in the body. However, the most common symptoms, such as fatigue, lethargy, sleepiness, cold intolerance, and dry skin, are nonspecific and are seen with many other disorders. The classic overt signs, such as myxedema and delayed deep tendon reflexes, are seen uncommonly now because more patients are screened or seek earlier medical attention. Patients with mild hypothyroidism may have subtle symptoms that progress so slowly that they are not noticed easily by the patient or family. The lack of overt or specific signs and symptoms emphasizes the importance of using the serum TSH level to identify patients with hypothyroidism.

❸ There are three major goals in the treatment of hypothyroidism: replace the missing hormones, relieve symptoms, and achieve a stable biochemical euthyroid state.

❹ Despite the availability of a wide array of thyroid hormone products, it is clear that synthetic levothyroxine (LT_4) is the treatment of choice for almost all patients with hypothyroidism. LT_4 mimics the normal physiology of the thyroid gland, which secretes mostly T_4 as a prohormone. As needed, based on metabolic demands, peripheral tissues convert thyroxine (T_4)

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to triiodothyronine (T_3). If T_3 is used to treat hypothyroidism, the peripheral tissues lose their ability to control local metabolic rates. LT_4 also has distinct pharmacokinetic advantages over T_3. With a 7-day half-life, LT_4 provides a very smooth dose-response curve with little peak and trough effect.

❺ There is no evidence that one LT_4 product is better than another. However, given the likelihood that these products do have different bioavailabilities, patients should be maintained on the same LT_4 product. Given the generic substitution regulations of most states, this is best accomplished by prescribing a brand-name product. The prescriber should not allow substitution in the way mandated by state regulations.

❻ The goals of treating hyperthyroidism are to relieve symptoms, to reduce thyroid hormone production to normal levels and achieve biochemical euthyroidism, and to prevent long-term adverse sequelae.

❼ Agranulocytosis is one of the most serious adverse effects of antithyroid drug therapy.

❽ The growth and spread of thyroid carcinoma are stimulated by TSH. An important component of thyroid carcinoma management is the use of LT_4 to suppress TSH secretion. Early in therapy, patients receive the lowest LT_4 dose sufficient to fully suppress TSH to undetectable levels. Controlled trials show that suppressive LT_4 therapy reduces tumor growth and improves survival.

❾ Patients receiving amiodarone must receive monitoring for thyroid abnormalities. Baseline measurements of serum TSH, FT_4, FT_3, antithyroid peroxidase antibody (anti-TPOAb) and TSH receptor-stimulating antibodies (TSHR-SAb) should be performed. TSH, FT_4, and FT_3 should be checked 3 months after initiation of amiodarone and then every 3 to 6 months.

Thyroid disorders are common. Over 2 billion people, or 38% of the world's population, have iodine deficiency, resulting in 74 million people with **goiters.** While iodine deficiency is not a significant problem in developed countries, a number of common thyroid problems exist. The most common problems related to thyroid function, **hypothyroidism** and **hyperthyroidism,** often require long-term pharmacotherapy. Undetected or improperly treated thyroid disease can result in long-term adverse sequelae, including increased mortality. It is important that clinicians are aware of the prevalence of thyroid disorders, methods of identifying thyroid disorders, and appropriate therapy. This chapter focuses on the most common pharmacologically treated thyroid disorders.

THYROID HORMONE PHYSIOLOGY AND BIOSYNTHESIS

The thyroid gland is the largest endocrine gland in the body, residing in the neck, anterior to the trachea, between the cricoid cartilage and the suprasternal notch. The thyroid gland produces two biologically active hormones, thyroxine (T_4) and triiodothyronine (T_3). Thyroid hormones are essential for proper fetal growth and development, particularly development of the central nervous system (CNS). After delivery, the primary role of thyroid hormone is in the regulation of energy metabolism. These hormones can affect the function of virtually every organ in the body. The parafollicular C cells of the thyroid gland produce calcitonin. The function of calcitonin and its therapeutic use are discussed in other chapters in this book.

T_4 and T_3 are produced by the organification (binding of iodine to tyrosine residues of thyroglobulin) of iodine in the thyroid gland. Iodine is actively transported into the thyroid follicular cells. This inorganic iodine is oxidized by **thyroid peroxidase** and covalently bound to tyrosine residues of **thyroglobulin**. The iodinated tyrosine residues monoiodotyrosine and diiodotyrosine couple to form T_4 and T_3. Eighty percent of thyroid hormone is synthesized as T_4 and is stored in the thyroid bound to thyroglobulin. Thyroid hormones are released from the gland when needed, primarily under the influence of thyroid-stimulating hormone (TSH) from the anterior pituitary. T_4 and T_3 are transported in the blood by three proteins, 70% to thyroid-binding globulin (TBG), 15% to transthyretin (thyroid-binding prealbumin), and 15% to albumin. T_4 is 99.97% protein-bound, and T_3 is 99.7% protein-bound, with only the unbound or free fractions physiologically active. The high degree of protein binding results in a long half-life of these hormones: approximately 7 days for T_4 and 24 hours for T_3.

Most of the physiologic activity of thyroid hormones is from the actions of T_3. T_4 can be thought of primarily as a prohormone. Eighty percent of needed T_3 is derived from the conversion of T_4 to T_3 in peripheral tissue under the influence of tissue deiodinases. These deiodinases allow end organs to produce the amount of T_3 needed to control local metabolic functions. These enzymes also catabolize T_3 and T_4 to biologically inactive metabolites. Thyroid hormones bind to intracellular receptors and regulate the transcription of various genes.

The production and release of thyroid hormones are regulated by the hypothalamic-pituitary-thyroid axis (Fig. 41–1). Hypothalamic thyrotropin-releasing hormone (TRH) stimulates the release of TSH (thyrotropin) when there are physiologically inadequate levels of thyroid hormones. TSH promotes the production and release of thyroid hormones from the gland. As circulating thyroid hormone levels rise to needed levels, negative feedback results in decreased release of TSH and TRH. The release of TRH is inhibited by somatostatin and its analogs, and the release of TSH can be inhibited by dopamine, dopamine agonists, and high levels of glucocorticoids.

SPECTRUM OF THYROID DISEASE

There are two general modes of presentation for thyroid disorders: changes in the size or shape of the gland and changes in secretion of hormone from the gland. In some cases, structural changes can result in changes in hormone secretion. Thyroid nodules and goiters in **euthyroid** patients

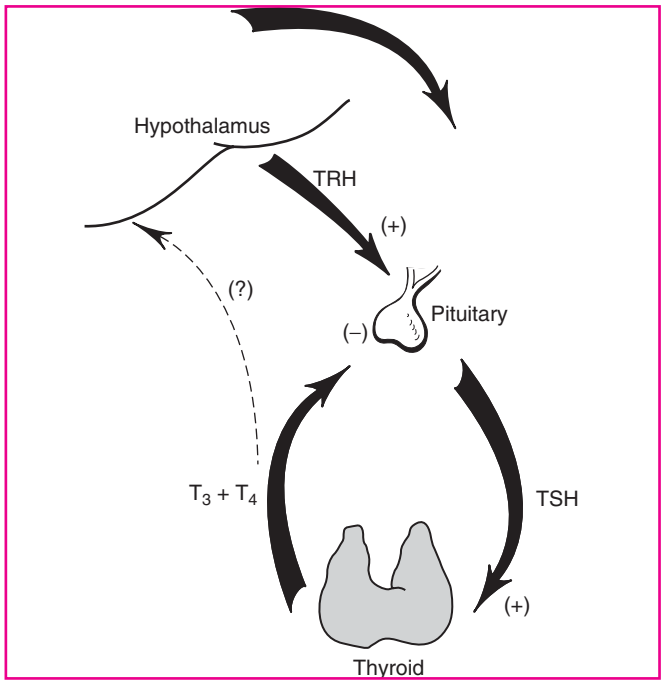


FIGURE 41–1. Hypothalamic-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) is synthesized in the neurons within the paraventricular nucleus of the hypothalamus. TRH is released into the hypothalamic-pituitary portal circulation and carried to the pituitary, where it activates the pituitary to synthesize and release thyrotropin (TSH). TSH activates the thyroid to stimulate the synthesis and secretion of thyroxine (T_4) and triiodothyronine (T_3). T_4 and T_3 inhibit TRH and TSH secretion, closing the feedback loop.

are common problems. Patients with a goiter often require no specific pharmacotherapy, unless the goiter is due to iodine deficiency. In developing countries, iodized salt is the primary therapy in treating goiter. Thyroid nodules, seen in 4% to 7% of adults, may be malignant or autonomously secrete thyroid hormones. A discussion of thyroid nodules is beyond the scope of this chapter. However, thyroid cancer will be discussed briefly in the context of levothyroxine (LT_4) suppressive therapy. The reader is referred to other resources for a more extensive review of thyroid cancer management.

Changes in hormone secretion can result in hormone deficiency or excess. While patients with overt hypothyroidism and hyperthyroidism may have dramatic signs and symptoms, most patients have subtle signs and symptoms that progress slowly over time. The availability of sensitive and specific biochemical tests for the diagnosis of thyroid hormone disorders has facilitated screening and earlier diagnosis, including those with subclinical thyroid disorders. Screening of newborns for congenital hypothyroidism has reduced the incidence of mental retardation and **cretinism** dramatically in the United States. However, congenital hypothyroidism owing to iodine deficiency remains a significant worldwide public health problem.

Epidemiology of Thyroid Disease

A number of studies have assessed the epidemiology of thyroid hormone abnormalities. The Third National Health and Nutrition Examination Survey (NHANES III)[1] reported the prevalence of thyroid hormone disorders in 17,353 people 12 years and over in a sample representing the geographic and ethnic distribution of the United States population. Hypothyroidism was found in 4.6% (4.3% subclinical) and hyperthyroidism in 1.3% (0.7% subclinical) of the sample. Antithyroid peroxidase antibodies (anti-TPOAb) were found in 11.3% of this population. The prevalence of hypothyroidism was higher in older age groups and in whites and Hispanics, whereas blacks had a lower prevalence of antithyroid antibodies and hypothyroidism. The Colorado Thyroid Health Survey[2] assessed thyroid function in 25,862 subjects attending a health fair. The overall prevalence of an abnormal TSH level was 11.7% of the study population, with 9.4% hypothyroid (9% subclinical) and 2.2% hyperthyroid (2.1% subclinical). Of the 916 subjects taking thyroid medication, 60% were euthyroid, with an equal distribution between subclinical hypothyroidism and hyperthyroidism. These findings imply that many patients who are receiving thyroid medications are not being managed successfully.

PATIENT ASSESSMENT AND MONITORING

The assessment of patients for thyroid disorders entails a history and physical examination. In many patients with subclinical or mild thyroid disease, there may be an absence of specific signs and symptoms, and the physical examination may be normal. Various diagnostic tests can be used, including serum thyroid hormone(s), TSH, and thyroid antibody levels and imaging techniques to evaluate patients for thyroid disorders. Normal values for selected laboratory tests are given in Table 41–1.

TABLE 41–1. Selected Thyroid Tests for Adults

Test	Normal Range	Comments
TSH	0.5–2.5 milliunits/L (0.5–2.5 microunits/mL)[a]	Gold standard; may be lowered by dopamine, dopamine agonists, glucocorticoids, octreotide, recovery from severe nonthyroidal illness
Free T_4	0.7–1.9 ng/dL (9.0–24.5 pmol/L)	May be normal in mild thyroid disease
Anti-TPOAb	Less than 100 units/mL	Present in autoimmune hypothyroidism; predicts more rapid progression from subclinical to overt hypothyroidism
TSHR-SAb	Undetectable	Confirms Graves' disease

[a]milliunits/L = microunits/mL; clinical laboratories use either unit of measurement. Anti-TPOAb, antithyroid peroxidase antibody; T_4, thyroxine; TSH, thyroid-stimulating hormone; TSH-SAb, TSH receptor-stimulating antibodies.

TSH Levels

❶ *In most patients with thyroid hormone disorders, the measurement of a serum TSH level is adequate for the diagnosis of hypothyroidism and hyperthyroidism.* TSH is a highly sensitive bioassay of the thyroid axis. A two-fold change in serum free T_4 levels will result in a 100-fold change in TSH levels. This biologic magnification by TSH allows the TSH to be used in early diagnosis as well as in closely titrating therapy in hypothyroidism and hyperthyroidism.[3] In patients with hypothyroidism or hyperthyroidism resulting from gland dysfunction (primary thyroid disease), there is an inverse relationship between the TSH level and thyroid function. High TSH signifies hypothyroidism (or iatrogenic underreplacement), and low TSH signifies hyperthyroidism (or iatrogenic overreplacement). There is controversy regarding the normal or laboratory reference ranges for TSH. NHANES III[1] showed that the mean TSH level in a normal population was 1.4 milliunits/L (milliunits/L = microunits/mL; clinical laboratories use either unit of measurement), but the values were not normally distributed. While most laboratories quote the upper limit of normal for TSH as 4.5 milliunits/L based on the NHANES III data, 95% of subjects had a TSH level of between 0.5 and 2.5 milliunits/L. The population of subjects whose TSH level was 2.5 to 4.5 milliunits/L probably had mild hypothyroidism and should not have been included as part of the normal reference range for TSH. It has been proposed that the reference TSH range be redefined with an upper limit of normal of 2.5 or 3 milliunits/L.[4] ❶ *The target TSH for most patients being treated for thyroid disorders should be the mean normal value of 1.4 milliunits/L or 1.4 microunits/mL (target range 0.5–2.5 milliunits/L or 0.5–2.5 microunits/mL).*

Serum Hormone Levels

Serum T_4 and T_3 levels were used commonly to assess thyroid function. Screening thyroid function tests measure total serum T_4 or T_3 levels. Because of the high degree of protein binding of these hormones, the free fraction can be altered by changes in the levels of binding proteins or the degree of protein binding. Since a number of factors can alter protein binding, the older assays are very insensitive and should no longer be used, even with protein-binding adjustment factors such as the free thyroxine index. Free or unbound T_4 (FT_4) and T_3 (FT_3) assays are readily available and are more sensitive in identifying thyroid dysfunction than the older total assays.[5] However, patients with mild hypothyroidism or hyperthyroidism will have a normal FT_4 level despite an abnormal TSH level.

The laboratory assessment of patients with suspected thyroid disorders must be based on the continuum of disease from subclinical or mild to overt (Fig. 41–2).

Other Diagnostic Tests

Global tests of thyroid gland function can be performed to assess the rate of hormone synthesis. The radioactive iodine uptake (RAIU) will be elevated in hyperthyroidism and can aid in identifying **thyrotoxicosis** owing to non-thyroid gland sources. Radionuclide thyroid scans are used in the evaluation of thyroid nodules. Since many thyroid disorders are autoimmune, measurement of various serum antithyroid antibodies can be performed. Antithyroid peroxidase (anti-TPOAb) and antithyroglobulin antibodies (anti-TGAb) are present in many patients with hypothyroidism. Most patients with Graves' disease will have TSH stimulating receptor antibodies (TSHR-SAb) as well as elevated anti-TPOAb and antimicrosomal antibodies.

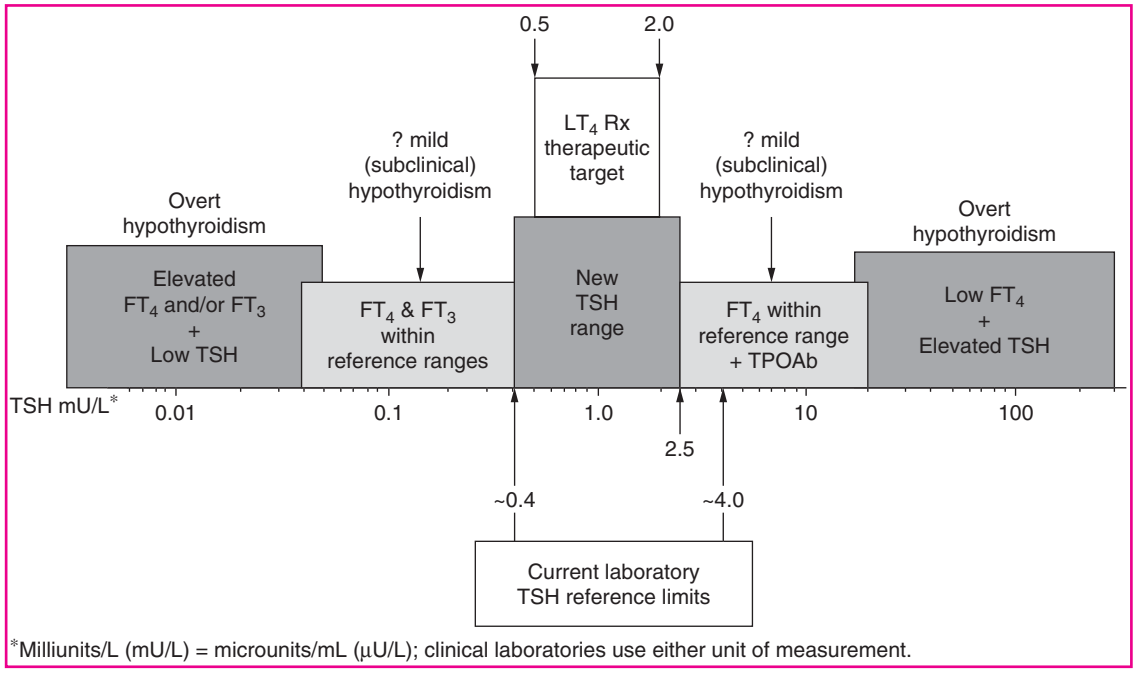


FIGURE 41–2. TSH and the continuum of thyroid disorders. FT_3, free T_3; FT_4, free T_4; LT_4, levothyroxine; TPOAb, thyroid peroxidase antibody; TSH, thyroid-stimulating hormone. (Reprinted, with permission, from reference 4.)

HYPOTHYROIDISM

Hypothyroidism is the most common clinical disorder of thyroid function. It is the clinical syndrome that results from inadequate secretion of thyroid hormones from the thyroid gland. The vast majority of hypothyroid patients have primary gland failure, whereas rare patients have pituitary or hypothalamic failure. Most studies define hypothyroidism based on a serum TSH level above the upper limit of the laboratory reference range. In adults, 1.4% of women and 0.1% of men are biochemically hypothyroid. However, the incidence is highly age-dependent. In the Colorado Thyroid Health study,[2] by age 64, 12% of women and 5% of men were hypothyroid, and in the over 74 years age group, the incidence in men approached that of women. Most epidemiologic studies of hypothyroidism in the elderly show a prevalence of 6% to 12%. There is a strong correlation between the presence of anti-TPOAb or anti-TGAb and the risk of developing hypothyroidism. In patients with subclinical hypothyroidism and positive anti-TPOAb, 5% per year will progress to overt hypothyroidism.[6] Other risk factors for the development of hypothyroidism include postpartum state, family history of autoimmune thyroid disorders, a previous history of head and neck or thyroid surgery, head and neck irradiation, other autoimmune endocrine disorders such as type 1 diabetes and Addison's disease, other non-endocrine autoimmune diseases such as celiac disease and pernicious anemia, prior history of treatment for thyrotoxicosis, and treatment with amiodarone or lithium.

Screening for Hypothyroidism

Because the prevalence of hypothyroidism is high in certain populations, screening may be useful. Screening for hypothyroidism in women over age 35 is as cost-effective as screening for breast cancer and hypertension,[7] although some organizations recommend screening of adults over the ages of 50 or 60. Others advocate a case-finding approach, i.e., to perform a TSH determination in patients based on risk factors or the presence of signs and symptoms.[8,9]

Causes of Hypothyroidism

The most common causes of hypothyroidism are listed in Table 41–2. Up to 90% of patients with autoimmune thyroiditis have circulating anti-TPOAbs. The autoimmune inflammatory response results in a lymphocytic infiltration of the thyroid gland and its eventual destruction.

Iatrogenic hypothyroidism can follow thyroid irradiation or surgery and excessive doses of antithyroid drugs. Several drugs can cause hypothyroidism, including iodine-containing drugs such as amiodarone and radiocontrast media, lithium, interferon-α, p-aminosalicylic acid, and aminoglutethimide.[5] Iodine deficiency is a common worldwide cause of hypothyroidism, including congenital hypothyroidism in newborns. Patients with hypothalamic or pituitary disease often have other signs of pituitary disease, such as hypogonadism, and the TSH level will be low.

TABLE 41–2. Common Causes of Hypothyroidism[10,12]

Primary Hypothyroidism
Autoimmune thyroiditis (Hashimoto's disease)
Iatrogenic (irradiation, surgery)
Drugs (amiodarone, radiocontrast media, lithium, α-interferon)
Silent thyroiditis (including postpartum)
Secondary Hypothyroidism
Pituitary disease
Hypothalamic disease

Signs and Symptoms of Hypothyroidism

❷ *Hypothyroidism can affect virtually any tissue or organ in the body. The most common symptoms, such as fatigue, lethargy, sleepiness, cold intolerance, and dry skin, are non-specific and can*



Clinical Presentation and Diagnosis of Hypothyroidism[10]

Symptoms
- Fatigue
- Lethargy
- Sleepiness
- Mental impairment
- Depression
- Cold intolerance
- Hoarseness
- Dry skin
- Decreased perspiration
- Weight gain
- Decreased appetite
- Constipation
- Menstrual disturbances
- Arthralgia
- Paresthesia

Signs
- Slow movements
- Slow speech
- Hoarseness
- Bradycardia
- Dry skin
- Non-pitting edema (myxedema)
- Hyporeflexia
- Delayed relaxation of reflexes

Screening/Diagnosis

A TSH level of 4.5 to 10 milliunits/L constitutes mild or subclinical hypothyroidism, and some patients with a TSH level of 2.5 to 4.5 milliunits/L also may be mildly hypothyroid. A TSH level greater than 10 milliunits/L signifies overt hypothyroidism.* The free T_4 level will be normal (0.7–1.9 ng/dL or 9.0–24.5 pmol/L) in mild or subclinical hypothyroidism and low (less than 0.7 ng/dL or 9.0 pmol/L) in patients with obvious signs and/or symptoms.

*Milliunits/L (mU/L) = microunits/mL (μU/L); clinical laboratories use either unit of measurement.

be seen with many other disorders. The classic overt signs, such as ***myxedema*** *and delayed deep tendon reflexes, are seen uncommonly now because more patients are screened or seek medical attention earlier. Patients with mild hypothyroidism may have subtle symptoms that progress so slowly that they are not noticed easily by the patient or family. The lack of overt or specific signs and symptoms emphasizes the importance of using the serum TSH level to identify patients with hypothyroidism.*

Sequelae of Hypothyroidism

Hypothyroidism is a chronic disease that may result in significant long-term sequelae. Hypercholesterolemia is associated with hypothyroidism, increasing the long-term risk of cardiovascular disease. Between 4% and 14% of patients with hypercholesterolemia are found to be hypothyroid. The Colorado Thyroid Health Study[2] showed a direct correlation between the degree of TSH elevation and the rise in serum cholesterol. Hypothyroidism also may result in increased systemic vascular resistance, decreased cardiac output, and increased diastolic blood pressure. Hypothyroidism can cause significant neuropsychiatric problems, including a dementia-like state in the elderly that is reversible with levothyroxine (LT_4) therapy. Maternal hypothyroidism can have dire consequences for the developing fetus. The fetus is almost completely dependent on maternal thyroid hormones during the first trimester, a time crucial for development of the CNS. Inadequately treated maternal hypothyroidism results in increased risk of miscarriage and developmental impairment in the child.[11]

Myxedema coma is seen in advanced hypothyroidism. These patients develop CNS depression, respiratory depression, cardiovascular instability, and fluid and electrolyte disturbances. Myxedema coma often is triggered by an underlying acute medical condition such as infection, stroke, trauma, or administration of CNS depressant drugs.

TREATMENT

Pharmacotherapy of Hypothyroidism

❸ *There are three major goals in the treatment of hypothyroidism: replace the missing hormones, relieve symptoms, and achieve a stable biochemical euthyroid state.* While these goals should not be difficult to achieve, 20% to 40% of treated patients are not receiving optimal pharmacotherapy.

Thyroid Hormone Products

A number of thyroid hormone products are marketed in the United States (Table 41–3). These products include synthetic LT_4 and T_3, combinations of synthetic LT_4 and T_3, and animal-derived products. ❹ *Despite the availability of a wide array of thyroid hormone products, it is clear that synthetic LT_4 is the treatment of choice for almost all patients with hypothyroidism.*[12] *Using LT_4 mimics the normal physiology of the thyroid gland, which secretes mostly T_4 as a prohormone. Peripheral tissues convert T_4 to T_3 as needed, based on metabolic demands. If T_3 is used to treat hypothyroidism, the peripheral tissues lose their ability to control local metabolic rates. LT_4 also has distinct pharmacokinetic advantages over T_3. With a 7-day half-life, LT_4 provides a very smooth dose-response curve with little peak and trough effect.* T_3, with a 24-hour half-life, provides a significant peak and trough effect, and many patients will have symptoms of thyrotoxicosis after each dose is administered. For patients who have difficulty adhering to a once-daily regimen, a once-weekly LT_4 regimen is safe and effective.

Animal-derived products such as desiccated thyroid and thyroglobulin are derived from cow and pig thyroid and have various degrees of purity. These products contain both LT_4 and T_3, but the amount of T_3 is much higher (T_4:T_3 = 4:1) than what would be found in the human thyroid gland (T_4:T_3 = 14:1). With the desiccated thyroid products, there are concerns about standardizing the amount of hormone and lot-to-lot variability. While some patients want to use these agents because they are "natural," they are not natural for humans. With the strong evidence supporting the safety and efficacy of LT_4 in the treatment of hypothyroidism, there is no rationale for the use of these animal-derived products. Patients who are being treated with these agents should be strongly encouraged to switch to synthetic LT_4. Also, patients should be encouraged not to purchase thyroid-containing products from health food stores or from questionable Internet sites.

Liotrix is a fixed-ratio LT_4/T_3 product, although the LT_4:T_3 ratio is not physiologic for humans. Several studies have been published that evaluate the use of LT_4 and T_3 combinations in ratios that mimic human physiology. While early studies with these combinations showed improved neuropsychiatric and quality-of-life outcomes compared with LT_4 monotherapy, subsequent randomized, controlled trials have shown no outcome benefit.[13] Except in rare circumstances (such as patients with impaired T_4-to-T_3 conversion), there is no rationale for using combinations of LT_4 and T_3 to treat hypothyroidism.

Bioequivalence and LT_4 Product Selection

LT_4 products have a long history of bioavailability problems.[14] Over the years, LT_4 bioavailability has increased, so maintenance doses today are significantly lower than those seen in the 1970s and early 1980s. Currently, the average bioavailability of LT_4 products is about 80%. Because of long-standing concerns about LT_4 bioequivalence, and because LT_4 products had never undergone formal approval by the Food and Drug Administration (FDA) under the 1938 Food, Drug, and Cosmetics Act, the FDA mandated that all manufacturers of LT_4 products submit an Abbreviated New Drug Application (ANDA) to keep their products on the United States market after 2001.[15] Products approved under this process would have to comply with FDA manufacturing and bioequivalence standards. This FDA action has resulted in many changes in the United States LT_4 market, as well as renewed interest in LT_4 bioequivalence. By 2006, several brand and generic products had been approved by the FDA. Some of the generic products carry AB ratings (bioequivalence) to certain brand products.[16]

TABLE 41–3. Thyroid Preparations

Drug/Dosage Form	Content	Relative Dose	Comments
Levothyroxine (Synthroid®, Levoxyl®, Unithroid®), other brands, and generics	Synthetic LT_4; 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg tablets; 500 mcg vial for injection	60 mcg	Gold standard for treating hypothyroidism; products not therapeutically equivalent; full replacement dose 1–1.6 mcg/kg per day; when switching from animal product, lower calculated daily dose by 25–50 mcg; intravenous form rarely needed
Liothyronine (Cytomel®)	Synthetic T_3; 5, 25, and 50 mcg tablets	15 mcg	Rarely needed in treatment of hypothyroidism; rapid absorption and pharmacologic effect; increased toxicity versus LT_4; no outcome benefit to combining with LT_4
Thyroid (desiccated) USP (Armour®, others)	Desiccated pork or beef thyroid glands; contains T_3 and T_4; 0.25, 0.5, 1, 1.5, 2, 3, 4, and 5-grain tablets	1 grain (65 mg)	Non-physiologic for humans; unpredictable hormone content and stability; T_3 content may cause toxicity
Thyroglobulin (Proloid®)	Partially purified pork thyroglobulin; 32, 65, 100, 130, and 200 mg tablets	65 mg	Non-physiologic T_4: T_3 ratio; T_3 content may cause toxicity; removed from United States market
Liotrix (Thyrolar®)	Synthetic T_4, T_3 in fixed 4:1 ratio; $\frac{1}{4}$, $\frac{1}{2}$, 1, 2, 3 strength tablets	12.5/50 mcg T_3: T_4 (1 strength)	Non-physiologic T_4: T_3 ratio; T_3 content may cause toxicity

LT_4, levothyroxine; T_3, triiodothyronine; T_4, thyroxine.

For many years, there have been concerns regarding the FDA bioequivalence methodology for LT_4 products. FDA bioequivalence standards allow a –20% to +25% variance in pharmacokinetic parameters between the test and reference products. Many people feel that this degree of allowed variance is not appropriate for a narrow-therapeutic-index (NTI) drug such as LT_4.[17] Also, there are unique challenges to performing bioequivalence studies in an endogenous hormone such as LT_4. Since these single-dose pharmacokinetic studies are done in healthy volunteers, the pharmacokinetic data are a combination of endogenous and exogenous LT_4. Seventy percent of the area under the curve (AUC) in these studies consists of the subjects' endogenous T_4. Thus, it is doubtful that bioavailability differences among products could be detected. Blakesley and colleagues[18] showed that the standard FDA bioequivalence methodology would rate 600, 450, and 400 mcg LT_4 doses as bioequivalent. This study also showed that mathematically removing the subjects' endogenous T_4 level (baseline correction) improves the sensitivity of the analysis, allowing a distinction between 33% and 25% but not 12.5% dose differences. Based on these data, the FDA, since 2003, has required that LT_4 bioequivalence data undergo baseline correction. While this method has improved the ability to identify large differences in LT_4 bioequivalence, small but clinically significant differences will not be identified.

More important than bioequivalence is the therapeutic equivalence of LT_4 products. Will patients have the same outcomes if bioequivalent products are used? The study by Dong and colleagues[19] helps to answer this question. Twenty-two well-controlled hypothyroid women were randomly switched to the same dose of four different products every 6 weeks. Non-baseline corrected bioequivalence data showed these products to be bioequivalent. However, as each product switch occurred, more of the subjects had an abnormal TSH level.[20] By the end of the third product switch, 52% had an abnormal TSH level. This is strong evidence that LT_4 products are not therapeutically equivalent even if they are rated as bioequivalent by the FDA.

Evidence does exist that small differences in the LT_4 dose can result in large changes in TSH. The impact on TSH of small changes in LT_4 dose was assessed in 21 adult hypothyroid patients.[21] When the daily dose was reduced by 25 mcg, 78% had an elevated TSH level. When the daily dose was increased by 25 mcg, 55% had a low TSH level. Clearly, differences in the LT_4 dose or bioavailability within the FDA-allowed variance for bioequivalent products can cause significant changes in TSH.

❺ *There is no evidence that one LT_4 product is better than another. However, given the likelihood that these products do have different bioavailabilities, patients should be maintained on the same LT_4 product. Given the generic substitution regulations of most states, this is best accomplished by prescribing a brand-name product and not allowing substitution in the way mandated by state regulations.* While practitioners are pressured by managed-care organizations and employers to substitute LT_4 products as a cost-saving measure, such switching is not in the best interest of the patient and should not be allowed. If patients are

switched to a different product, a TSH determination should be done in 6 to 8 weeks to allow retitration. The economic impact of retitration must be considered when formularies are changed to reduce the drug acquisition cost.

Therapeutic Use of LT_4

LT_4 is indicated for patients with overt hypothyroidism.[22] However, the need for treatment is controversial in patients with mild or subclinical disease (TSH less than 10 milliunits/L). There are no large clinical trials that show an outcome benefit with treating these patients, and the therapeutic decision must be individualized.[1,23] Many patients with "subclinical" hypothyroidism do, in fact, have subtle symptoms that improve with LT_4 replacement. If the patient's serum cholesterol is elevated,[24] or if serum anti-TPOAbs are present, many clinicians recommend LT_4 therapy.

In patients younger than age 65 with overt hypothyroidism, the average LT_4 replacement dose is 1.6 mcg/kg per day (use ideal body weight in obese patients[25]). If there is no history of cardiac disease, these patients may be started on the full replacement dose. The full replacement dose in patients over age 75 is lower, about 1 mcg/kg per day.[26] In the elderly, the starting dose is 25 to 50 mcg/day, and the dose is titrated to the full replacement dose. In patients with ischemic heart disease, start with 12.5 to 25 mcg/day and slowly titrate to the full replacement dose. If the patient develops angina or other forms of myocardial ischemia, lower the dose and titrate more slowly. At the start of therapy and with each change in dose, recheck the TSH in 6- to 8-week intervals. If the TSH is not in the target range (0.5–2.5 milliunits/L), change the dose by 10% to 20% and then recheck the TSH 6 to 8 weeks later. As the dose is titrated, assess the patient's symptoms. Many patients will improve quickly, and many patients will feel the best if the TSH is titrated to low-normal to middle-normal levels (0.5–1.5 milliunits/L).

Patients with mild or subclinical hypothyroidism do not need to be started on the full replacement dose because they still have some endogenous hormone production. Start these patients on 25 to 50 mcg/day, and titrate every 6 to 8 weeks based on TSH levels. Over time, it is likely that the LT_4 dose will need to be increased slowly as the patient's thyroid gland loses residual function.



Patient Encounter 1, Part 1

HT, a 34-year-old woman, comes to the clinic complaining of fatigue, lethargy, and having a "fuzzy head" for the past 6 months. She thought it was because she was working too hard, but the symptoms have not improved despite a better work schedule. She has noticed a 5-lb (2.3-kg) weight gain, her menses have become heavier, she feels cold all the time, and her skin is drier. She takes no medications other than occasional acetaminophen for headache and milk of magnesia for constipation. Her vital signs and physical examination, including pelvic examination are normal.

Labs

Serum cholesterol: 220 mg/dL (5.7 mmol/L; normal less than 200 mg/dL, or 5.2 mmol/L)
TSH: 9.7 milliunits/L (normal 0.5–2.5 milliunits/L)*
Free T_4: 0.6 ng/dL (7.7 pmol/L; normal 0.7–1.9 ng/dL, or 9–24.5 pmol/L)
She weighs 66 kg (145 lb), and she is 5 ft, 7 in (170 cm) tall.

- Why should HT receive LT_4 therapy?
- What dose would you initiate?
- How would you monitor and titrate her therapy?
- What would you tell HT regarding the significance of her symptoms, elevated TSH level, and risk versus benefits of LT_4 therapy?

*Milliunits/L (mU/L) = microunits/mL (μU/L); clinical laboratories use either unit of measurement.

Risks of Over- and Undertreatment

Patients receiving LT_4 therapy who are not maintained in a euthyroid state are at risk for long-term adverse sequelae. In general, overtreatment and a suppressed TSH is more common than undertreatment[27] with an elevated TSH. Patients with long-term overtreatment may be at higher risk for atrial fibrillation and other cardiovascular morbidities, depression, and post-menopausal osteoporosis. Patients who are undertreated are at higher risk for hypercholesterolemia and other cardiovascular problems, depression, and obstetric complications.

Alterations in LT_4 Dose Requirements

A number of factors can alter LT_4 dose requirements (Table 41–4). The most common cause of increased dose requirement is the co-administration of LT_4 with calcium or iron supplements. Counsel patients that they should take the LT_4 dose at least 2 hours before or 6 hours after the calcium or iron dose.

Patient Monitoring

Patients on stable LT_4 therapy do not need frequent monitoring. In most patients, measuring a TSH every 6 to 12 months, along with an assessment of clinical status, is adequate (Table 41–5). If the patient's clinical status changes (e.g., pregnancy, etc.), more frequent monitoring may be necessary. LT_4 prescriptions should be written as microgram doses to avoid potential errors when written as milligram doses (e.g., 250 mcg dispensed when 0.025 mg is ordered).

Patient education is an important component of care. Educate patients about the benefits of proper therapy, the importance of adherence, and the importance of receiving a consistent LT_4 product. Some patients will take excessive amounts of LT_4 in an effort to "feel better" or as a weight-loss treatment. Explain to patients that excessive amounts of LT_4 will not improve symptoms more than therapeutic doses and that this drug is not an effective treatment for obesity.

TABLE 41–4. Factors That Alter LT_4 Dose Requirements

Increased Dose Requirement	Decreased Dose Requirement
Decreased LT_4 absorption	Aging
Malabsorption syndromes	Delivery of pregnancy
	Withdrawal of interacting substance
Drugs/Diet:	
Calcium	
Iron	
Aluminum	
Fiber	
Soy	
Cholestyramine/colestipol	
Sucralfate	
Sodium polystyrene sulfonate	
Increased TBG:	
Pregnancy	
Cirrhosis	
Estrogen therapy	
Tamoxifen, raloxifene therapy	
Hereditary	
Increased clearance:	
Rifampin	
Carbamazepine	
Phenytoin	
Phenobarbital	
Impaired deiodination:	
Amiodarone	
Mechanism unknown:	
Sertraline	
Lovastatin	

LT_4, levothyroxine; TBG, thyroxine-binding globulin.

Special Populations and Conditions

Hypothyroidism and Pregnancy

Hypothyroidism during pregnancy has a variety of maternal and fetal adverse effects.[11] During pregnancy, β-human chorionic gonadotropin (β-hCG) acts as a TSH receptor agonist, increasing the amount of thyroid hormone available for fetal growth and development. Maternal hypothyroidism results in an increased rate of miscarriage and decreased intellectual capacity of the child. Endocrinologists recommend a TSH measurement as soon as the pregnancy is confirmed. Most hypothyroid women who become pregnant will quickly need an increased dose of LT_4, averaging 50% above the pre-pregnancy dose.[28] The increased dose should be maintained throughout the pregnancy, with monthly TSH monitoring to keep the TSH in the middle- to low-normal range. After delivery, the LT_4 dose can be reduced to pre-pregnancy levels. Since prenatal vitamins contain significant amounts of calcium and iron, remind these patients to take the LT_4 dose at least 2 hours before or 6 hours after the vitamin.

TABLE 41–5. Monitoring LT_4 Therapy

Serum TSH:
Every 6–12 months or if change in clinical status
6–8 weeks after any dose or product change
In first trimester pregnancy, then monthly
Same product prescribed/dispensed with every refill.
Watch for mg/mcg dosing errors.
Assess patient's understanding of disease, therapy, and need for adherence and tight control.
Assess for signs/symptoms of over- and undertreatment.
Identify potential interactions between LT_4 and foods and/or drugs.

LT_4, levothyroxine; TSH, thyroid-stimulating hormone.



Patient Encounter 1, Part 2

One year later, HT comes to you and excitedly states that she is pregnant. She just saw her obstetrician, who started her on a prenatal vitamin. She states that she has felt very well since her LT_4 was started and that she is amazed at how much better she feels ("I didn't know how bad I felt until I started the thyroid medicine"). The most recent TSH determination, obtained 6 months ago, was 1.5 milliunits/L (normal 0.5–2.5 milliunits/L).* Her current LT_4 dose is 88 mcg/day.

- How will pregnancy affect HT's LT_4 dose requirement?
- What would you recommend regarding her LT_4 dose and monitoring?
- What would you tell HT regarding the potential impact of her pregnancy on her LT_4 therapy and the potential risks to her baby if she is not given an adequate dose of LT_4 during her pregnancy?

*Milliunits/L (mU/L) = microunits/mL (μU/L); clinical laboratories use either unit of measurement.

Children

Congenital hypothyroidism is still seen in the United States, and all newborns in the United States undergo screening with a TSH level. As soon as the hypothyroid state is identified, the newborn should receive the full LT_4 replacement dose. The replacement dose of LT_4 in children is age-dependent. In newborns, the usual dose is 10 to 17 mcg/kg per day. LT_4 tablets may be crushed and mixed with breast milk or formula. Serum FT_4 levels (target 1.6–2.2 ng/dL or 20.59–28.31 pmol/L) are used for dose titration in infants because the TSH level may not respond to treatment as it does in older children and adults. By 6 months of age, the required dose is reduced to 5 to 7 mcg/kg per day, and from ages 1 to 10 years, the dose is 3 to 6 mcg/kg per day. After age 12, adult doses can be given.

Myxedema Coma

This is a life-threatening condition owing to severe, long-standing hypothyroidism and has a mortality rate of 60% to 70%. These patients are given 300 to 500 mcg intravenous LT_4 initially, using caution in patients with underlying cardiac disease. While administration of T_3 would provide a more



Hypothyroidism Patient Care and Monitoring

1. Use serum TSH to identify patients with hypothyroidism and to monitor LT_4 replacement therapy.
2. Use synthetic LT_4 as the treatment of choice for hypothyroidism.
3. Provide LT_4 replacement to patients with overt hypothyroidism.
4. Consider replacement therapy in patients with a TSH level of greater than 2.5 but less than 10 milliunits/L* who have subtle symptoms (e.g., mild fatigue, lethargy, etc.), elevated cholesterol, or positive anti-TPOAbs.
5. Provide the calculated full replacement LT_4 dose (1.6 mcg/kg per day based on ideal body weight if obese) to patients with overt hypothyroidism who are older than 12 and younger than 65 years of age and who do not have cardiac disease.
6. Patients with mild hypothyroidism may be started at 25 to 50 mcg/day of LT_4.
7. Elderly patients or those with cardiac disease should be started at a lower LT_4 dose (e.g., 12.5–25 mcg/day).
8. Measure serum TSH 6 to 8 weeks after starting or any dose change. If the TSH level is not in the target range, alter the dose by 10% to 20% increments.
9. The target TSH for patients on LT_4 replacement therapy for hypothyroidism is 0.5 to 2.5 milliunits/L. Most patients feel best at a TSH level in the low- to middle-normal range (i.e., 0.5–1.5 milliunits/L).*
10. Provide a brand-name LT_4 product, and do not allow the patient to be switched to different products. If the product is switched, check a TSH in 6 weeks and retitrate the dose.
11. Write LT_4 prescriptions as microgram not milligram doses to avoid errors.
12. Check a TSH every 6 to 12 months in stable patients receiving LT_4 replacement.
13. Make sure that patients understand the importance of adherence and the risks of over- and underuse of LT_4.
14. At each visit, assess the patient for signs and symptoms of over- and undertreatment.
15. Monitor for drug interactions, such as LT_4 absorption problems caused by calcium and iron.
16. Check a TSH in pregnant women as soon as the pregnancy is diagnosed. In hypothyroid pregnant women, check the TSH monthly, and expect to raise the LT_4 dose during the first trimester. Maintain the TSH in the low- to middle-normal range. After delivery, reduce the LT_4 dose to the pre-pregnancy dose.

*Milliunits/L (mU/L) = microunits/mL (μU/L); clinical laboratories use either unit of measurement.

rapid onset of action, there is no evidence that T_3 improves outcomes in myxedema coma. Historically, glucocorticoids, such as hydrocortisone 50 to 100 mg every 6 hours, are administered owing to concern about simultaneous adrenal insufficiency. While there is no strong evidence for an outcome benefit, the use of glucocorticoids is reasonable because such treatment may be lifesaving, and the risks of a short course of corticosteroids at this dose are low. As patients improve, the LT_4 dose can be given orally in a typical full replacement dose.

HYPERTHYROIDISM/THYROTOXICOSIS

Hyperthyroidism is much less common than hypothyroidism. In NHANES III,[1] 1.3% of the population was hyperthyroid (0.5% overt, 0.8% subclinical), with the highest incidences in women overall and in men and women in the 20 to 39 and over 80 years of age groups. The Colorado Thyroid Health Study[2] showed a hyperthyroid incidence of 2.2% (2.1% subclinical).

Causes of Thyrotoxicosis

The common causes of thyrotoxicosis are shown in Table 41–6.[29,30] Thyrotoxicosis can be related to the presence or absence of excess hormone production (hyperthyroidism). Graves' disease is the most common cause of hyperthyroidism. Thyrotoxicosis in the elderly is more likely due to toxic thyroid nodules or multinodular goiter than to Graves' disease. Excessive intake of thyroid hormone may be due to overtreatment with prescribed therapy. Surreptitious use of thyroid hormones also may occur, especially in health professionals or as a self-remedy for obesity. Thyroid hormones can be obtained easily without a prescription from health food stores or Internet sources.

Clinical Manifestations of Thyrotoxicosis

Many of the signs and symptoms seem to be related to autonomic hyperactivity. As with hypothyroidism, the clinical

TABLE 41–6. Causes of Thyrotoxicosis[29]

Primary hyperthyroidism
Graves' disease
Toxic multinodular goiter
Toxic adenoma
Thyroid cancer
Struma ovarii
Iodine excess (including radiocontrast, amiodarone)
Thyrotoxicosis without hyperthyroidism
Subacute thyroiditis
Silent (painless) thyroiditis
Excess thyroid hormone intake (thyrotoxicosis factitia)
Secondary hyperthyroidism
TSH-secreting pituitary tumors
Trophoblastic (hCG-secreting) tumors
Gestational thyrotoxicosis

Adapted, with permission. hCG, human chorionic gonadotropin; TSH, thyroid-stimulating hormone.



Clinical Presentation and Diagnosis of Hyperthyroidism[29,30]

Symptoms
- Nervousness
- Fatigue
- Weakness
- Increased perspiration
- Heat intolerance
- Tremor
- Hyperactivity, irritability
- Palpitations
- Appetite change (usually increased)
- Weight change (usually weight loss)
- Menstrual disturbances (often oligomenorrhea)
- Diarrhea

Signs
- Hyperactivity
- Tachycardia
- Atrial fibrillation (especially in elderly)
- Hyperreflexia
- Warm, moist skin
- Ophthalmopathy, dermopathy (Graves' disease)
- Goiter
- Muscle weakness

Screening/Diagnosis
- Low TSH level (less than 0.5 milliunit/L) will signify thyrotoxicosis.
- Free T_4 is elevated in overt hyperthyroidism.
- Increased radioiodine uptake in the thyroid indicates increased hormone production by the thyroid gland.
- Almost all patients with Graves' disease will have positive TSHR-SAbs and positive anti-TPOAbs.

manifestations may be subtle initially and slowly progressive. Screening of patients for thyroid disease may identify patients with subclinical or mild thyrotoxicosis. Patients may seek medical attention only after a long period of thyrotoxicosis or owing to an acute complication such as atrial fibrillation. The clinical manifestations of thyrotoxicosis in the elderly may be blunted or atypical. These patients may present only with atrial fibrillation or depression.

Subclinical Thyrotoxicosis

Subclinical or mild thyrotoxicosis is defined as a low TSH with a normal FT_4 level. While there may be few or no symptoms in these patients, there are several areas of concern.[31,32] Many patients will progress to overt thyrotoxicosis. Patients with subclinical hyperthyroidism have been shown to suffer long-term cardiovascular and bone sequelae. In a 10-year follow-up of 2007 patients over age 60,[33] patients with an undetectable TSH level had a 3.1-fold increased risk of atrial fibrillation versus those with a normal TSH. In a different 10-year follow-up study[34] of 1191 patients over age 60, patients with a suppressed TSH had a 2.1-fold increased risk of all-cause mortality and a 3.3-fold increased risk of cardiovascular mortality versus patients with a normal TSH. Recent studies have shown that prolonged subclinical thyrotoxicosis speeds the loss of bone mineral density and increases fracture rates in postmenopausal women.[35,36]

Graves' Disease

Graves' disease[30] is an autoimmune syndrome that includes hyperthyroidism, diffuse thyroid enlargement, **exophthalmos** and other eye findings, and skin findings. The prevalence of Graves' disease in the United States is approximately 0.4% in women and 0.1% in men. The peak age of incidence is 20 to 49 years, with a second peak after 80 years of age. Hyperthyroidism results from the production of TSHR-SAbs in at least 80% of patients. These antibodies have TSH agonist activity, thereby stimulating hormone synthesis and release. These antibodies cross-react with orbital and fibroblastic tissue, resulting in ophthalmopathy and dermopathy. While the underlying cause of Graves' disease is not known, heredity seems to play a role. Subclinical Graves' disease may become acutely overt in the presence of iodine excess, infection, stress, parturition, smoking, and lithium and cytokine therapy.

There are several features of Graves' disease that are distinct from other forms of thyrotoxicosis. Clinically apparent ophthalmopathic changes are seen in 20% to 40% of patients and include exophthalmos, **proptosis, chemosis, conjunctival injection,** and periorbital edema. Lid retraction causes a typical staring or startled appearance (Fig. 41–3). Patients may complain of vague eye discomfort and excess tearing. In severe cases, the eyelids are unable to close completely, resulting in corneal damage. In very severe cases, the optic nerve can be compressed, resulting in permanent vision loss. All patients with suspected or known Graves' disease must be evaluated and monitored by an ophthalmologist.

Dermopathy occurs in 5% to 10% of patients with Graves' disease and usually is associated with severe ophthalmopathy. Skin findings include hyperpigmented, non-pitting induration of the skin, typically over the pretibial area (pretibial myxedema), the dorsa of the feet, and shoulder areas. **Clubbing** of the digits (thyroid acropachy) is associated with long-standing thyrotoxicosis.

Treatment of Hyperthyroidism

Treatment of thyrotoxicosis due to hyperthyroidism is similar, regardless of the underlying cause. ❻ *The goals of treating hyperthyroidism are to relieve symptoms, to reduce thyroid hormone production to normal levels and achieve biochemical euthyroidism, and to prevent long-term adverse sequelae.*

β-Blockers

Because many of the manifestations of hyperthyroidism appear to be mediated by the β-adrenergic system, β-adrenergic



FIGURE 41–3. Features of Graves' disease. *A*. Facial appearance: exophthalmos, lid retraction, periorbital edema, and proptosis. *B*. Thyroid dermopathy over lateral aspects of shins. *C*. Thyroid clubbing (acropachy). (Reprinted, with permission, from Jameson JL, Weetman AP. Disorders of the thyroid gland. In: Kasper DL, Braunwald E, Fauci AS, et al, (eds.) *Harrison's Principles of Internal Medicine*. 16th edition. New York: McGraw-Hill; 2004: 2114.)

blockers are used to rapidly relieve palpitations, tremor, anxiety, and heat intolerance. Since β-blockers do not reduce the synthesis of thyroid hormones, they are used only until more specific antithyroid therapy is effective. Since non-selective agents can impair the conversion of T_4 to T_3, propranolol and nadolol are used. An initial propranolol dose of 20 to 40 mg four times daily should be titrated to relieve signs and symptoms. β-Blockers should not be used in patients with decompensated heart failure or asthma. When a contraindication to β-blockers exists, clonidine or diltiazem may be used.

Methods to Reduce Thyroid Hormone Synthesis

Excess production of thyroid hormone can be reduced in four ways: iodides, antithyroid drugs, radioactive iodine, and surgery.[30,37,38]

Iodide

Large doses of iodide inhibit the synthesis and release of thyroid hormones. Serum T_4 levels may be reduced within 24 hours, and the effects may last for 2 to 3 weeks. Iodides are used most commonly in Graves' disease patients prior to surgery and to quickly reduce hormone release in patients with thyroid storm. Potassium iodide is administered either as a saturated solution (SSKI) that contains 38 mg iodide per drop or as Lugol's solution, which contains 6.3 mg iodide per drop. The typical starting dose is 120 to 400 mg/day. Iodide therapy should start 7 to 14 days prior to surgery. Iodide should not be given prior to radioactive iodine treatment because the iodide will inhibit concentration of the radioactivity in the thyroid. Iodides also are used to protect the thyroid from radioactive iodine fallout after a nuclear accident or attack. Daily administration of 30 to 100 mg iodide will markedly reduce thyroid gland uptake of radioactive iodine. The most frequent toxic effects with iodide therapy are hypersensitivity reactions, "iodism" (characterized by palpitations, depression, weight loss, and pustular skin eruptions), and gynecomastia.

Antithyroid Drugs

The thionamide agents propylthiouracil and methimazole are used in the United States to treat hyperthyroidism.[39] Carbimazole, a methimazole analog, is available in Europe. These drugs inhibit thyroid hormone synthesis by interfering with thyroid peroxidase–mediated iodination of tyrosine residues in thyroglobulin. Propylthiouracil has the added effect of inhibiting the conversion of T_4 to T_3. The thionamides also have immunosuppressant effects. In patients with Graves' disease treated with thionamides, TSHR-SAb levels and other immune mediators decrease over time. Both drugs are well absorbed from the gastrointestinal tract. Propylthiouracil has a half-life of 1 to 2.5 hours, whereas the half-life of methimazole is 6 to 9 hours.

Antithyroid drugs are used as primary therapy for Graves' disease or as preparative therapy before surgery or radioactive iodine administration. The decision to use antithyroid drugs as

primary therapy must be weighed against the risks and benefits of radioiodine or surgery. Patient preference must be considered.

In most patients, there is no clear advantage of one thionamide over the other. While propylthiouracil has the advantage of inhibiting T_4- to T_3-conversion, methimazole can be given as a single daily dose. The usual starting dose of methimazole is 15 to 30 mg/day, and the usual starting dose of propylthiouracil is 100 mg three times daily. Thyroid hormone levels drop in 2 to 3 weeks, and after 6 weeks, 90% of patients with Graves' disease will be euthyroid. Thyroid function testing should be performed every 4 to 6 weeks until stable. After the patient becomes euthyroid, the antithyroid drug dose often can be decreased (5–10 mg/day methimazole, 100–200 mg/day propylthiouracil) to maintain the euthyroid state. Excessive doses of antithyroid drugs will result in hypothyroidism. Methimazole is preferred to normalize thyroid function prior to radioactive iodine therapy because propylthiouracil increases the failure rate of radioactive iodine therapy.

Remission of Graves' disease occurs in 40% to 60% of patients after 1 to 2 years of therapy. Levels of TSHR-SAb after a course of treatment may have predictive value in that antibody-positive patients almost always will relapse. However, antibody-negative patients also may relapse after therapy is stopped. Antithyroid therapy may be stopped or tapered after 12 to 24 months. Relapse usually occurs in the first 3 to 6 months after stopping antithyroid therapy. About 75% of women in remission who become pregnant will have a postpartum relapse. When therapy is discontinued, a therapeutic strategy should be in place in the event of relapse. Many patients will opt for radioactive iodine as a long-term solution.

Antithyroid drugs are associated with a low rate of adverse effects. Skin rash, arthralgias, and gastrointestinal upset are seen in 5% of patients. While the drug can be continued in the presence of a minor skin rash, the development of arthralgia warrants discontinuation. Hepatotoxicity is an uncommon but potentially serious adverse effect, occurring in 0.1% to 0.2% of patients. However, transient rises in aminotransferase enzyme levels are seen in up to 30% of patients treated with propylthiouracil. Severe hepatocellular damage can occur from propylthiouracil, whereas methimazole can cause cholestatic jaundice. Vasculitis is another potentially serious but uncommon reaction that is more common with propylthiouracil. Patients may develop a drug-induced lupus syndrome, and some, particularly Asians, can develop antineutrophil cytoplasmic antibody-positive vasculitis.

Agranulocytosis is the most feared side effect of antithyroid drug therapy. Agranulocytosis must be distinguished from a transient decrease in white blood cell count seen in up to 12% of adults and 25% of children with Graves' disease. Agranulocytosis occurs in 0.3% of patients, and the incidence is the same with propylthiouracil and methimazole. Agranulocytosis almost always occurs within the first 3 months of therapy, and it occurs suddenly and unpredictably. Patients will present with fever, malaise, and sore throat, and the absolute neutrophil count will be less than 1000/mm^3. Patients may develop sepsis and die rapidly. Agranulocytosis is thought to be autoimmune-mediated. If agranulocytosis occurs, discontinue the antithyroid drug immediately, administer broad-spectrum antibiotics if the patient is febrile, and consider the administration of granulocyte colony-stimulating factor. The white blood cell count should recover in a week or two. Patients who develop agranulocytosis should not be switched to another thionamide drug. Monitoring for agranulocytosis is controversial owing to its sudden and predictable nature. Most practitioners do not recommend routine monitoring of the complete blood count, although early detection could improve patient outcomes. Patients initiating thionamide therapy must be informed about the signs



Patient Encounter 2, Part 1

GD is a 24-year-old woman who comes to the clinic stating, "I'm so nervous and hungry, and I'm losing weight. What is wrong with me?" She first noticed these symptoms 2 months ago, and they have worsened steadily. She feels anxious for no reason and has trouble sleeping. She has noticed that her appetite has increased, although she has lost about 5 lb (2.3 kg). Sometimes she can feel her heart beating in her chest, but she denies chest pain or syncope. She also has noticed that she is always sweaty and that her menses have become very light. Her only medications are a hormonal oral contraceptive and occasional naproxen for dysmenorrhea. She thinks that her mother had some kind of thyroid problem when she was pregnant.

PE

VS: Pulse 112 beats per minute, blood pressure 108/72, RR 12, temperature 37.4°C (99.32°F)
HEENT: Diffusely enlarged thyroid; mild exophthalmos
CV: Tachycardic, RRR
Exts: Fine tremor
Skin: Warm and moist
ECG: Sinus tachycardia

Labs

Electrolytes, complete blood count normal. Urine hCG negative. TSH less than 0.5 milliunit/L (normal 0.5–2.5 milliunits/L);* FT_4 3.1 ng/dL (39.9 pmol/L; normal 0.7–1.9 ng/dL, or 9.0–24.5 pmol/L); +TSHR-SAbs

- What therapeutic options exist for GD's Graves' disease?
- What would you recommend?
- How would you initiate and titrate therapy?
- What would you tell GD regarding the cause of her signs and symptoms, significance of her abnormal thyroid function tests, and therapeutic options?

*Milliunits/L (mU/L) = microunits/mL (μU/L); clinical laboratories use either unit of measurement.

and symptoms of agranulocytosis and other serious side effects. Patients should be asked to report signs and symptoms suggestive of infection such as fever and sore throat lasting more than 2 or 3 days or any bruising.

Radioactive Iodine

Radioactive iodine, typically ^{131}I, produces thyroid **ablation** without surgery. ^{131}I is well absorbed after oral administration. The iodine is concentrated in the thyroid gland and has a half-life of 8 days. Over a period of weeks, thyroid cells that have taken up the ^{131}I begin to develop abnormalities and necrosis. Eventually, thyroid cells are destroyed, and hormone production is reduced. After a single dose, 40% to 70% of patients will be euthyroid in 6 to 8 weeks, and 80% will be cured. In most patients, hypothyroidism will develop, and long-term LT_4 replacement will be necessary. Because ^{131}I has a slow onset of action, most patients are treated initially with β-blockers and antithyroid drugs. Thionamide drugs must be withdrawn for at least 4 to 6 days prior to ^{131}I administration to allow adequate accumulation of the radioactive iodine in the gland. β-Blockers can be continued during ^{131}I therapy. The dose of ^{131}I is based on the estimated weight of the patient's thyroid gland. Radioactive iodine therapy is contraindicated during pregnancy and breastfeeding. Radioactive iodine therapy may acutely worsen Graves' ophthalmopathy. Patients with prominent eye disease may be started on prednisone 40 mg/day, with the dose tapered over 2 to 3 months. Radioactive iodine also may cause a painful thyroiditis, which may necessitate anti-inflammatory therapy. Any long-term carcinogenic effect of ^{131}I has not been demonstrated in long-term clinical trials.

Surgery

Subtotal thyroidectomy is indicated in patients with very large goiters and thyroid malignancies and those who do not respond or cannot tolerate other therapies. Patients must be euthyroid prior to surgery, and patients often are administered iodide preoperatively to reduce gland vascularity. The overall surgical complication rate is 2.7%. Postoperative hypothyroidism occurs in 10% of patients who undergo subtotal thyroidectomy.

Special Conditions and Populations

Graves' Disease and Pregnancy

Pregnancy may worsen or precipitate thyrotoxicosis in women with underlying Graves' disease owing to the TSH agonist effect of hCG. Untreated maternal thyrotoxicosis may result in increased rates of miscarriage, premature delivery, eclampsia, and low-birth-weight infants. Fetal and neonatal hyperthyroidism may occur as a result of transplacental passage of TSHR-SAbs. Because radioactive iodine is contraindicated and surgery is best avoided during pregnancy, most patients are treated with antithyroid drugs. Propylthiouracil is considered the treatment of choice, and the lowest possible dose to maintain maternal euthyroidism should be used. Antithyroid therapy in excessive doses may suppress fetal thyroid function.



Patient Encounter 2, Part 2

One month later, GD is back for a follow-up visit. She notes that her thyrotoxic symptoms are gone, and overall, she feels great. She is receiving propylthiouracil 100 mg three times daily. Her most recent TSH was 0.9 milliunit/L (normal 0.5–2.5 milliunits/L)*, and her free T_4 was 1.6 ng/dL (20.6 pmol/L; normal 0.7–1.9 ng/dL, or 9.0–24.5 pmol/L). However, over the past few days she has developed a sore throat and feels achy. She wonders if she has the flu. Her vital signs show a pulse of 92 beats/minute and a temperature of 38.3°C (101°F). A complete blood count reveals a total white blood cell count of 100/mm^3 or 0.1 × 10^9/L (normal 4000–10,000/mm^3 or 4–10 × 10^9/L) with 15 neutrophils (absolute neutrophil count 150).

- What has happened to GD?
- What are you concerned about?
- How will you manage this problem?
- What will you tell GD regarding the possible cause of her new symptoms, the significance of her low white blood cell count, and recommended actions?

*Milliunits/L (mU/L) = microunits/mL (μU/L); clinical laboratories use either unit of measurement.

Neonatal and Pediatric Hyperthyroidism

Some neonates born to mothers with Graves' disease will be hyperthyroid at delivery. Antithyroid drug therapy (propylthiouracil 5–10 mg/kg per day or methimazole 0.5–1 mg/kg per day) may be required for up to 12 weeks. One drop per day of SSKI may be used in the first few days to rapidly reduce thyroid hormone synthesis and release.

Thyroid Storm

Thyroid storm is a life-threatening condition caused by severe thyrotoxicosis. Signs and symptoms include high fever, tachycardia, tachypnea, dehydration, delirium, coma, and gastrointestinal disturbances. Thyroid storm is precipitated in a previously hyperthyroid patient by infection, trauma, surgery, radioactive iodine treatment, and sudden withdrawal from antithyroid drugs. Patients are treated with a short-acting β-blocker such as intravenous esmolol, intravenous or oral iodide, and large doses of propylthiouracil (900–1200 mg/day in three to four divided doses). Supportive care with acetaminophen to suppress fever, fluid and electrolyte management, and antiarrhythmic agents are important components of therapy. Intravenous hydrocortisone 100 mg every 8 hours is used often due to the potential presence of adrenal insufficiency.



Hyperthyroidism Patient Care and Monitoring

1. A low or undetectable TSH level identifies thyrotoxicosis.
2. Refer the patient for a diagnostic assessment to identify the underlying cause. Identify Graves' disease by the presence of eye and/or skin findings and the presence of TSHR-SAbs.
3. Refer patients with Graves' disease to an ophthalmologist for assessment and monitoring.
4. Treat severe or troublesome autonomic signs and symptoms with a non-selective β-blocker such as propranolol 20 to 40 mg four times daily. Titrate the β-blocker dose based on signs and symptoms.
5. In patients with excess thyroid hormone production, reduce hormone production with an antithyroid drug and/or radioactive iodine. Choose therapy based on patient-specific factors and preference.
6. Antithyroid drugs have a delayed effect. After 2 to 4 weeks of therapy, adjust the dose if the TSH is not in the target range (0.5–2.5 milliunits/L).* Once the patient is euthyroid, consider reducing the dose of antithyroid drug to avoid hypothyroidism.
7. Consider stopping antithyroid therapy in Graves' disease after 12 to 18 months to see if remission has occurred.
8. Monitor patients on antithyroid drugs for signs and symptoms of adverse effects.
9. Monitor for symptoms of neutropenia (e.g., fever or sore throat), and check white blood cell count if symptoms occur.
10. If radioactive iodine is given, make sure that antithyroid drugs are stopped 4 to 6 days prior to treatment.
11. Several months after radioactive iodine, expect that the patient will require permanent LT_4 replacement.
12. Treat pregnant hyperthyroid women with propylthiouracil.

*Milliunits/L (mU/L) = microunits/mL (μU/L); clinical laboratories use either unit of measurement.

NON-THYROIDAL ILLNESS (EUTHYROID SICK SYNDROME)

A number of changes in the hypothalamic-pituitary-thyroid axis occur during acute illness.[40] These changes are termed nonthyroidal illness or euthyroid sick syndrome. The type and degree of abnormalities depend on the severity of illness. Mild to moderate medical illness, surgery, or starvation causes a decrease in serum T_3 levels owing to decreased peripheral conversion of T_4 to T_3. The reduced T_3 levels do not correlate with ultimate mortality and are thought to be an adaptive response to stress. Patients with more severe illness, especially those in the intensive-care unit, frequently have reduced total T_4 levels, although FT_4 levels usually are normal. In the critically ill, there is a correlation between the degree of serum T_4 reduction and mortality. In most acutely ill patients who are euthyroid, the TSH level is normal. However, administration of dopamine, octreotide, or high doses of glucocorticoids can reduce TSH levels. During recovery from acute illness, the TSH level may become modestly elevated to renormalize serum T_4 levels. During this time, thyroid function tests may be misinterpreted to indicate hypothyroidism. Despite the sometimes very low T_4 levels, there is no evidence that LT_4 administration has any benefit. Patients with possible thyroid abnormalities during acute illness should be evaluated by an endocrinologist.

THYROID CANCER AND LT_4 SUPPRESSION

The growth and spread of thyroid carcinoma is stimulated by TSH. An important component of thyroid carcinoma management is the use of LT_4 to suppress TSH secretion. Early in therapy, patients receive the lowest LT_4 dose sufficient to fully suppress TSH to undetectable levels. Controlled trials show that suppressive LT_4 therapy reduces tumor growth and improves survival. These patients are purposefully "overtreated" with LT_4 and rendered subclinically hyperthyroid. Postmenopausal women should receive aggressive osteoporosis therapy to prevent LT_4-induced bone loss. Other thyrotoxic complications, such as atrial fibrillation, should be monitored and managed appropriately.

DRUG-INDUCED THYROID ABNORMALITIES

Drugs can affect thyroid function in a number of ways.[41] Effects of drugs on thyroid hormone protein binding, LT_4 absorption, and metabolism have been discussed previously. Several commonly used medications can alter thyroid hormone secretion.

Amiodarone

Amiodarone[42] is a commonly prescribed antiarrhythmic drug that contains two iodide atoms, constituting 38% of its mass. Each 200 mg dose of amiodarone provides 75 mg iodide. Amiodarone deiodination releases about 6 mg of free iodine daily, 20 to 40 times more than the average daily intake of iodine in the United States. Amiodarone blocks conversion of T_4 to T_3, inhibits entry of T_3 into cells, and decreases T_3 receptor binding. Amiodarone will cause thyroid abnormalities in 11% of previously euthyroid patients. Amiodarone causes rapid reduction in serum T_3 levels, increases free and total T_4 levels, and increases TSH level. After 3 months of therapy, TSH levels usually return to normal, although the serum T_3 and T_4 level changes may remain. Most of these patients are euthyroid because the free T_3 levels are in the low-normal range. Amiodarone-induced hypothyroidism is more common in iodine-sufficient areas of the world. Patients with

underlying autoimmune thyroiditis are much more likely to develop amiodarone-induced hypothyroidism. Amiodarone-induced hypothyroidism occurs most commonly within the first year of therapy. If amiodarone cannot be discontinued, LT_4 therapy will be effective in most patients. If amiodarone can be stopped, thyroid function will return to normal in 2 to 4 months.

Amiodarone is more likely to cause thyrotoxicosis in iodine-deficient areas. Type 1 amiodarone-induced thyrotoxicosis is caused by iodine excess and typically occurs in patients with preexisting multinodular goiter or subclinical Graves' disease. Type 2 amiodarone-induced thyrotoxicosis is a destructive thyroiditis that occurs in patients with no underlying thyroid disease. Amiodarone-induced thyrotoxicosis is more common in men. Because amiodarone has β-blocking activity, palpitations and tachycardia may be absent. In type 1 thyrotoxicosis, amiodarone should be discontinued. If amiodarone therapy cannot be stopped, larger doses of antithyroid drugs may be needed to control thyrotoxicosis. In type 2 thyroiditis, stopping amiodarone may not be necessary because spontaneous resolution may occur. Prednisone 40 to 60 mg/day will quickly improve thyrotoxic symptoms. Prednisone may be tapered after 1 to 2 months of therapy.

❾ *Patients receiving amiodarone must receive monitoring for thyroid abnormalities. Baseline measurements of serum TSH, FT_4, FT_3, anti-TPOAbs, and TSHR-SAbs should be performed. TSH, FT_4, and FT_3 should be checked 3 months after initiation of amiodarone and then every 3 to 6 months.*

Lithium

Lithium is associated with hypothyroidism in up to 34% of patients, and hypothyroidism may occur after years of therapy. Lithium appears to inhibit thyroid hormone synthesis and secretion. Patients with underlying autoimmune thyroiditis are more likely to develop lithium-induced hypothyroidism. Patients may require LT_4 replacement even if lithium is discontinued.

Interferon-α

Interferon-α causes hypothyroidism in up to 39% of patients being treated for hepatitis C infection. Patients may develop a transient thyroiditis with hyperthyroidism prior to becoming hypothyroid. The hypothyroidism may be transient as well. Asians and patients with preexisting anti-TPOAbs are more likely to develop interferon-induced hypothyroidism. The mechanism of interferon-induced hypothyroidism is not known. If LT_4 replacement is initiated, it should be stopped after 6 months to re-evaluate the need for replacement therapy.

Outcome Evaluation

- Desired outcomes include relieving signs and symptoms and achieving a euthyroid state.
- Success of therapy for thyroid disorders must be based not only on short-term improvement of the patient's clinical status and abnormal laboratory values but also on achievement of a long-term euthyroid state. Maintaining the TSH level in the normal range improves symptoms and reduces the risk of long-term complications.
- Because pharmacotherapy often is lifelong, especially in patients with hypothyroidism, patients must undergo periodic monitoring to avoid the long-term complications of hypothyroidism and hyperthyroidism. In the hypothyroid patient, such monitoring may involve simply asking the patient about signs and symptoms and a yearly measurement of the TSH level.
- Any change in the patient's clinical status, such as a new pregnancy or a major change in body weight, necessitates a reevaluation of therapy. Patients at high risk for complications, such as pregnant women, the elderly, and patients with underlying cardiac disease, must be monitored more closely.
- Patients should be educated and periodically reminded about the importance of adherence and long-term tight control, the need for periodic clinical and laboratory monitoring, and the importance of staying on one LT_4 product.
- In the hyperthyroid patient, relieving signs and symptoms and achieving a euthyroid state are the desired outcomes. The method of achieving these outcomes may change over time with the use of antithyroid drugs versus radioactive iodine.
- Patients with hyperthyroidism also must undergo periodic clinical and laboratory monitoring, with more frequent monitoring if there is a change in the patient's clinical status.
- Patients who receive antithyroid drugs must be monitored for adverse drug events such as agranulocytosis.
- Patients who receive radioactive iodine must be monitored for the development of hypothyroidism.
- In patients with thyroid cancer, the desired outcomes with LT_4 therapy often are different from those in the hypothyroid patient.
- LT_4 doses sufficient to suppress tumor growth may result in a suppressed TSH and mild hyperthyroidism. These patients must be monitored closely for complications of the mild hyperthyroid state, such as bone mineral loss and development of atrial fibrillation.

ABBREVIATIONS

ANDA:	Abbreviated New Drug Application
anti-TGAb:	antithyroglobulin antibody
anti-TPOAb:	antithyroid peroxidase antibody
AUC:	area under the (time-concentration) curve
β-hCG:	beta-human chorionic gonadotropin
CNS:	central nervous system
FDA:	Food and Drug Administration (United States)
FT_3:	free T_3
FT_4:	free T_4
hCG:	human chorionic gonadotropin
LT_4:	levothyroxine
NHANES:	National Health and Nutrition Examination Survey

NTI:	narrow therapeutic index
RAIU:	radioactive iodine uptake
SSKI:	saturated solution of potassium iodide
T_3:	triiodothyronine
T_4:	thyroxine
TBG:	thyroxine-binding globulin
TPOAb:	thyroid peroxidase antibody
TRH:	thyrotropin-releasing hormone
TSH:	thyroid-stimulating hormone
TSHR-SAb:	TSH receptor-stimulating antibodies

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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42 Adrenal Gland Disorders

Devra K. Dang, Judy T. Chen, Frank Pucino, Jr., and Karim Anton Calis



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Explain the regulation and physiologic roles of hormones produced by the adrenal glands.
2. Recognize the clinical presentation of patients with adrenal insufficiency.
3. Describe the pharmacologic management of patients with acute and chronic adrenal insufficiency.
4. Recommend therapy monitoring parameters for patients with adrenal insufficiency.
5. Recognize the clinical presentation of Cushing's syndrome and the physiologic consequences of cortisol excess.
6. Recommend strategies to prevent the development of Cushing's syndrome associated with exogenous glucocorticoid administration.
7. Describe the pharmacologic and nonpharmacologic management of patients with Cushing's syndrome.
8. Recommend therapy monitoring parameters for patients with Cushing's syndrome.

Key Concepts

❶ Signs and symptoms of adrenal insufficiency reflect the disturbance of normal physiologic carbohydrate, fat, and protein homeostasis caused by inadequate cortisol production and inadequate cortisol action.

❷ Lifelong glucocorticoid replacement therapy may be necessary for patients with adrenal insufficiency, and mineralocorticoid replacement therapy usually is required for those with Addison's disease.

❸ During an acute adrenal crisis, the immediate treatment goals are to correct volume depletion, manage hypoglycemia, and provide glucocorticoid replacement.

❹ Patients who experience excessive stress should be educated regarding the need for additional glucocorticoid replacement and prompt medical attention.

❺ Patients with Cushing's syndrome owing to endogenous or exogenous glucocorticoid excess typically present with similar clinical manifestations.

❻ Surgical resection is considered the treatment of choice for Cushing's syndrome from endogenous causes if the tumor can be localized and if there are no contraindications.

❼ Pharmacotherapy generally is reserved for patients: (1) in whom the ectopic adrenocorticotropic hormone–secreting tumor cannot be localized; (2) who are not surgical candidates; (3) who have failed surgery; (4) who have had a relapse after surgery; or (5) in whom adjunctive therapy is required to achieve complete remission.

❽ In drug-induced Cushing's syndrome, discontinuation of the offending agent is the best management option. However, abrupt withdrawal of the glucocorticoid can result in adrenal insufficiency or exacerbation of the underlying disease.

❾ Glucocorticoid doses of less than 7.5 mg/day of prednisone (or its equivalent) for fewer than 3 weeks generally would not be expected to lead to suppression of the hypothalamic-pituitary-adrenal axis.

The adrenal glands are important in the synthesis and regulation of key hormones. They play a crucial role in water and electrolyte homeostatsis, as well as regulation of blood pressure, carbohydrate and fat metabolism, physiologic response to stress, and sexual development and differentiation. This chapter focuses on pharmacologic and nonpharmacologic management of the two most common conditions associated

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with adrenal gland dysfunction: glucocorticoid insufficiency (e.g., Addison's disease) and glucocorticoid excess (Cushing's syndrome). Other adrenal disorders such as **congenital adrenal hyperplasia, pheochromocytoma,** hypoaldosteronism, and hyperaldosteronism are beyond the scope of this chapter.

PHYSIOLOGY, ANATOMY, AND BIOCHEMISTRY OF THE ADRENAL GLAND

The adrenal gland is located on the upper segment of the kidney (Fig. 42–1). It consists of an outer cortex and an inner medulla. The adrenal medulla secretes the catecholamines epinephrine (also called adrenaline) and norepineprhine (also called noradrenaline), which are involved in regulation of the sympathetic nervous system. The adrenal cortex consists of three histologically distinct zones: zona glomerulosa, zona fasciculata, and an innermost layer called the zona reticularis. Each zone is responsible for production of different hormones (Fig. 42–2).

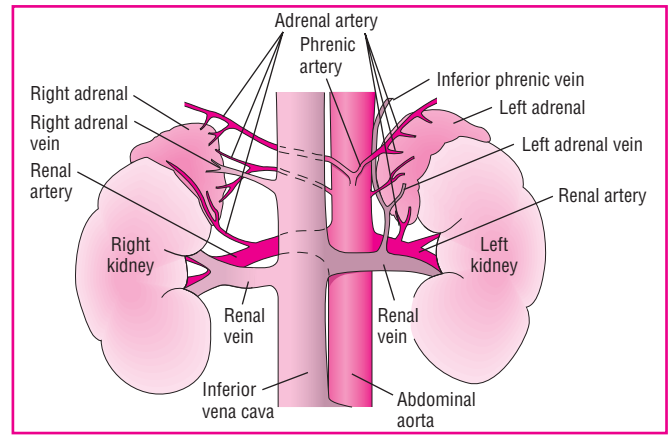


FIGURE 42–1. Anatomy of the adrenal gland. (Reprinted, with permission, from Gums JG, Tovar JM. Adrenal gland disorders. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. New York: McGraw-Hill; 2005: 1391–1406.)

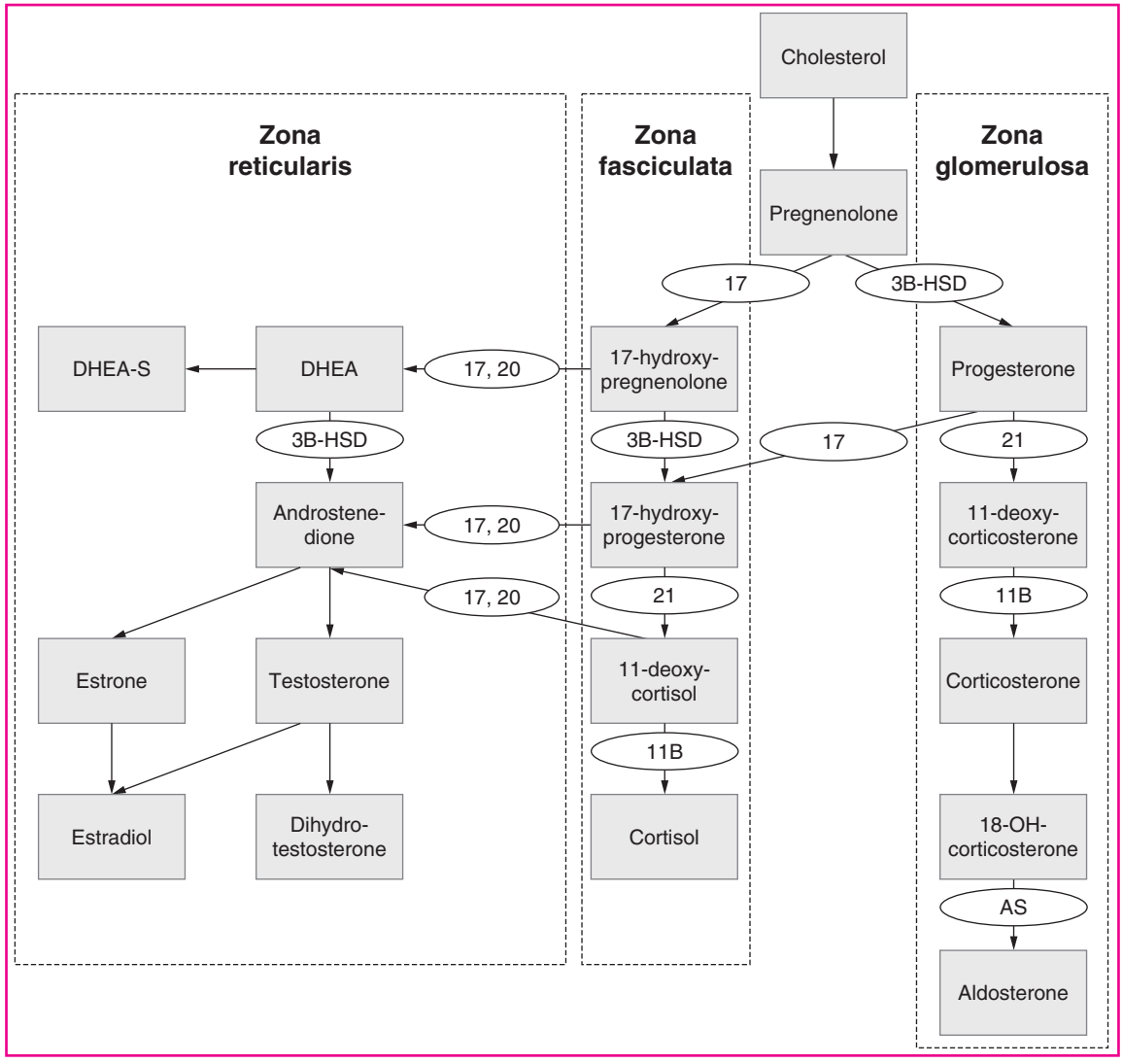


FIGURE 42–2. Adrenal steroid synthesis. The adrenal cortex consists of three histologically distinct zones: the zona glomerulosa, zona fasciculata, and an innermost layer called the zona reticularis. Each zone is responsible for production of different hormones. (17 = 17-hydroxylase; 3B-HSD = 3β-hydroxysteroid dehydrogenase; 21 = 21α-hydroxylase; 17,20 = 17,20-lyase; 11B = 11β-hydroxylase; AS = aldosterone synthase; DHEA = dehydroepiandrosterone; DHEA-S = sulfated form of dehydroepiandrosterone.)

The zona glomerulosa is responsible for the production of the mineralocorticoids **aldosterone,** deoxycorticosterone, and 18-hydroxy-deoxycorticosterone. Aldosterone promotes renal sodium retention and excretion of potassium. Its synthesis and release are regulated by renin in response to decreased vascular volume and renal perfusion. Adrenal aldosterone production is regulated by the **renin-angiotensin-aldosterone system.**

The zona fasciculata produces the glucocorticoid hormone **cortisol.** Cortisol is responsible for maintaining homeostasis of carbohydrate, protein, and fat metabolism. Its secretion follows a circadian rhythm, with the highest secretion occurring in the early-morning hours (peaking around 8 A.M.). Thereafter, cortisol levels decrease throughout the day, approach 50% of the peak value by 4 P.M., and reach their nadir around midnight.[1] The normal rate of cortisol production is approximately 8 to 15 mg/day.[2] Cortisol plays a key role in the body's response to stress. Its production increases markedly during physiologic stress, such as during acute illness, surgery, or trauma. In addition, certain conditions, such as alcoholism, depression, anxiety disorder, obsessive-compulsive disorder, poorly controlled diabetes, morbid obesity, starvation, anorexia nervosa, and chronic renal failure, are associated with increased cortisol levels. High total cortisol levels are also observed in the presence of increased cortisol-binding globulin (the carrier protein for 80% of circulating cortisol molecules), which is seen in pregnancy or other high-estrogen states (e.g., exogenous estrogen administration).[1] Cortisol is converted in the liver to an inactive metabolite known as cortisone.

The zona reticularis produces the androgens androstenedione, dehydroepiandrosterone (DHEA), and the sulfated form of dehydroepiandrosterone (DHEA-S). Only small amounts of testosterone and estrogen are produced in the adrenal glands. Androstenedione and DHEA are converted in the periphery, largely to testosterone and estrogen.

Adrenal hormone production is controlled by the hypothalamus and pituitary gland. **Corticotropin-releasing hormone** (CRH) is secreted by the hypothalamus and stimulates secretion of **adrenocorticotropic hormone** (ACTH), also known as *corticotropin* from the anterior pituitary. ACTH, in turn, stimulates the adrenal cortex to produce cortisol. When sufficient or excessive cortisol levels are reached, a negative feedback is exerted on the secretion of CRH and ACTH, thereby decreasing overall cortisol production. The control of adrenal androgen synthesis also follows a similar negative-feedback mechanism.

ADRENAL INSUFFICIENCY

Epidemiology and Etiology

Adrenal insufficiency generally refers to the inability of the adrenal glands to produce adequate amounts of cortisol for normal physiologic functioning or in times of stress. The condition is usually classified as primary, secondary, or tertiary depending on the etiology (Table 42–1). Chronic adrenal insufficiency is rare. The estimated prevalences of primary and secondary adrenal insufficiency are approximately 60 to 143 and 150 to 280 cases per 1 million persons, respectively. Primary adrenal insufficiency usually is diagnosed in the third to fifth decades of life, whereas secondary adrenal insufficiency is commonly detected during the sixth

TABLE 42–1. Etiologies of Adrenal Insufficiency[1,4–6,21,22]

Primary Adrenal Insufficiency (Addison's Disease)
- Autoimmune—accounts for 70%–90% of all cases of primary adrenal insufficiency
- Infectious or granulomatous diseases
  - Tuberculosis
  - Sarcoidosis
  - Cytomegalovirus
  - Fungal (histoplasmosis, coccidioidomycosis, cryptococcosis, *Blastomyces dermatitidis* infection)
  - Human immunodeficiency virus, AIDS
    - Mycobacterial, cytomegaloviral, and *Pneumocystis carinii* (*P. jiroveci*) infection
- Medications—inhibitors of steroidogenesis (aminoglutethimide, etomidate, ketoconazole, metyrapone, mitotane)
- Hemorrhagic
  Bilateral adrenal hemorrhage or infarction—usually due to anticoagulant therapy, coagulopathy, thromboembolic disease, or meningococcal infection. Causes acute adrenal insufficiency.
- Adrenalectomy
- Adrenoleukodystrophy (in males)
- Adrenomyeloneuropathy
- Infiltrative disorders—amyloidosis, hemochromatosis
- Genetic causes
  - Congenital adrenal hyperplasia
  - Familial glucocorticoid deficiency and hypoplasia
- Metastatic malignancy

Secondary Adrenal Insufficiency
- Drug-induced (most common cause of secondary adrenal insufficiency)
  - Chronic glucocorticoid administration at supraphysiologic doses
  - Megestrol acetate—has glucocorticoid-like activity
  - Mifepristone (RU 486)—antagonizes glucocorticoid receptors
- Post-cure of Cushing's syndrome

Panhypopituitarism
- Pituitary tumor
- Transsphenoidal pituitary microsurgery
- Pituitary irradiation
- Traumatic brain injury

Tertiary Adrenal Insufficiency
- Hypothalamic failure
- Drug-induced—chronic glucocorticoid administration at supraphysiologic doses

AIDS, acquired immunodeficiency syndrome
Partially adapted, with permission, from Aron DC, Findling JW, Tyrrell JB. Glucocorticoids and adrenal androgens. In: Greenspan FS, Gardner DG, (eds.) *Basic and Clinical Endocrinology*. New York: Lange Medical Books/McGraw-Hill; 2004: 362–413.

decade.[1,3] Adrenal insufficiency is more prevalent in women than in men with a ratio of 2.6:1.[1]

Pathophysiology

Primary adrenal insufficiency (also known as Addison's disease) occurs when the adrenal glands are unable to produce cortisol. It occurs from destruction of the adrenal cortex, usually from an autoimmune process. In general, the clinical manifestations are observed when destruction of the cortex exceeds 90%.[4] ❶ *Signs and symptoms of adrenal insufficiency reflect the disturbance of normal physiologic carbohydrate, fat, and protein homeostasis caused by inadequate cortisol production and inadequate cortisol action.* Primary adrenal insufficiency usually develops gradually. Patients may remain asymptomatic in the early stages, with signs and symptoms present only during times of physiologic stress. Persistent signs and symptoms of hypocortisolism typically occur with disease progression. Additionally, adrenal insufficiency may be accompanied by a reduction in aldosterone and androgen production.

Secondary adrenal insufficiency occurs as a result of a pituitary gland dysfunction whereby decreased production and secretion of ACTH leads to a decrease in cortisol synthesis. Tertiary adrenal insufficiency is a disorder of the hypothalamus that results in decreased production and release of CRH, which, in turn, decreases pituitary ACTH production and release. In contrast to Addison's disease (i.e., primary adrenal insufficiency), aldosterone production is unaffected in the secondary and tertiary forms of the disease. Chronic adrenal insufficiency often has a good prognosis if diagnosed early and treated appropriately.

Acute adrenal insufficiency (i.e., adrenal crisis) results from the body's inability to increase endogenous cortisol sufficiently during periods of excessive physiologic stress. Adrenal crisis can occur when patients with chronic adrenal insufficiency do not receive adequate glucocorticoid replacement during stressful conditions (such as those experienced during surgery, infection, acute illness, invasive medical procedures, or trauma). Acute adrenal insufficiency also can result from bilateral adrenal infarction owing to hemorrhage, embolus, sepsis, or adrenal vein thrombosis. Additionally, abrupt discontinuation or rapid tapering of glucocorticoids (given chronically in supraphysiologic doses) may lead to adrenal crisis. This condition results from prolonged suppression of the hypothalamic-pituitary-adrenal (HPA) axis and subsequent adrenal gland atrophy and hypocortisolemia. Other drugs associated with adrenal insufficiency include those that inhibit production (e.g., ketoconazole) or increase metabolism [e.g., the cytochrome P-450 subfamily IIIA polypeptide 4 (CYP450 3A4) inducer rifampin] of cortisol.[4] Regardless of etiology, patients experiencing an adrenal crisis require immediate glucocorticoid treatment because manifestations (such as circulatory collapse) can lead to life-threatening sequelae.



Clinical Presentation and Diagnosis of Chronic Adrenal Insufficiency[1,3,4,6]

General
- The symptoms, especially in the early stages, may be vague and mimic those of other medical conditions.
- The cardinal symptoms and signs are weakness and fatigue requiring rest periods, gastrointestinal symptoms, weight loss, and hypotension.
- Patients with autoimmune adrenal insufficiency may have other autoimmune disorders such as type 1 diabetes mellitus and autoimmune **thyroiditis.**

Symptoms
- Weakness and fatigue are the most common.
- Anorexia, nausea, and diarrhea (these may range from mild to severe with vomiting and abdominal pain).
- Hypoglycemia may occur in some patients.
- **Amenorrhea**
- Salt craving may occur in some patients with primary adrenal insufficiency.

Signs
- Weight loss
- Hypotension (less than 110/70 mm Hg) and **orthostasis**
- Dehydration, hypovolemia, and hyperkalemia (in primary adrenal insufficiency only)
- Decreased serum sodium and chloride levels
- Increased serum blood urea nitrogen (BUN) and creatinine owing to dehydration
- **Hyperpigmentation** of skin (usually around creases, pressure areas, areolas, genitalia, and new scars) and mucous membranes. Dark freckles and patches of vitiligo may be present. Hyperpigmentation, owing to increased ACTH levels, occurs in primary adrenal insufficiency.
- Personality changes (irritability and restlessness)
- Loss of axillary and pubic hair in women owing to decreased androgen production
- Blood count abnormalities (e.g., normocytic, normochromic anemia, relative lymphocytosis, neutrophilia, eosinophilia)

Laboratory Tests (Table 42–2)
- Decreased basal and stress-induced cortisol levels
- Decreased aldosterone level (in primary adrenal insufficiency only)
- Lack of increase in cortisol and aldosterone level after ACTH stimulation

Other Diagnostic Tests (Table 42–2)
- Computed tomography (CT) or magnetic resonance imaging (MRI) of the adrenal glands, pituitary, and/or hypothalamus can aid in determining the etiology.
- The presence of anti-adrenal antibodies is suggestive of an autoimmune etiology.

TABLE 42–2. Tests for Diagnosing Adrenal Insufficiency[4,6]

Test	Test Procedure and Measurement Rationale	Typical Finding in Adrenal Insufficiency	Comments
Screening Tests to Confirm Diagnosis of Adrenal Insufficiency			
Rapid ACTH stimulation test (also called **cosyntropin** stimulation test)	Measure serum cortisol 30–60 minutes after administering cosyntropin 1 mcg IV or 250 mcg IV[a] Increased cortisol secretion in normal individuals in response to ACTH stimulation but not in adrenal insufficiency	• Serum cortisol concentration less than 18 mcg/dL (497 nmol/L)	• False negative results occur if the ACTH deficiency is of recent onset. • To differentiate between primary and secondary or tertiary adrenal insufficiency, use same blood samples to measure plasma aldosterone level (see below).
Unstimulated serum cortisol measurement	Measure serum cortisol at 6–8 A.M. Serum cortisol level peaks in the early morning.	• Serum cortisol greater than 18 mcg/dL (497 nmol/L) is normal • Serum cortisol less than 3 mcg/dL (83 nmol/L) is indicative of adrenal insufficiency	
Insulin tolerance test (insulin-induced hypoglycemia test)	Administer insulin IV to induce hypoglycemia; then measure serum cortisol during symptomatic hypoglycemia [confirm that blood glucose is less than 40 mg/dL (2.22 mmol/L)]. Evaluates ability of entire HPA axis to respond to stress (hypoglycemia)	• Serum cortisol concentration less than 18 mcg/dL (497 nmol/L) is indicative of secondary adrenal insufficiency	• Distinguishes between normal individuals and patients with secondary adrenal insufficiency • Contraindicated in patients with a seizure history, older than 60 years, or with cardiovascular or cerebrovascular disease • Requires close medical supervision • Contraindicated in adrenal crisis
Overnight metyrapone test (rarely used)	Administer metyrapone at midnight then measure serum cortisol at 8 A.M. the next day. Metyrapone inhibits cortisol synthesis. Its administration leads to rise in levels of ACTH and the precursor of cortisol. Patients with adrenal insufficiency do not exhibit this.	• Normal response is a decrease in serum cortisol to less than 5 mcg/dL (138 nmol/L) and an increase in the cortisol precursor to more than 7 mcg/dL (193 nmol/L). Response not seen in secondary adrenal insufficiency.	• Distinguishes between normal individuals and patients with secondary adrenal insufficiency • Contraindicated in adrenal crisis

Tests to Determine Diagnosis of Primary, Secondary, and Tertiary Adrenal Insufficiency		
Test	**Test Procedure and Measurement**	**Rationale to Distinguish Between Etiologies**
Plasma aldosterone concentration	Measure plasma aldosterone from same blood samples as those used in ACTH stimulation test.	• Primary adrenal insufficiency: low plasma aldosterone level. • Secondary or tertiary adrenal insufficiency: aldosterone level is normal [greater than or equal to 5 ng/dL (139 pmol/L)]
Plasma ACTH concentration	Measure plasma ACTH	• Primary adrenal insufficiency: hypocortisolism leads to elevated plasma ACTH (via positive HPA axis feedback). • Secondary or tertiary adrenal insufficiency: plasma ACTH low or inappropriately normal.

ACTH, adrenocorticotropic hormone or corticotropin; FDA, Food and Drug Administration; HPA, hypothalamic-pituitary-adrenal; IV, intravenously.
[a]The 250 mcg dose has also been administered intramuscularly in an outpatient setting. The 1 mcg dose is not FDA-approved.

TABLE 42–3. Pharmacologic Characteristics of Commonly Used Glucocorticoids[4]

Glucocorticoid	Estimated Potency Relative to Hydrocortisone: Glucocorticoid (Anti-Inflammatory) Activity	Mineralocorticoid (Sodium-Retaining) Activity	Equivalent Dose Expressed in Milligrams
Short-Acting (Half-Life Less than 12 Hours)			
Hydrocortisone	1	1	20
Cortisone	0.8	0.8	25
Intermediate-Acting (Half-Life 12–36 Hours)			
Prednisone	4	0.25	5
Prednisolone	4	0.25	5
Methylprednisolone	5	Less than 0.01	4
Triamcinolone	5	Less than 0.01	4
Long-Acting (Half-Life Greater than 48 Hours)			
Betamethasone	25	Less than 0.01	0.6–0.75
Dexamethasone	30–40	Less than 0.01	0.75

Modified, with permission, from Williams GH, Dluhy RG. Disorders of the adrenal cortex. In: Kasper DL, Braunwald E, Fauci A, et al, (eds.) *Harrison's Principles of Internal Medicine*. New York: McGraw-Hill; 2005: 2127–2148.

Treatment and Outcome Evaluation

Chronic Adrenal Insufficiency

The general goals of treatment are to manage symptoms and prevent development of adrenal crisis. ❷*Lifelong glucocorticoid replacement therapy may be necessary for patients with adrenal insufficiency, and mineralocorticoid replacement therapy usually is required for those with Addison's disease.* Glucocorticoids with sufficient mineralocorticoid activity generally are required. However, the addition of a potent mineralocorticoid such as fludrocortisone (along with adequate salt intake) sometimes is needed to prevent sodium loss, hyperkalemia, and intravascular volume depletion. Mineralocorticoid supplementation typically is not indicated for the treatment of secondary or tertiary adrenal insufficiency because aldosterone production often is unaffected. Moreover, patients with secondary or tertiary adrenal insufficiency may require only replacement therapy until the HPA axis recovers. Hydrocortisone often is prescribed because it most closely resembles endogenous cortisol (with its relatively high mineralocorticoid activity and short half-life) and allows the design of regimens that simulate the normal circadian cycle.[6] Other glucocorticoids, however, can be used. The pharmacologic characteristics of commonly used glucocorticoids are presented in Table 42–3. Since patients with primary adrenal insufficiency can experience DHEA deficiency, DHEA replacement also has been tried. Several small clinical studies, consisting mostly of women, suggest that treatment with DHEA can improve mood and fatigue and provide a general sense of well-being.[7–9] Nonetheless, use of DHEA remains controversial and requires further study. Table 42–4 lists the treatment guidelines and monitoring parameters for chronic adrenal insufficiency.



Patient Encounter 1, Part 1: Presentation and Medical History

AB is a 60-year-old woman presenting to the clinic with a chief complaint of fatigue and weakness. She has noticed a gradual increase in symptoms over the past year but attributed this to "old age." Recently, she has required more frequent rest breaks than before. On further questioning, she complained of intermittent nausea leading to decreased appetite and a 10 lb (4.55 kg) weight loss over the past year. She also reported darkening of a recent scar.

PMH
- Type 1 diabetes mellitus since age 5, currently controlled
- Hypothyroidism, currently controlled
- Osteoarthritis (knees) for 5 years

FH
Unknown

SH
Retired secretary; denies smoking, alcohol use, or illicit drug use

Current meds
- Insulin glargine 30 units at bedtime
- Lispro insulin three times daily with meals—practices carbohydrate counting
- Levothyroxine 75 mcg once daily
- Acetaminophen 1000 mg every 8 hours as needed for joint pain
- Capsaicin 0.075% cream three times a day for joint pain

(*Continued*)

PE

VS: Sitting BP: 108/70 mm Hg; P: 74 beats/minute; standing BP: 96/68 mm Hg; P: 86; RR: 14 breaths/minute; weight: 150 lb (68.18 kg); height: 5 ft, 5 in (165.1 cm)
Skin: Hyperpigmentation on creases of palms and around nipples, darkening of scar on left leg
CV: RRR, normal S_1, S_2; no murmurs, rubs, or gallops

Labs

Serum electrolytes: sodium 132 mEq/L (132 mmol/L), potassium 5.2 mEq/L (5.2 mmol/L), chloride 98 mEq/L (98 mmol/L), bicarbonate 30 mEq/L (30 mmol/L), blood urea nitrogen (BUN) 25 mg/dL (8.9 mmol/L), creatinine 1.3 mg/dL (115 µmol/L), glucose 120 mg/dL (6.66 mmol/L)

- Which signs or symptoms of adrenal insufficiency does AB exhibit?
- Does AB's presentation offer any clues as to the etiology or classification of adrenal insufficiency?
- Which tests would be most useful for determining the etiology and confirming the diagnosis of adrenal insufficiency?



Clinical Presentation and Diagnosis of Acute Adrenal Insufficiency (Adrenal Crisis)[1,3,4]

General

Onset of symptoms is acute and precipitated by excessive physiologic stress.

Symptoms

- Severe weakness and fatigue
- Abdominal or flank pain

Signs

- Severe dehydration leading to hypotension and shock (circulatory collapse). Hypovolemia may not be responsive to intravenous hydration and may require the use of vasopressors.
- Tachycardia
- Nausea, vomiting
- Fever
- Confusion
- Hypoglycemia
- Laboratory abnormalities are similar to those observed in chronic adrenal insufficiency.

Laboratory Tests

The unstimulated serum cortisol and rapid ACTH stimulation tests are useful in the diagnosis of adrenal crisis (Table 42–2). The insulin tolerance test is contraindicated owing to preexisting hypoglycemia. The metyrapone test is also contraindicated because metyrapone inhibits cortisol production.
Note: Given the life-threatening nature of this condition, empirical treatment should be started before laboratory confirmation in patients who present with the clinical picture of an acute adrenal crisis.

TABLE 42–4. Management Strategies for Chronic Adrenal Insufficiency[1,3,6]

Primary Adrenal Insufficiency (Addison's Disease)

- Give oral hydrocortisone 12–15 mg/m^2 divided into two doses, with two-thirds of the dose given in the morning upon awakening (to mimic the early-morning rise in endogenous cortisol) and the remaining one-third of the dose given in the late afternoon (to avoid insomnia).
  - Monitor weight, blood pressure, and serum electrolytes and assess resolution of clinical features and patient's feeling of general well-being. Adjust dosages accordingly.
  - Monitor for adverse reactions from hydrocortisone administration. Glucocorticoid therapy at physiologic replacement doses should not lead to the development of Cushing's syndrome. However, careful monitoring should still be performed. Use the smallest effective dose.
  - Doses of hydrocortisone may need to be increased or decreased in patients taking CYP450 3A4 inducers (e.g., phenytoin, rifampin, barbiturates) or inhibitors (e.g., protease inhibitors), respectively.
  - Educate patients regarding need for increased hydrocortisone dosage during excessive physiologic stress.
- Give oral fludrocortisone at a daily dose of approximately 0.05–0.2 mg in the morning.
  - Monitor for resolution of hypotension, dizziness, dehydration, hyponatremia, and hyperkalemia. Increase the dose as clinically necessary.
  - Monitor for adverse reactions from mineralocorticoid administration (e.g., hypertension, hypokalemia, fluid retention) and decrease the dose if these occur. Remember that hydrocortisone also possesses mineralocorticoid activity.
  - Maintain an adequate sodium intake (about 3–4 g/day).
- Although controversial, consider giving DHEA 50 mg/day (in the morning) to female patients who do not experience an improvement in mood and well-being even with adequate glucocorticoid and mineralocorticoid replacement.
  - Monitor serum DHEA-S (aim for the middle range of normal levels in healthy young people) and free testosterone level.

Secondary and Tertiary Adrenal Insufficiency

- Give 2–15 mg/m^2 of oral hydrocortisone as described above. Patients may require a lower dose of glucocorticoid than those with primary adrenal insufficiency. Some patients will only require glucocorticoid replacement temporarily, which can be discontinued after recovery of the HPA axis (e.g., drug-induced adrenal insufficiency, adrenal insufficiency following treatment for Cushing's syndrome).
- Fludrocortisone therapy is generally not needed.
- Monitor for progression of the underlying etiology.

CYP450 3A4, cytochrome P-450 subfamily IIIA polypeptide 4; DHEA, dehydroepiandrosterone; DHEA-S, the sulfated form of dehydroepiandrosterone; HPA, hypothalamic-pituitary-adrenal.



Patient Encounter 1, Part 2: Treatment

After appropriate laboratory and diagnostic tests are performed, AB is diagnosed with Addison's disease.

- How should her chronic adrenal insufficiency be treated?
- What monitoring parameters (therapeutic and toxic) should be implemented?



Adrenal Insufficiency: Patient Care and Monitoring

1. Evaluate patients presenting with the typical clinical manifestations for chronic or acute adrenal insufficiency.
2. Perform initial screening tests to confirm the presence of adrenal insufficiency.
3. Once diagnosis is confirmed, perform further testing to differentiate between primary, secondary, and tertiary adrenal insufficiency.
4. In patients presenting with acute adrenal crisis who have not been diagnosed previously with adrenal insufficiency, immediate treatment with injectable hydrocortisone and intravenous saline and dextrose solutions should be initiated prior to confirmation of the diagnosis because of the life-threatening nature of this condition. Determine and correct the underlying cause of the acute adrenal crisis (e.g., infection).
5. Glucocorticoid replacement therapy is necessary for patients with adrenal insufficiency, and mineralocorticoid replacement therapy is required for those with Addison's disease.
6. In patients with chronic adrenal insufficiency, when excessive physiologic stress is anticipated (e.g., pending surgery), devise a strategy to give supplemental doses of glucocorticoid during this period. Monitor the patient for signs of an acute adrenal crisis, and develop a plan to treat this emergency condition.
7. Monitor the patient for adequacy of treatment, as well as adverse reactions from glucocorticoid and/or mineralocorticoid therapy.
8. Determine the duration of treatment for patients with secondary and tertiary adrenal insufficiency.
9. Provide patient education regarding disease state and treatment:
   - Causes of adrenal insufficiency, including drug-induced etiologies.
   - How to recognize the clinical manifestations.
   - How to prevent an acute adrenal crisis (adhere to therapy, and do not stop glucocorticoid treatment abruptly). There may be a need to increase the dose of glucocorticoid during excessive physiologic stress.
   - Administration of parenteral glucocorticoid during an acute adrenal crisis.
   - Need to notify all health care providers of the condition.
   - Encourage wearing or carrying medical alert identification (e.g., bracelet or card).
   - Counsel on dietary and pharmacologic therapy, including duration of treatment and potential adverse consequences of glucocorticoid and mineralocorticoid replacement.

Acute Adrenal Insufficiency

❸*During an acute adrenal crisis, the immediate treatment goals are to correct volume depletion, manage hypoglycemia, and provide glucocorticoid replacement* (Table 42–5). In patients with known adrenal insufficiency, additional glucocorticoid replacement (higher dose and parenteral route) must be given prior to major surgery to prevent adrenal crisis (Table 42–6 lists a sample protocol). ❹*Patients who experience excessive stress should be educated regarding the need for additional glucocorticoid replacement and prompt medical attention*. Although the dosage of glucocorticoid generally is individualized, a common recommendation is to double the maintenance dose of hydrocortisone if the patient experiences fever or undergoes invasive dental or diagnostic procedures.[6] Patients who experience vomiting or diarrhea may not absorb oral glucocorticoids adequately and may benefit from parenteral therapy until symptoms resolve.

TABLE 42–5. Treatment of Acute Adrenal Crisis

General and Supportive Measures
1. Promptly correct volume depletion, dehydration, and hypoglycemia with large volumes of intravenous normal saline and 5% dextrose (about 2–3 L).
2. Evaluate and correct infection or other precipitating factors.

Glucocorticoid Replacement
1. Administer hydrocortisone sodium phosphate or hydrocortisone sodium succinate, 100 mg intravenously every 6 to 8 hours for 24 hours.
2. If the patient is hemodynamically stable, reduce the dosage to 50 mg every 6 to 8 hours.
3. Increase the dose of hydrocortisone to 200–400 mg/day if complications occur or persist.
4. Taper hydrocortisone to maintenance therapy by day 4 or 5 and add fludrocortisone as needed.

Adapted, with permission, from Aron DC, Findling JW, Tyrrell JB. Glucocorticoids and adrenal androgens. In: Greenspan FS, Gardner DG, (eds.) *Basic and Clinical Endocrinology*. New York: Lange Medical Books/McGraw-Hill; 2004: 362–413.

TABLE 42–6. Glucocorticoid Treatment of Adrenal Insufficiency in Patients Undergoing Surgery

1. Correct electrolytes, blood pressure, and fluid status as necessary.
2. Give 100 mg of hydrocortisone sodium phosphate or hydrocortisone sodium succinate intramuscularly (provide "on call" to the operating room).
3. Give 50 mg of hydrocortisone intramuscularly or intravenously in the recovery room and then every 6 hours for the first 24 hours.
4. If patient is hemodynamically stable, reduce dosage to 25 mg every 6 hours for 24 hours and then taper to maintenance dosage over 3–5 days.
5. Resume previous fludrocortisone dose when the patient is taking oral medications.
6. Maintain or increase hydrocortisone dosage to 200–400 mg/day if fever, hypotension, or other complications occur.

Adapted, with permission, from Aron DC, Findling JW, Tyrrell JB. Glucocorticoids and adrenal androgens. In: Greenspan FS, Gardner DG, (eds.) *Basic and Clinical Endocrinology*. New York: Lange Medical Books/McGraw-Hill, 2004:362–413. Originally from Miller WL, Tyrrell JB, in: *Endocrinology and Metabolism*. Felig P, Baxter JD, Frohman LA, (eds.) New York: McGraw-Hill, 1995:555–711.

HYPERCORTISOLISM (CUSHING'S SYNDROME)

Epidemiology and Etiology

Cushing's syndrome refers to the pathophysiologic changes associated with exposure to supraphysiologic cortisol concentrations (endogenous hypercortisolism) or pharmacologic doses of glucocorticoids (exogenous hypercortisolism). Cushing's syndrome from endogenous causes is a rare condition, with an estimated incidence of 2 to 5 cases per 1 million persons per year.[10] Patients receiving chronic supraphysiologic doses of glucocorticoids, such as those with rheumatologic disorders, are at high risk of developing Cushing's syndrome.

Pathophysiology

Cushing's syndrome can be classified as ACTH-dependent or ACTH-independent (Table 42–7). ACTH-dependent Cushing's syndrome results from ACTH-secreting (or rarely, CRH-secreting) **adenomas.** ACTH-independent Cushing's syndrome is due either to excessive cortisol secretion by the adrenal glands (independent of ACTH stimulation) or to exogenous glucocorticoid administration. ❺*Patients with Cushing's syndrome owing to endogenous or exogenous glucocorticoid excess typically present with similar clinical manifestations.* The term *Cushing's disease* refers specifically to Cushing's syndrome from an ACTH-secreting pituitary adenoma. The plasma ACTH concentration is elevated in ACTH-dependent conditions but not in ACTH-independent cases because elevated cortisol concentrations suppress pituitary ACTH secretion via negative feedback. Adrenocorticotropic hormone and cortisol concentrations are elevated episodically in ACTH-dependent disease due to random hypersecretion of ACTH.[4] Other major differences among the vast etiologies of Cushing's syndrome are shown in Table 42–8.

Physiologic cortisol secretion follows a circadian pattern, with cortisol levels rising in the early morning, peaking at approximately 8 A.M., and then declining steadily throughout the remainder of the day until they reach a nadir at midnight. This circadian rhythm is lost in most patients with Cushing's syndrome. As such, detection of elevated midnight cortisol concentrations can be useful in the diagnosis of Cushing's syndrome.

Cushing's disease and adrenal **carcinomas** cause adrenal androgen hypersecretion in high enough concentrations to result in signs of androgen excess (such as acne, menstrual irregularities, and **hirsutism**) and cause **virilization** in women.[4]

Drug-induced Cushing's syndrome from glucocorticoid administration occurs most commonly in patients receiving oral therapy, but other routes (e.g., inhalation, dermal, nasal, and intra-articular) also have been implicated.[11] Over-the-counter products, including non-prescription medications and herbal products, also should be evaluated because they may contain corticosteroids or agents that possess glucocorticoid-like activity. The risk of glucocorticoid-induced Cushing's syndrome appears to increase with higher doses and/or longer treatment durations.[11]

Left untreated, patients with Cushing's syndrome may experience severe complications of hypercortisolism, resulting in up to a nearly four-fold increase in mortality.[14] Mortality in patients with Cushing's syndrome is mostly attributed to cardiovascular disease. Hypertension, hyperglycemia, and hyperlipidemia are common findings and can be associated with cardiac hypertrophy, atherosclerosis, and hypercoagulability. Osteopenia, osteoporosis, and increased fractures also have been reported.[14] Children may experience linear growth retardation from reduced growth hormone secretion and inhibition of epiphyseal cartilage development in long bones.[10,14]

TABLE 42–7. Etiologies of Cushing's Syndrome[1,11–13]

ACTH-Dependent
- ACTH-secreting pituitary tumor (Cushing's *disease*)—70% of cases of endogenous Cushing's syndrome
- ACTH-secreting non-pituitary tumors (ectopic ACTH syndrome)—15% of cases of endogenous Cushing's syndrome; usually from small cell lung carcinoma, bronchial carcinoids, pheochromocytoma, or thymus, pancreatic, ovarian, or thyroid tumor. The tumor is usually disseminated (difficult to localize).
- CRH-secreting non-pituitary tumors (ectopic CRH syndrome)—rare

ACTH-Independent—15% of cases of endogenous Cushing's syndrome
- Unilateral adrenal adenoma
- Adrenal carcinoma
- Bilateral nodular adrenal hyperplasia—rare (less than 1%)

Drug-Induced Cushing's Syndrome (ACTH-independent)—most common cause of Cushing's syndrome
- Prescription glucocorticoid preparations (most routes of administration)
- Non-prescription and herbal products with glucocorticoid activity (e.g., non-prescription anti-itch products with hydrocortisone, herbal products with magnolia bark or those claiming to contain adrenal cortex extracts or other by-products)
- Other drugs with glucocorticoid activity (e.g., megestrol acetate, medroxyprogesterone)

ACTH, adrenocorticotropic hormone or corticotropin; CRH, corticotropin-releasing hormone.

Treatment

The goal of treatment in patients with Cushing's syndrome is reversal of hypercortisolism and management of the associated comorbidities, including the potential for long-term sequelae such as cardiac hypertrophy. ❻*Surgical resection is considered the treatment of choice for Cushing's syndrome from endogenous causes if the tumor can be localized and if there are no contraindications.* The treatment of choice for Cushing's syndrome from exogenous causes is gradual discontinuation of the offending agent.



Clinical Presentation and Diagnosis of Cushing's Syndrome[1,10,11]

General

- Patients with Cushing's syndrome due to either endogenous or exogenous glucocorticoid excess typically present with similar clinical manifestations.
- Differential diagnoses include diabetes mellitus and metabolic syndrome because patients with these conditions share several similar characteristics with Cushing's syndrome patients (e.g., obesity, hypertension, hyperlipidemia, hyperglycemia, and insulin resistance). In women, the presentations of hirsutism, menstrual abnormalities, and insulin resistance are similar to those of polycystic ovary syndrome. Cushing's syndrome can be differentiated from these conditions by identifying the classic signs and symptoms of truncal obesity, "moon faces" with facial plethora, a "buffalo hump" and supraclavicular fat pads, red-purple skin striae, and proximal muscle weakness.
- True Cushing's syndrome also must be distinguished from other conditions that share some clinical presentations (as well as elevated plasma cortisol concentrations), such as depression, alcoholism, obesity, and chronic illness—the so-called pseudo-Cushing's states.

Signs and Symptoms (Percent Prevalence)

General appearance

- Weight gain and obesity, manifesting as truncal obesity (90%)
- A rounded and puffy face ("moon face") (75%)
- Dorsocervical ("buffalo hump") and supraclavicular fat accumulation
- Hirsutism (excessive hair growth) (75%)

Skin changes (from atrophy of dermis and connective tissue)

- Thin skin
- Facial plethora (70%)
- Skin striae ("stretch marks" that are usually red or purple in appearance and greater than 1 cm) (50%)
- Acne (35%)
- Easy bruising (40%)
- Hyperpigmentation

Metabolic

- Hyperglycemia that can range from impaired glucose tolerance (75%) to diabetes mellitus (20% to 50%)
- Hyperlipidemia (70%)
- Polyuria (30%)
- Kidney stones (15% to 50%)
- Hypokalemic alkalosis (from mineralocorticoid effect of cortisol)

Cardiovascular

- Hypertension (from mineralocorticoid effect of cortisol) (85%)
- Patients are at risk for the cardiovascular complications of hypertension, hyperlipidemia, and hyperglycemia.
- Peripheral edema

Genitourinary

- Menstrual irregularities (the most typical presentation is amenorrhea) (70%)
- Erectile dysfunction (85%)

Other

- Psychiatric changes such as depression, emotional lability, psychosis, euphoria, anxiety, and decreased cognition (85%)
- Sleep disturbances
- Osteopenia (80%) and osteoporosis, usually affecting trabecular bone
- Linear growth impairment in children
- Proximal muscle weakness (65%)
- Avascular necrosis (more common in iatrogenic cases)
- Glaucoma and cataracts
- Impaired wound healing and susceptibility to opportunistic infections
- Hypothyroidism

Laboratory Tests

- The diagnosis of Cushing's syndrome and its etiology often are complex and generally require the involvement of endocrinologists and specialized testing centers.
- Initial screening tests to confirm the presence of hypercortisolism and differentiate Cushing's syndrome from conditions with similar presentations include 24-hour urinary free cortisol determination and overnight low-dose dexamethasone suppression test (DST) (Table 42–9).
- The midnight plasma cortisol determination and combined dexamethasone suppression plus CRH test are used less commonly.
- Typically, a combination of at least two screening tests is used to establish the preliminary diagnosis.
- Once the diagnosis is confirmed, additional tests can be performed to determine the etiology.

Other Diagnostic Tests

Imaging studies may be used to distinguish between pituitary, ectopic, and adrenal tumors (Table 42–8).

Nonpharmacologic Therapy

Transsphenoidal pituitary microsurgery is the treatment of choice for Cushing's disease. Removal of the pituitary tumor can bring about complete remission (cure) in 78% to 97% of cases. HPA axis suppression associated with chronic hypercortisolism can result in prolonged adrenal insufficiency lasting for months after surgery and requiring exogenous glucocorticoid administration. Pituitary irradiation or bilateral **adrenalectomy** usually is reserved for patients who are not surgical candidates or for those who relapse or do not achieve complete remission following pituitary surgery. Because the response to pituitary irradiation can be delayed (several months to years), concomitant treatment with cortisol-lowering medication may be necessary. Bilateral adrenalectomy is also used for the management of adrenal carcinoma and in patients with poorly controlled ectopic Cushing's in whom the ACTH-producing lesion cannot

TABLE 42–8. Differences among the Major Etiologies of Cushing's Syndrome[4,9,14,23]

	ACTH-Dependent		ACTH-Independent		
	Pituitary Dependent (Cushing's Disease)	Ectopic ACTH Syndrome	Exogenous Glucocorticoid Administration	Adrenal Adenoma	Adrenal Carcinoma
Onset of signs and symptoms	Gradual	Rapid	Gradual to rapid	Gradual	Rapid
Symptoms severity	Mild to moderate	Atypical	Mild to severe	Mild to moderate	Severe
Dominant sex/age	Female; 20–40 years (range: childhood to 70 years)	Male; adults	Female and male; all ages	Female	Female; children
Virilization	+	+	+	+	+++
Abdominal mass	0	0	0	0	++
Plasma ACTH concentration	Slightly elevated	Elevated	Low	Low	Low
CRH stimulation test	Response	Rare response	Decreased or no response	No response	No response
High-dose dexamethasone suppression test	Between 50% and 80% cortisol suppression	Less cortisol suppression	No cortisol suppression	No cortisol suppression	No cortisol suppression
Pituitary MRI	Tumor	Normal	Normal	Normal	Normal
Adrenal gland CT or MRI	Normal or bilateral hyperplasia	Normal or bilateral hyperplasia	No change	Mass(es)	Mass(es)

ACTH, adrenocorticotropic hormone or corticotropin; CRH, corticotropin-releasing hormone; CT, computed tomography; MRI, magnetic resonance imaging; 0, none; +, mild; ++, moderate; +++, pronounced.
Adapted in part, with permission, from Gums JG, Tovar JM. Adrenal gland disorders. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1391–1406.

be localized. Bilateral laparoscopic adrenalectomy achieves an immediate and total remission (nearly 100% cure rate), but these patients will require lifelong glucocorticoid and mineralocorticoid supplementation.[15,16] **Nelson's syndrome** may develop in nearly 20% to 50% of patients who undergo bilateral adrenalectomy without pituitary irradiation. This condition presumably results from persistent hypersecretion of ACTH by the intact pituitary adenoma, which continues to grow because of the loss of feedback inhibition by cortisol. Treatment of Nelson's syndrome may involve pituitary irradiation or surgery.[4]

The treatment of choice in patients with adrenal adenomas is unilateral laparoscopic adrenalectomy. These patients require glucocorticoid supplementation during and after surgery owing to atrophy of the contralateral adrenal gland and suppression of the HPA axis. Glucocorticoid therapy is continued until recovery of the remaining adrenal gland is achieved. Patients with adrenal carcinomas have a poor prognosis (5-year survival of 20% to 58%) due to the advanced nature of the condition (metastatic disease). Surgical resection to reduce tumor burden and size, pharmacologic therapy, and bilateral laparoscopic adrenalectomy are the treatment options used commonly to manage this condition.[1,16]

Pharmacologic Therapy

❼ *Pharmacotherapy generally is reserved for patients: (1) in whom the ectopic ACTH-secreting tumor cannot be localized; (2) who are not surgical candidates; (3) who have failed surgery; (4) who have had a relapse after surgery; or (5) in whom adjunctive therapy is required to achieve complete remission.*[17] The drugs used are classified according to their mechanism and site of action (Table 42–10). The most widely used therapeutic class is the adrenal steroidogenesis inhibitors.[17] Agents in this class include ketoconazole, mitotane, metyrapone, and aminoglutethimide. Steroidogenesis inhibitors can improve hypercortisolism by inhibiting enzymes involved in the biosynthesis of cortisol. Because of their potential to cause adrenal suppression, temporary glucocorticoid replacement (and, in some cases, mineralocorticoid supplementation) may be needed during and after treatment.

❽ *In drug-induced Cushing's syndrome, discontinuation of the offending agent is the best management option. However, abrupt withdrawal of the glucocorticoid can result in adrenal insufficiency or exacerbation of the underlying disease.*[11]

❾ *Glucocorticoid doses less than 7.5 mg/day of prednisone (or its equivalent) for fewer than 3 weeks generally would not be expected to lead to suppression of the HPA axis.*[2,5] However, in patients receiving pharmacologic doses of glucocorticoids for prolonged periods, gradual tapering to near-physiologic levels (5–7.5 mg/day of prednisone or its equivalent) should precede drug discontinuation. Administration of a short-acting glucocorticoid in the morning and use of alternate-day dosing may reduce the risk of

TABLE 42–9. First-Line Screening Tests in Patients with Characteristics of Cushing's Syndrome[1,10,14]

Test	Test Procedure and Measurement Rationale	Typical Finding in Cushing's Syndrome	Comments
24-Hour urinary free cortisol	Collect urine over 24 hours and measure unbound cortisol that is excreted by kidneys Urinary cortisol is elevated in hypercortisolic states	Urinary free cortisol greater than 4 times the upper reference limit is indicative of Cushing's syndrome. Values between 1 and 4 times the upper reference limit suggest either Cushing's syndrome or pseudo-Cushing's syndrome	• Easy to perform but should not be used alone because sensitivity and specificity depend on the assay used. • To exclude periodic hypercortisolism, three or more samples should be obtained (with urinary creatinine measurement to assess completeness of the collection). • Distinguishes Cushing's syndrome from obesity (no elevation). However, false-positive if other pseudo-Cushing's states, physiologic stress, or pregnancy. • False-negative if decreased renal function or subclinical hypercortisolism.
Overnight low-dose dexamethasone suppression test (DST)	Give 1 mg oral dexamethasone at 11 P.M., then measure plasma cortisol at 8–9 A.M. the next morning Dexamethasone administration suppresses morning plasma cortisol in normal individuals	Plasma cortisol greater than 14.3 mcg/dL (395 nmol/L) is diagnostic for Cushing's syndrome. Plasma cortisol less than 1.2 mcg/dL (33 nmol/L) is not suggestive of Cushing's syndrome	• Simple to perform and inexpensive. • Can be used in conjunction with or instead of the urinary free cortisol test. • Can also use the two-day 2 mg DST. • False-positive if pseudo-Cushing's states, physiologic stress, pregnancy, estrogen treatment, uremia, taking inducers of dexamethasone metabolism (phenytoin, etc.), or decreased dexamethasone absorption. • False-negative if subclinical hypercortisolism or slow metabolism of dexamethasone.
Late-night salivary cortisol	Collect salivary cortisol concentration at 11 P.M. Loss of circadian rhythm of cortisol secretion (no nadir at night) in Cushing's syndrome but not in pseudo-Cushing's states	Elevated late-night salivary cortisol	• Diagnostic criteria need further validation. • Easiest screening test to perform (sample can be collected at home by patient). • Can be used in conjunction with, or instead of, the urinary free cortisol test.

DST, dexamethasone suppression test.



Patient Encounter 2

EF is a 45-year-old woman who presents to the dermatologist for evaluation of facial acne. She has a history of a 25 lb (11.36 kg) weight gain, irregular menses, and frequent vaginal yeast infections over the past 2 years. She complains of increased facial hair growth and lower extremity muscle weakness. Physical examination reveals facial acne, facial hirsutism, truncal obesity, thin skin, and purple abdominal striae. Her past medical history is significant for hypertension, type 2 diabetes mellitus, hyperlipidemia, and rheumatoid arthritis.

- Which findings are suggestive of Cushing's syndrome?
- Is there anything in EF's history that would suggest an exogenous cause of her presumed Cushing's syndrome?

adrenal suppression. Testing of the HPA axis may be useful in assessing adrenal reserve. In some cases, supplemental glucocorticoid administration during excessive physiologic stress may be needed for up to 1 year after glucocorticoid discontinuation.[11] Table 42–11 lists strategies to prevent the development of hypercortisolism and hypocortisolism.

Outcome Evaluation

- Monitor patients receiving surgical, medical, or radiation therapy for resolution of the clinical manifestations of hypercortisolism. Symptoms often improve immediately after surgery and soon after initiation of drug therapy. However, it may take months for symptoms to resolve following radiation therapy.
- Monitor for normalization of serum cortisol concentrations.
- The Patient Care and Monitoring text box (page 699) discusses additional evaluation strategies.

TABLE 42–10. Pharmacologic Treatments for Cushing's Syndrome[17–20]

Drug	Mechanism of Action	Dosage: Initial, Usual, Maximum	Common and/or Major Adverse Reactions	Comment
Inhibitors of Adrenal Steroidogenesis				
Aminoglutethimide (oral administration)	Inhibits conversion of cholesterol to pregnenolone, 11β-hydroxylase, 18-hydroxylase, and conversion of androstenedione to estrone.	250 mg every 6 hours Increase by 250 mg per day every 1–2 weeks 2 g/day	High incidence of adverse reactions: lethargy, somnolence, dizziness, ataxia, rash, nausea, headache. Tolerance to adverse reactions develops with continued use. Hematologic disturbances and hypothyroidism also seen.	• Used in ACTH-independent cases and ectopic ACTH syndrome. • Less effective as monotherapy due to reflex rise in ACTH but can be combined with metyrapone or with pituitary radiation. • Glucocorticoid and mineralocorticoid replacements needed. • High potential for drug interactions due to potent induction of hepatic enzymes.
Ketoconazole (oral administration)	Inhibits several cytochrome P-450 enzymes, including 17,20-lyase, 17-hydroxylase, and 11β-hydroxylase. Also inhibits cholesterol synthesis.	200 mg twice daily 600–800 mg/day in two divided doses 1200 mg/day in two divided doses	Generally well tolerated. Transaminase elevations, GI intolerance, and rash. Gynecomastia, testicular function impairment, and adrenal insufficiency at high doses (more than 600 mg/day).	• Effective in a majority of causes; rapid clinical improvement seen. • May be used with aminoglutethimide if inadequate efficacy as monotherapy. • Monitor efficacy with urinary cortisol. • Monitor liver transaminases for hepatotoxicity. • Useful in women with hirsutism and patients with hyperlipidemia.
Metyrapone (oral administration)	Inhibits 11-hydroxylase. Also suppresses aldosterone synthesis.	750 mg/day 500–4000 mg/day in four divided doses 6 g/day	Generally well tolerated. Hirsutism, acne, adrenal insufficiency, GI intolerance, rash, hypokalemia, edema, hypertension.	• Used in Cushing's disease, ectopic ACTH syndrome, and adrenal carcinoma. • Allows lower doses of aminoglutethimide if used in combination.
Etomidate (intravenous administration)	Inhibits 17, 20-lyase, 17-hydroxylase, and 11β-hydroxylase.	Limited clinical experience, 1.6–4.2 mg/hour intermittently	Injection-site pain, nausea, vomiting, myoclonus.	• Intravenous route of administration limits use.
Adrenolytic Agent				
Mitotane (oral administration)	Inhibits steroidogenesis at lower doses and is adrenolytic at higher doses. Inhibits 11β-hydroxylase and cholesterol side-chain cleavage. Reduces aldosterone synthesis.	2–6 g/day in 3–4 divided doses 9–10 g/day in 3–4 divided doses 16 g/day in 3–4 divided doses	GI intolerance (high incidence), fatigue, dizziness, somnolence, gynecomastia. Hyperlipidemia requiring lipid-lowering treatment. Adrenal insufficiency requiring glucocorticoid replacement therapy.	• Used primarily for adrenal carcinoma but can be used in other types of Cushing's syndrome. • Efficacy takes several weeks. • Lower rate of relapse when used with pituitary radiation. Also enables lower doses and therefore lower rate of adverse reactions.

(*Continued*)

TABLE 42–10. Pharmacologic Treatments for Cushing's Syndrome[17–20] (*Continued*)

Drug	Mechanism of Action	Dosage: Initial, Usual, Maximum	Common and/or Major Adverse Reactions	Comment
Central Neuromodulators of ACTH Release				
Bromocriptine (oral administration)	Dopamine agonist	3.75–30 mg/day, also reported up to 40 mg/day	Postural hypotension, dizziness, nausea, nasal congestion.	• Low rate of efficacy in Cushing's disease and Nelson's syndrome.
Cyproheptadine (oral administration)	Antagonizes serotonin receptors. May also inhibit histamine receptors. May have direct inhibitory effect on hypothalamus or pituitary.	20–32 mg/day	Sedation, increased appetite, GI intolerance.	• Efficacy variable. • Slow onset of clinical improvement (2–3 months). • Has been used in pregnant Cushing's disease patients.
Octreotide (subcutaneous or intravenous administration)	Long-acting somatostatin analog	300–1200 mcg/day reported	Injection site pain, nausea, diarrhea, hypoglycemia or hyperglycemia, hypothyroidism, dizziness, biliary disease.	• Most useful in Nelson's syndrome and ectopic ACTH syndrome. • Not effective as monotherapy in Cushing's disease but may be effective when used with ketoconazole. • Not effective in adrenal tumors.
Ritanserin (oral administration)	Selectively antagonizes central serotonin-2 receptors.	10–15 mg/day	Low incidence of central nervous system reactions.	• Few clinical experiences. • Published reports of efficacy in some cases of Cushing's disease.
Sodium valproate (oral administration)	Inhibits GABA aminotransferase. May decrease CRH secretion.	600–1200 mg/day	Neurologic disturbances, GI intolerance, weight gain.	• Variable efficacy seen in Cushing's disease and Nelson's syndrome.
Peripheral Glucocorticoid Antagonist				
Mifepristone (RU 486) (oral administration)	Antagonizes glucocorticoid receptors.	Up to 20 mg/kg per day	GI intolerance, rash, drowsiness, gynecomastia, hypoadrenalism. Has abortifacient and embryotoxic properties.	• Requires cautious use since few clinical experiences and no biochemical markers available to monitor efficacy of treatment. • Increases cortisol level via antagonism of negative feedback of ACTH secretion.

ACTH, adrenocorticotropic hormone or corticotropin; CRH, corticotropin-releasing hormone; GABA, γ-aminobutyric acid; GI, gastrointestinal.

TABLE 42–11. Principles of Glucocorticoid Administration to Avoid Hypercortisolism or Hypocortisolism

To Prevent Hypercortisolism and Development of Cushing's Syndrome

- Give the lowest glucocorticoid dose that will manage the disease being treated and for the shortest possible duration.
- If possible, give glucocorticoid via administration routes that minimize systemic absorption (such as inhalation or dermal).
- Administer glucocorticoid treatment every other day (calculate the total 48-hour dose and give as a single dose of intermediate-acting glucocorticoid in the morning).[4]
- Avoid concurrent administration of drugs that can inhibit glucocorticoid metabolism.

To Prevent Hypocortisolism and Development of Adrenal Insufficiency or Adrenal Crisis

- Assess patients at risk for adrenal insufficiency with screening tests (serum cortisol, plasma ACTH stimulation, etc.)
- If the patient requires discontinuation from chronic treatment with supraphysiologic doses of glucocorticoid, the following discontinuation protocol can be used:[4]
  - Gradually taper the dose to approximately 20 mg of prednisone or equivalent per day, given in the morning, then
  - Change glucocorticoid to every other day administration, in the morning.
  - Stop the glucocorticoid when the equivalent physiologic dose is reached (20 mg/day of hydrocortisone or 5–7.5 mg/day of prednisone or equivalent).
  - Understand that recovery of the HPA axis may take up to a year after glucocorticoid discontinuation during which the patient may require supplementation therapy during periods of physiologic stress.
- Evaluate patients at risk for adrenal insufficiency as a result of treatment(s) of Cushing's syndrome and initiate glucocorticoid and mineralocorticoid replacement therapy as appropriate.
- Avoid concurrent administration of drugs that can induce glucocorticoid metabolism.
- Educate patients about:
  - The need for replacement or supplemental glucocorticoid and mineralocorticoid therapy
  - How to administer parenteral glucocorticoid if unable to immediately access medical care during an emergency
  - Need to wear or carry medical identification regarding their condition (e.g., card, bracelet)

ACTH, adrenocorticotropic hormone or corticotropin; HPA, hypothalamic-pituitary-adrenal.



Cushing's Syndrome: Patient Care and Monitoring

1. Patient evaluation should include a thorough history of all medications and herbal or dietary supplements.
2. Perform initial screening tests to confirm Cushing's syndrome and rule out those with pseudo-Cushing's conditions (in other words, until it is determined that it is not a pseudo-Cushing's syndrome).
3. Once diagnosis is confirmed, perform further testing to determine the etiology of Cushing's syndrome.
4. Attempt to taper glucocorticoid if Cushing's syndrome is from exogenous administration.
5. If endogenous Cushing's syndrome, determine if patient is an appropriate candidate for surgical resection of the tumor. Does the patient have any conditions that contraindicate surgical resection, such as advanced disease (metastatic adrenal carcinoma)?
6. Develop a formal plan to assess the response and complications associated with surgery:[15]
   - Measure plasma cortisol after surgery to determine if the patient displays persistent hypercortisolism (surgical treatment failure) or hypocortisolism (adrenal insufficiency requiring steroid replacement therapy).
   - In patients demonstrating hypocortisolism:
     - Monitor for signs and symptoms of glucocorticoid withdrawal (e.g., headache, fatigue, malaise, and myalgia).
     - Monitor for signs and symptoms of adrenal insufficiency.
     - Monitor morning cortisol or response to ACTH stimulation every 3 to 6 months to assess for HPA axis recovery. Discontinue glucocorticoid replacement therapy when cortisol concentrations are greater than 19 mcg/dL (524 nmol/L) on either test.
     - Monitor cortisol, ACTH, low-dose dexamethasone suppression, or other tests to assess for risk of relapse of hypercortisolism.
   - Monitor for development of pituitary hormone deficiency.
7. If surgical resection does not achieve satisfactory disease control or is not indicated, evaluate the patient for pituitary radiation or bilateral adrenalectomy with concomitant pituitary radiation.
   - Monitor patients treated with pituitary radiation for development of pituitary hormone deficiency.
8. Evaluate patients with adrenal adenomas for unilateral adrenalectomy.
9. Give glucocorticoid and mineralocorticoid replacement to patients who undergo adrenalectomy (permanently in the case of bilateral adrenalectomy).
10. Evaluate the patient for appropriateness of pharmacologic therapy depending on etiology of Cushing's syndrome.
11. Monitor patient for response to therapy, need for dose adjustments, and presence of adverse drug reactions.
12. Once disease control is achieved, continue to monitor biochemical markers and patient for development of complications of Cushing's syndrome because relapse may occur.
13. Provide patient education regarding disease state and treatment:
    - Causes of Cushing's syndrome, including drug-induced etiologies.
    - How to recognize the clinical manifestations of Cushing's syndrome.
    - Possible sequelae of Cushing's syndrome.
    - How to reduce the modifiable cardiovascular and metabolic complications.
    - Advantages and disadvantages of potential treatment options.
    - Possible adverse consequences of treatment.
    - Need for glucocorticoid and mineralocorticoid replacement after treatment, if appropriate.
    - Importance of adherence to therapy.

ABBREVIATIONS

3B-HSD:	3β-hydroxysteroid dehydrogenase
11B:	11β-hydroxylase
17:	17-hydroxylase
17,20:	17,20-lyase
21:	21α-hydroxylase
ACTH:	adrenocorticotropic hormone or corticotropin
AIDS:	acquired immunodeficiency syndrome
AS:	aldosterone synthase
BUN:	blood urea nitrogen
CRH:	corticotropin-releasing hormone
CT:	computed tomography
CYP450 3A4:	cytochrome P-450 subfamily IIIA, polypeptide 4
DHEA:	dehydroepiandrosterone
DHEA-S:	sulfated form of dehydroepiandrosterone
DST:	dexamethasone suppression test
GABA:	γ-aminobutyric acid
GI:	gastrointestinal
HPA:	hypothalamic-pituitary-adrenal
IM:	intramuscularly
IV:	intravenous or intravenously
MRI:	magnetic resonance imaging

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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43 Pituitary Gland Disorders

Judy T. Chen, Devra K. Dang, Frank Pucino, Jr., and Karim Anton Calis



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. List the mediators and primary effects of the pituitary hormones.
2. Identify the clinical features of patients with acromegaly.
3. Discuss the role of surgery and radiation therapy for patients with acromegaly.
4. Select appropriate pharmacotherapy for patients with acromegaly based on patient-specific factors.
5. Identify the clinical features of children and adults with growth hormone deficiency and select appropriate pharmacotherapy for these patients.
6. List the monitoring parameters necessary to assess therapeutic outcomes and adverse effects in patients receiving growth hormone therapy.
7. List the common etiologies of hyperprolactinemia.
8. Identify the clinical features of patients with hyperprolactinemia.
9. Select appropriate pharmacologic and nonpharmacologic treatments for patients with hyperprolactinemia based on patient-specific factors.

Key Concepts

❶ Surgical resection of the pituitary tumor through transsphenoidal pituitary microsurgery is the treatment of choice for most patients with growth hormone–producing pituitary adenomas.

❷ Somatostatin analogs are the mainstay of pharmacotherapy for the treatment of acromegaly when surgery and radiation are contraindicated or have failed.

❸ Pegvisomant is indicated for patients who do not tolerate or fail other treatments or for those with extremely elevated insulin-like growth factor I levels.

❹ Dopamine agonists may be appropriate for patients with mildly elevated insulin-like growth factor I levels who have growth hormone and prolactin co-secreting tumors.

❺ Prolonged exposure to elevated growth hormone and insulin-like growth factor I levels can lead to serious complications in patients with acromegaly. Aggressively manage comorbid conditions such as hypertension, diabetes, arrhythmias, coronary artery disease, and heart failure to prevent vascular and neuropathic complications.

❻ Recombinant growth hormone therapy is the main pharmacologic treatment for growth hormone deficiency in both children and adults.

❼ Although comparative trials have not been conducted, recombinant growth hormone products appear to have similar efficacy for treating growth hormone deficiency.

❽ Dopamine agonists are the first-line treatment of choice for all patients with hyperprolactinemia; transsphenoidal surgery and radiation therapy are reserved for patients who are resistant to or severely intolerant of pharmacologic therapy.

❾ Women who become pregnant while on a dopamine agonist should discontinue treatment immediately to minimize fetal exposure. Because cabergoline has a long half-life, women who plan to become pregnant should discontinue the drug at least 1 month before planned conception.

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PHYSIOLOGY OF THE PITUITARY GLAND

The pituitary gland, located at the base of the brain, is a small endocrine gland about the size of a pea weighing approximately 600 mg. The pituitary gland is referred to as the "master gland" because it is responsible for the regulation of other endocrine glands and body systems. Growth, development, metabolism, reproduction, and stress homeostasis are among the functions influenced by the pituitary. Functionally, the gland consists of two distinct sections: the anterior pituitary lobe (adenohypophysis) and the posterior pituitary lobe (neurohypophysis). The human intermediate pituitary lobe has minimal structure and function. The pituitary receives neural and hormonal input from the inferior hypothalamus via blood vessels and neurons contained in the pituitary stalk.

The posterior pituitary is innervated by direct nervous stimulation from the hypothalamus, resulting in the release of specific hormones. The hypothalamus synthesizes two hormones, oxytocin and vasopressin. These hormones are stored in and released from the posterior pituitary lobe. Oxytocin exerts two actions: (1) it promotes uterine contractions during labor, and (2) it contracts the smooth muscles in the breast to stimulate the release of milk from the mammary gland during lactation. Vasopressin is an antidiuretic hormone (ADH) essential for proper fluid and electrolyte balance in the body. Specifically, vasopressin increases the permeability of the distal convoluted tubules and collecting ducts of the nephrons to water. This causes the kidney to excrete less water in the urine. Consequently, the urine becomes more concentrated as water is conserved.

In contrast to the posterior pituitary lobe, the anterior pituitary lobe is under the control of several releasing and inhibiting hormones secreted from the hypothalamus via a portal vein system. The anterior pituitary lobe, in turn, synthesizes and secretes six major hormones. Figure 43–1 summarizes the physiologic mediators and effects of each of these hormones.

HORMONAL FEEDBACK REGULATORY SYSTEMS

The hypothalamus is responsible for the synthesis and release of hormones that regulate the pituitary gland. Stimulation or inhibition of the pituitary hormones elicits a specific cascade of responses in peripheral target glands. In response, these glands secrete hormones that exert a negative feedback on other hormones in the hypothalamic-pituitary axis (Fig. 43–1). This negative feedback serves to maintain body system homeostasis. High circulating hormone levels inhibit the release of hypothalamic and anterior pituitary hormones.

Damage and destruction of the pituitary gland may result in secondary hypothyroidism, **hypogonadism,** adrenal insufficiency, growth hormone deficiency, hypoprolactinemia, or insufficiency or absence of all anterior pituitary hormones (i.e., **panhypopituitarism**). A tumor located in the pituitary gland may result in excess secretion of a hormone or may physically compress the gland and suppress adequate hormone release. The type, location, and size of a pituitary tumor often determine a patient's clinical presentation. This chapter discusses the pathophysiology and role of pharmacotherapy in the treatment of acromegaly, growth hormone deficiency, and **hyperprolactinemia**. The following hormones are discussed elsewhere in this book: adrenocorticotropic hormone (ACTH or corticotropin), thyroid-stimulating hormone (TSH or thyrotropin), luteinizing hormone (LH), follicle-stimulating hormone (FSH), vasopressin (antidiuretic hormone or ADH), and oxytocin.

GROWTH HORMONE (SOMATOTROPIN)

Somatotropin or growth hormone (GH) is the most abundant hormone produced by the anterior pituitary lobe. The GH-secreting **somatotropes** account for 50% of hormone-secreting cells in the anterior pituitary. GH is regulated primarily by the hypothalamic-pituitary axis. The hypothalamus releases growth hormone–releasing hormone (GHRH) to stimulate GH synthesis and secretion, whereas **somatostatin** inhibits it.[1] On stimulation by GHRH, somatotropes release GH into the circulation, thereby stimulating the liver and other peripheral target tissues to produce insulin-like growth factors (IGFs). These IGFs, also known as somatomedins, are the peripheral GH targets. There are two types of IGFs: IGF-I and IGF-II. IGF-II is responsible primarily for regulating fetal growth, whereas IGF-I is the hormone responsible for growth of bone and other tissues. High levels of IGF-I inhibit GH secretion through negative feedback, thereby inhibiting GHRH secretion.[1] The hypothalamus also may stimulate the release of somatostatin to inhibit GH secretion. Effects of IGF-I in peripheral tissues are both GH-dependent and GH-independent.[2] GH is an anabolic hormone with direct "anti-insulin" metabolic effects. By stimulating protein synthesis and shifting the body's energy source from carbohydrates to fats, GH promotes a diabetic state[2] (Table 43–1). GH controls somatic growth and has a critical role in the development of normal skeletal muscle, myocardial muscle, and bone.

In healthy individuals, GH is secreted in a pulsatile pattern throughout a 24-hour period, with several short bursts occurring mostly during the night. The most intense period of GH secretion occurs within the first 1 to 2 hours of slow-wave sleep (stage 3 or 4 deep sleep).[1] In between these bursts, basal concentration of GH falls to very low or undetectable levels because of its short half-life in the blood (19 minutes). The amount of GH secretion fluctuates throughout a person's lifetime. Secretion of GH is lowest during infancy, increases during childhood, peaks during adolescence, and then declines gradually during the middle years.[1] These changes are parallel

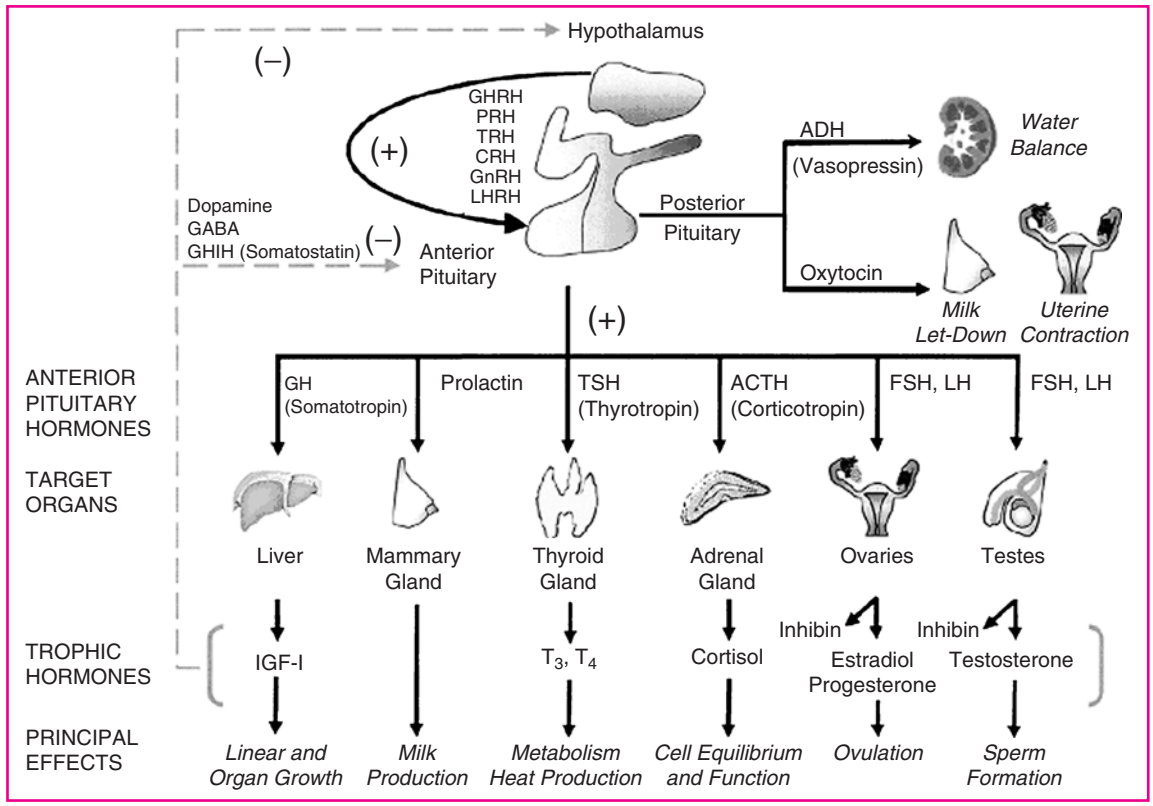


FIGURE 43–1. Hypothalamic-pituitary-target-organ axis. Trophic hormones are hormones that regulate the activity of endocrine glands. The hypothalamic hormones regulate the biosynthesis and release of eight pituitary hormones. Stimulation of each of these pituitary hormones produces and releases trophic hormones from their associated target organs to exert their principal effects. Subsequently, increased serum concentration of the trophic hormones released from the target organs can inhibit both the hypothalamus and the anterior pituitary gland to maintain homeostasis (negative feedback). Inhibin is produced by the testes in the male and ovaries in the female during pregnancy. Inhibin acts in direct negative feedback on pituitary production of follicle-stimulating hormone (FSH). Melanocyte-stimulating hormone (MSH) produced by the anterior pituitary is not illustrated in the figure.
(–) = inhibit; (+) = stimulate; ACTH = adrenocorticotropic hormone (corticotropin); ADH = antidiuretic hormone (vasopressin); CRH = corticotropin-releasing hormone; FSH = follicle-stimulating hormone; GABA = γ-aminobutyric acid; GH = growth hormone (somatotropin); GHIH = growth hormone–inhibiting hormone (somatostatin); GHRH = growth hormone–releasing hormone; GnRH = gonadotropin-releasing hormone; IGF-I = insulin-like growth factor I; LH = luteinizing hormone; LHRH = luteinizing hormone–releasing hormone; PRH = prolactin-releasing hormone; T_3 = triiodothyronine; T_4 = thyroxine; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone (thyrotropin).

to an age-related decline in lean muscle mass. In addition to GH itself, several internal and external factors also modulate GH synthesis (e.g., serotonin, dopamine, and γ-adrenergic agonists), including low plasma glucose, exercise, stress, trauma, emotional excitement, and ingestion of protein-rich meals.[1]

Growth Hormone Excess

Epidemiology and Etiology

Acromegaly affects both genders equally; the average age of presentation is 44 years. Approximately 50 to 70 people per 1 million population are affected, with an estimated annual incidence of 3 to 4 cases per 1 million people.[3,4] In more than 95% of the cases, overproduction of GH is due to a benign pituitary tumor (adenoma), whereas malignant tumors occur in less than 1%.[4] Most pituitary adenomas occur spontaneously as a result of a genetic mutation acquired during life. Depending on the size of the tumor, pituitary adenomas are classified as: (1) microadenomas if they are 10 mm or less in diameter or (2) macroadenomas if they are greater than 10 mm. Rarely, non-pituitary tumors may cause acromegaly. These tumors can produce GH, but more commonly they secrete GHRH and result in excessive GH and IGF-I production.

TABLE 43–1. Effects of Growth Hormone[2]

	Action(s)	Effect(s)
Lipid metabolism	Increases the use of fat by stimulating triglyceride breakdown and oxidation of adipocytes.	Increases breakdown of fat (lipolysis) Increases circulating fatty acid levels Increases lean body mass
Protein metabolism	Stimulates protein anabolism by increasing amino acid uptake and protein synthesis and decreasing oxidation of proteins.	Increases muscle mass
Carbohydrate metabolism	Suppresses the ability of insulin to stimulate uptake of glucose in peripheral tissues.	Decreases glucose utilization
	Decreases insulin receptor sensitivity.	Insulin resistance
	Impairs post–receptor insulin action.	Hyperglycemia
	Stimulates glucose synthesis in the liver (gluconeogenesis)	Increases hepatic glucose output

Pathophysiology

Acromegaly is a rare, insidious disorder that manifests gradually over time. It is caused by an adenoma of the pituitary that overproduces GH and stimulates excessive production of IGF-I during adulthood. This typically occurs after fusion of the epiphyses (growth plates) of the long bones.[4] The facial features of an acromegalic patient are depicted in Fig. 43–2. **Gigantism** refers to GH excess that occurs during childhood before epiphyseal closure and results in excessive linear growth.

Diagnosis of acromegaly is based on both clinical and biochemical findings. Because secretion of GH fluctuates throughout the day, a single random measurement is never reliable for diagnosing GH excess. However, GH-mediated IGF-I production results in relatively stable serum IGF-I concentrations during the day, which correlate positively with 24-hour mean GH levels.[1] This makes elevated IGF-I levels an ideal screening test for acromegaly and a reliable monitoring biochemical marker to assess disease activity and response to therapy.[5,6] Because IGF-I levels may fluctuate with age and gender, it is important to compare IGF-I levels with age- and sex-matched population values.[5,6] Other conditions such as nutritional status, liver dysfunction, insulin levels, and illness also can affect IGF-I levels. Almost all IGF-I in the circulation is bound to IGF-binding proteins (IGFBPs), which also regulate IGF bioactivity. The major carrier protein for circulating IGF-I is the GH-dependent protein IGFBP-3, which also can be used to assess therapeutic response.[2] Low IGFBP-3 levels are associated with GH deficiency, GH insensitivity, and malnutrition. The measurement of serum GH secreted by the pituitary in response to an oral glucose tolerance test (OGTT) is considered the primary biochemical test for diagnosing acromegaly. GH is suppressed after administration of a 75 g oral glucose challenge because postprandial hyperglycemia inhibits secretion of GH for at least 1 hour. If the GH level does not decline to less than 1 ng/mL (1 mcg/L) during the test, the patient is diagnosed with acromegaly.[4] Elevation of IGF-I serum concentrations and the clinical presentation help to confirm the diagnosis.

Acromegaly Treatment Goals

Patients with acromegaly experience a two- to three-fold increase in mortality rate.[8] Normalization of GH and IGF-I levels reverses the mortality risk and alleviates significant comorbid complications, especially cardiovascular, pulmonary, and metabolic abnormalities. Reduction of IGF-I levels alone does



FIGURE 43–2. Before and after photographs of an acromegalic patient. Compare the photographs of an acromegalic woman (*A*) before the onset of acromegaly and (*B*) after approximately 20 years, when the diagnosis was well established. Notice the coarsening of facial features, with enlarged nose, lips, and forehead.



Clinical Presentation and Diagnosis of Acromegaly[3,7–9]

General

The patient will experience slow development of soft-tissue overgrowth affecting many body systems. Signs and symptoms may progress gradually over 10 to 15 years.

Symptoms

- Headache and compromised visual function (loss of peripheral vision and blurred vision) caused by the actual tumor mass and its close proximity to the optic structures.
- Loss of other hormonal functions (i.e., LH, FSH, TSH, and ACTH) caused by massive tumor size compressing the anterior pituitary lobe.
- Absence of regular menstrual periods (**amenorrhea**), impotence, and decreased libido caused by disruption of the gonadotropin secretion.
- Excessive sweating, joint pain, nerve pain, and abnormal neurologic sensations (paresthesias) related to elevated GH and IGF-I levels.

Signs

- Coarsening of facial features
- Increased hand volume
- Increased ring and shoe size
- Increased spacing between teeth
- Increased acne/oily skin
- Enlarged tongue
- Deepening of voice
- Thick, irregular, patchy skin discoloration
- Enlarged nose, lips, and forehead (frontal bossing)
- Abnormal protrusion of the mandible (prognathia)
- Inappropriate secretion of breast milk (**galactorrhea**)
- Abnormal enlargement of interior organs (organomegaly)
- Carpal tunnel syndrome caused by nerve compression from the swollen tissue

Laboratory Tests

- GH level greater than 1 ng/mL (1 mcg/L) following an oral glucose tolerance test (OGTT) and elevated IGF-I level compared with age- and sex-matched control values.
- Glucose intolerance may be present in up to 50% of patients.

Additional Clinical Sequelae

- Cardiovascular diseases: hypertension, coronary heart disease, cardiomyopathy, left ventricular hypertrophy, and arrhythmia.
- Osteoarthritis and joint damage develop in up to 90% of patients.
- Respiratory disorders and **sleep apnea** occur in up to 60% of patients.
- Type 2 diabetes mellitus develops in up to 40% of patients.
- Increase risk for the development of esophageal, colon, and stomach cancer.

Other Diagnostic Tests

- Perform magnetic resonance imaging (MRI) examination and computed tomography (CT) of the pituitary to locate the tumor and validate the diagnosis.
- Without obvious pituitary tumor but proven acromegaly, measurement of GHRH may be helpful to detect ectopic tumors.

Source: Adapted, with permission, from Heck AM, Yanovski JA, Calis KA. Pituitary Gland Disorders. In: Dipiro JT, Talbert RL, Yee GC, et al. (eds.) *Pharmacotherapy. A Pathophysiologic Approach.* 6th ed. New York: McGraw Hill; 2005: 1407–1423.



Patient Encounter 1: The Medical History, Physical Examination, and Diagnostic Tests

EB, a 48-year-old woman, presents to a new primary care clinic. EB's chief complaints are chronic pain of the knee and "pins and needles" and "numbness" in both hands. Over the past few years, she feels that her body has been changing. EB reports increased urinary frequency, excessive sweating, worsening headaches, an increase of two shoe sizes, and facial hair that she shaves once a week. She says that her hands have enlarged to the point that "my wedding band won't fit anymore."

PMH
Hypertension for 12 years, currently controlled
Hyperlipidemia for 10 years, currently controlled
Osteoarthritis for 5 years

FH
Mother died of colon cancer at age of 58 years. Father died of myocardial infarction at an unknown age.

SH
Married, a nurse practitioner, highly educated, and physically active (bikes four times per week)

Meds
Lisinopril/hydrochlorothiazide 20/12.5 mg once daily
Atorvastatin 10 mg once daily
Acetaminophen 500 mg every 8 hours as needed for joint pain

ROS
(+) coarse facial hair. Deepening of voice. Ophthalmic examination reveals normal visual acuity and fields.

PE
VS: 118/76 mm Hg, P 78 beats per minute, RR 18 breaths/minute, T 37.5°C (99.5°F)
ENT: (+) protruding jaw and large fleshy nose
CV: RRR, normal S_1, S_2; no murmurs, rubs, gallops
Abd: Soft, non-tender, non-distended; (+) bowel sounds, no hepatosplenomegaly, heme (–) stool

Labs
Electrolytes and renal function are within normal limits. Fasting blood glucose level is 206 mg/dL (11.43 mmol/L), HbA_{1c} is 8.5%, and (–) microalbumin. GH level following an oral glucose tolerance test is 8 ng/mL (8 mcg/L). Elevated IGF-I at 790 ng/mL (790 mcg/L)
MRI and CT scan: Both reveal a pituitary tumor approximately 5 mm in diameter.

- Given this information, what signs and symptoms does EB have for acromegaly?
- Identify your treatment goals for EB.
- What nonpharmacologic and pharmacologic treatment options are available for EB?

TABLE 43–2. Goals for Management of Acromegaly[4,8,11–13]

1. Normalize biochemical disease markers
   a. Reduce GH to less than 1 ng/mL (1 mcg/L) after oral glucose tolerance test (OGTT)[a]
   b. Normalize IGF-I levels to age- and sex-matched control values
2. Ablate or reduce tumor size to relieve tumor mass effect
3. Prevent tumor recurrence and control tumor size
4. Preserve normal pituitary function
5. Improve clinical signs and symptoms
6. Alleviate significant morbidities
7. Reduce mortality rates to that of the general population

[a]When using the older GH assay, suppression of GH levels to less than 1 ng/mL (1 mcg/L) after OGTT is the biochemical target. When using new, highly specific and sensitive assays, GH levels less than or equal to 0.4 ng/mL (0.4 mcg/L) are the biochemical target.[11–13]
GH, growth hormone; IGF-I, insulin-like growth factor I.

not appear to be a reliable predictor of long-term outcome.[6,10] The goals of therapy are presented in Table 43–2.[4,8,11–13]

General Approaches to Treatment

The American Association of Clinical Endocrinologists (AACE) published medical guidelines for the diagnosis and treatment of acromegaly (Fig. 43–3). According to these guidelines, ❶ *surgical resection of the pituitary tumor through* ***transsphenoidal pituitary microsurgery*** *is the treatment of choice for most patients with GH-producing pituitary adenomas.*[4] Most microadenomas can be resected successfully, resulting in prompt normalization of GH levels. Complete resection of a macroadenoma may be difficult if the tumor has already invaded the surrounding nerves and tissues. In such cases, debulking of the tumor, along with adjunctive radiation and/or pharmacotherapy, may improve treatment outcome. The success rate for normalization of GH levels is approximately 90% in patients with well-defined microadenomas and 46% to 48% in patients with macroadenomas.[14,15] Normalization of GH resulted in a 10-year survival rate of 88%, which is similar to that of the general population.[14] Major but infrequent surgical complications include meningitis, serious visual impairment, cerebrospinal fluid leakage requiring surgical repair, permanent **hypopituitarism,** and death. Minor complications include diabetes insipidus, local nasal complications, transient hyponatremia, and cerebrospinal fluid leakage not requiring surgical repair.[14] Repeat surgery is rarely an option because of the high risk of serious complications. The relative contraindications to surgery include patient frailty, acromegaly-associated comorbidities, and medically unstable conditions such as airway difficulties, severe hypertension, or uncontrolled diabetes.[4]

Pharmacologic Therapy

Pharmacologic therapy is often necessary for patients in whom surgery is not an option.[4] Somatostatin analogs, GH receptor antagonists, and dopamine agonists are the primary pharmacologic therapies used for the management of acromegaly (Table 43–3). Pharmacologic therapy avoids hypopituitarism and other surgical risks.

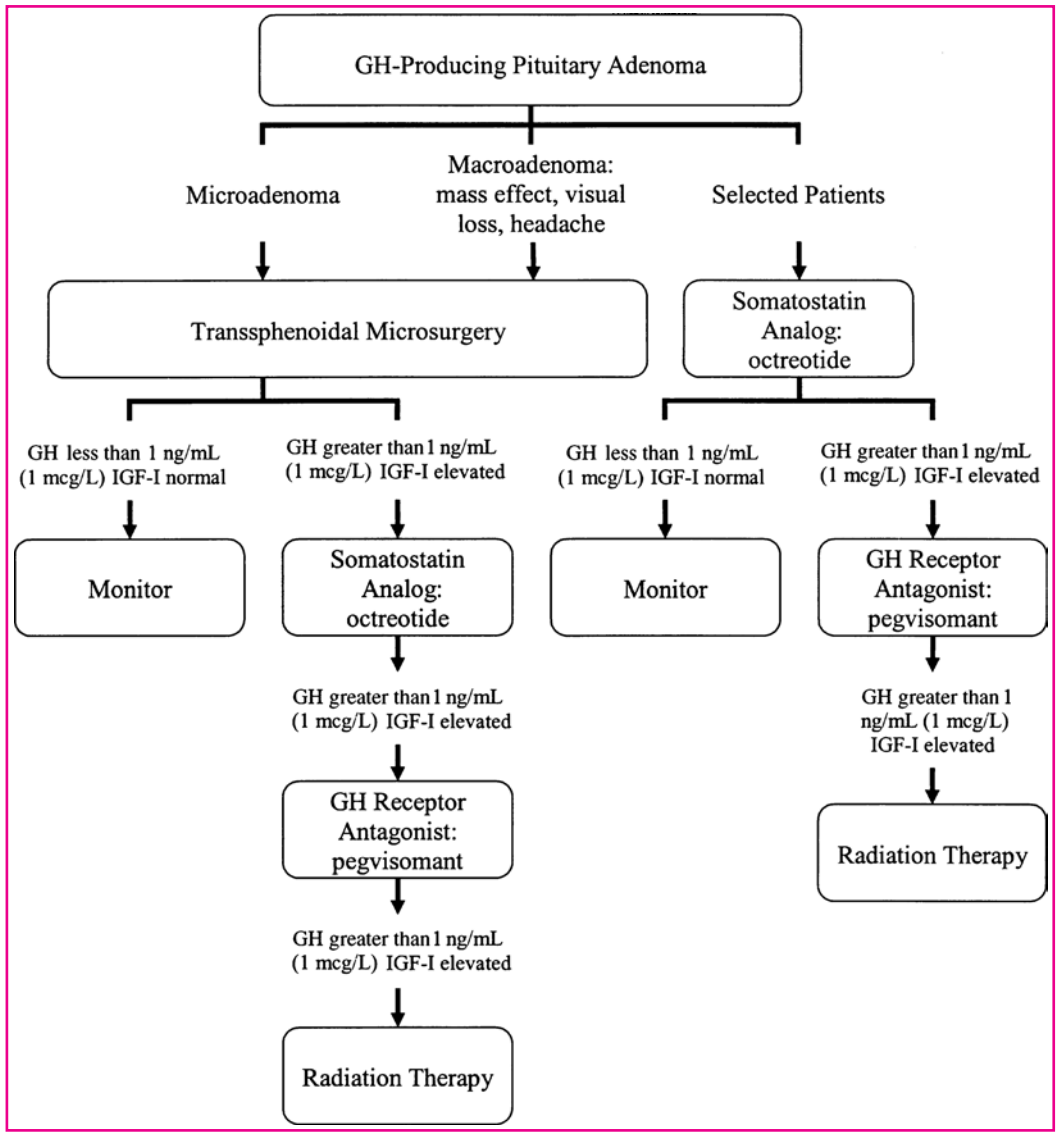


FIGURE 43–3.
Recommended schema for management of growth hormone–producing adenomas.[4] GH = growth hormone; IGF-I = insulin-like growth factor I. (Adapted, with permission, from AACE Medical Guidelines for Clinical Practice for the diagnosis and treatment of acromegaly. Endocr Pract 2004; 10(3):213–225.)

Somatostatin Analog (Growth Hormone–Inhibiting Hormone)

❷ *Somatostatin analogs are the mainstay of pharmacotherapy for the treatment of acromegaly when surgery and radiation are contraindicated or have failed.* These agents mimic endogenous somatostatins and bind to the somatostatin receptors in the pituitary to cause potent inhibition of GH, insulin, and glucagon secretion. Somatostatin analogs effectively control GH and IGF-I levels in 50% to 70% of patients, with 41% to 67% achieving normal IGF-I levels.[16,17] Previous epidemiologic studies reported that a reduction of GH levels of between 2 and 5 ng/mL (2 and 5 mcg/L) resulted in a mortality rate similar to that of the general population.[4,6] Long-term treatment can sustain hormone suppression and alleviate soft-tissue manifestations. Although somatostatin analogs can achieve substantial relief of clinical symptoms, they produce modest tumor size reduction in less than 50% of patients.[18] If treatment is discontinued, monitor patients for tumor recurrence.

Use of the first-generation somatostatin analog octreotide is limited by its extremely short duration of action and requirement for subcutaneous administration at least three times a day. If a patient's GH level returns to baseline before the end of an 8-hour dosing interval, the frequency of octreotide administration can be increased to every 4 to 6 hours. Most patients require octreotide in doses of 100 to 200 mcg three times daily.[19,20] To improve patient tolerance to gastrointestinal (GI) adverse effects, start octreotide at 50 mcg every 8 hours.[20] Assess IGF-I serum concentrations every 2 weeks after initiating therapy to further titrate dose in increments of 50 mcg per dose.

Transient GI disturbances such as diarrhea, abdominal pain, flatulence, constipation, and nausea are commonly associated with somatostatin analogs.[19,20] These adverse GI effects usually

TABLE 43–3. Comparison of Various Drugs for Treatment of Acromegaly[4]

Drug Type and Agent	Starting Dose	Maximal Dose	Side Effects	Monitoring Suggestions	Preferred Indication
Dopamine Agonist					
Cabergoline (Dostinex®)	1 mg/week orally	4 mg/week orally	Nausea, GI cramps, headache	GH, IGF-I	GH and prolactin co-secreting tumors
Somatostatin analog					
Octreotide (Sandostatin®)	50 mcg SQ three times daily	200 mcg SQ three times daily	Nausea, GI cramps, gallstones	GH, IGF-I, ultrasonography of gallbladder (if symptoms)	Somatostatin analog–responsive tumor
Octreotide LAR (Sandostatin LAR®)	10 mg IM every 4 weeks	30 mg IM every 4 weeks	Nausea, GI cramps, gallstones	GH, IGF-I, ultrasonography of gallbladder (if symptoms)	Somatostatin analog–responsive tumor
Lanreotide[a]	60 mg IM every 2 weeks	120 mg IM every 7 days	Nausea, GI cramps, gallstones	GH, IGF-I, ultrasonography of gallbladder (if symptoms)	Somatostatin analog–responsive tumor
Lanreotide Autogel[a]	60 mg deep SQ every 28 days	120 mg deep SQ every 28 days	Nausea, GI cramps, gallstones	GH, IGF-I, ultrasonography of gallbladder (if symptoms)	Somatostatin analog–responsive tumor
GH Receptor Antagonist					
Pegvisomant (Somavert®)	10 mg SQ daily	40 mg SQ daily	Headache, fatigue, abnormal liver enzymes	Liver function tests monthly for 6 months, then every 6 months; MRI every 6 months. IGF-I (not GH) after first year, then yearly.	High IGF-I levels not responsive to somatostatin analog–therapy

[a]Lanreotide is currently not available in the United States.
GH, growth hormone; GI, gastrointestinal; IGF-I, insulin-like growth factor I; IM, intramuscularly; LAR, long-acting release; MRI, magnetic resonance imaging; SQ, subcutaneously.
Adapted from AACE Medical Guidelines for Clinical Practice for the diagnosis and treatment of acromegaly. *Endocr Pract.* 2004; 10(3):213–225, by permission of publisher, AACE Corp.

subside within the first 3 months of therapy. Octreotide inhibits gallbladder contractility and decreases bile secretion. The major adverse effect of octreotide is development of **biliary sludge** and asymptomatic **gallstones (cholelithiasis).** Biliary sludge occurs in 20% of patients and is felt to be a predisposing factor for the high incidence of cholelithiasis observed in 10% to 20% of patients treated with octreotide.[19] Development of gallstones typically occurs in patients treated for 12 months or longer and is unrelated to age, gender, or dose. Octreotide may suppress pituitary release of TSH, leading to decreased thyroid hormone secretion and subsequent hypothyroidism in 12% of treated patients. Additionally, octreotide can alter the balance of the counterregulatory hormones (i.e., glucagon, insulin, and GH), resulting in either hypoglycemia or hyperglycemia. Sinus bradycardia, conduction abnormalities, and arrhythmias have been reported with octreotide therapy. Thus, patients taking insulin, oral hypoglycemic agents, β-blockers, or calcium channel blockers may require dose adjustment when these agents are used concurrently with octreotide.

To increase patient compliance, the long-acting formulation of octreotide acetate (Sandostatin LAR®) is preferred in the majority of cases. Sandostatin LAR® is administered as a deep intramuscular injection in doses of 10 to 30 mg every 4 weeks and is as effective as short-acting octreotide.[17,21,22] Typically, at least a 2-week trial of short-acting octreotide is recommended to determine efficacy and tolerance before switching to the long-acting preparation. Counsel patients to perform alternate injections in the gluteal region and to avoid injections in the deltoid region because of significant injection-site discomfort. Although antibody formation to octreotide occurs in up to 25% of patients, development of these antibodies does not cause serious adverse effects or compromise treatment efficacy.[23]

Growth Hormone Receptor Antagonist

Growth hormone receptor antagonist represents a novel approach to the treatment of acromegaly. Pegvisomant is the only genetically engineered GH-receptor antagonist that blocks the action of GH. The effects of pegvisomant work independently of

tumor characteristics, somatostatin, and dopamine receptors.[24] Up to 97% of acromegalic patients treated with pegvisomant (10–20 mg/day) achieved normal age-related IGF-I levels and experienced significant improvement in clinical symptoms of GH excess by 1 year of therapy.[25,26] Pegvisomant therapy is not associated with deterioration in glucose tolerance (body's ability to metabolize glucose) or insulin sensitivity (capacity of cells to respond to insulin). A preliminary study in seven acromegalic patients suggested that insulin sensitivity and glucose tolerance improved in patients converted from octreotide to pegvisomant.[27] However, use of pegvisomant is associated with statistically significant dose-dependent increases in GH despite the declining IGF-I levels.[25,26] The dose-dependent increase in GH is troubling because it has been suggested that persistent elevation of GH levels may be indicative of tumor growth. Although patients did not experience a significant change in tumor volume during studies, theoretical concerns remain because pituitary tumors are slow growing. Thus, practitioners should use caution when administering pegvisomant to patients with large tumors extended toward the optic chiasm to prevent visual damage caused by possible tumor growth. ❸ *Pegvisomant is indicated for patients who do not tolerate or fail other treatment options or for those with extremely elevated IGF-I levels (greater than 900 ng/mL or 900 mcg/L).*[4] Long-term efficacy and safety profiles of pegvisomant in acromegaly remain to be established. Available data to date suggest that pegvisomant appears well tolerated with minimal adverse effects such as self-limiting injection-site reactions, nausea, diarrhea, and flu-like symptoms. Safety concerns about antibody development with pegvisomant do not reduce the efficacy of therapy. Rare cases of hepatotoxicity have been reported in clinical trials;[25,26] therefore, use caution when administering pegvisomant to patients with elevated baseline liver function tests. Start subcutaneous pegvisomant at 10 mg/day, and increase at 3-month intervals until IGF-I levels are normalized. In a recent study, combination of pegvisomant once weekly and long-acting somatostatin analogs once monthly was as effective as daily pegvisomant monotherapy. This combination has the potential to improve patient adherence and cost-effectiveness of therapy.[28]

Dopamine Agonists

Dopamine is one of the neurotransmitters that can increase GH secretion in healthy adults. However, dopamine agonists administered to patients with acromegaly exert the opposite effect and suppress GH release from the tumor. The first dopamine agonist for acromegaly, bromocriptine, achieved normal IGF-I levels in fewer than 10% of patients and was associated with significant adverse effects, including nausea, dizziness, and headaches.[29] The large doses of bromocriptine required to achieve the desired response often are associated with dose-limiting toxicity, such as GI discomfort and orthostatic hypotension. Cabergoline, the newer, selective long-acting agonist with improved tolerability, effectively can normalize IGF-I levels in 35% of patients and reduce GH levels to less than 2 ng/mL (2 mcg/L) in 44% of treated patients.[30] Acromegalic patients with co-existing hyperprolactinemia also had a more favorable response to cabergoline, with 50% of patients achieving normal IGF-I levels, 56% GH suppression, and 65% tumor shrinkage.[30] Although orally administered dopamine agonists are the least expensive medical therapy for managing acromegaly, the major disadvantage is their relative lack of efficacy compared with existing therapeutic options. ❹ *Dopamine agonists may be appropriate for patients with mildly elevated IGF-I levels who have GH and prolactin (PRL) co-secreting tumors.*[4]

Radiation Therapy

Radiation therapy involves the use of radiation to kill rapidly growing tumor cells and often results in a reduction in tumor size. Radiation therapy is extremely effective but may take 10 to 20 years before the full effects become evident. A major complication resulting from radiation therapy is hypopituitarism, requiring lifelong hormone replacement.[4] There is also the potential for optic nerve damage if the pituitary tumor is near the optic tracts. Radiation therapy is an important adjunctive therapy in patients with residual GH excess after surgery or pharmacologic therapies. Owing to delay in onset of radiation effectiveness, pharmacologic therapies often are indicated as bridge therapy.[4,19,20] Men and women who desire to have children should be warned that radiation therapy may impair the function of the ovaries and testes.[4]

Outcome Evaluation

- Following a baseline evaluation, monitor patients regularly for symptom relief.
- Lifelong biochemical assessment is critical for determining therapeutic outcomes. Although some patients may experience a rapid decline in GH levels following transsphenoidal microsurgery, stabilization of IGF-I levels usually occurs 3 months following surgery but rarely may be delayed for up to 12 months. Measure GH and IGF-I levels 3 months postoperatively to assess treatment response.[6]
- Since up to 10% of pituitary tumors may recur within 15 years following surgery,[6,14] continual postoperative monitoring is recommended.
- For patients treated with somatostatin analogs, assess baseline fasting blood glucose, thyroid function tests, and heart rate. Thereafter, periodically monitor patients for adverse reactions such as GI disturbances, glucose intolerance, signs and symptoms of thyroid abnormalities, bradycardia, and arrhythmias in patients receiving long-term octreotide therapy. Reevaluate IGF-I and GH levels at 3-month intervals to determine therapeutic response. Since the frequency of symptomatic gallstones associated with octreotide varies among studies, the need for routine ultrasound evaluation remains controversial. However, ultrasonography of the gallbladder would be indicated if the patient develops symptoms of biliary abnormalities.
- For patients treated with a GH receptor antagonist, GH levels are not measured because pegvisomant is a modified GH molecule that is detected in commercial GH assays, resulting in falsely

elevated GH levels.[31] Therefore, IGF-I level is the principal biochemical marker used to assess response to pegvisomant therapy. After appropriate dose titration, monitor IGF-I levels every 6 months.[6] Concern for tumor growth requires careful monitoring of tumor size; therefore, performing magnetic resonance imaging (MRI) every 6 months during the first year of therapy and annually thereafter is recommended.[6] Because of abnormal liver function associated with pegvisomant therapy, it is mandatory to monitor all patients' liver function tests monthly during the first 6 months and every 6 months thereafter.[6]

- For patients receiving dopamine agonists, the maximal suppression of GH and IGF-I levels may take up to 3 months to achieve. Once stable control of biochemical markers is achieved with dopamine agonists or somatostatin analogs, monitor GH and IGF-I levels annually.[6]
- With conventional multidose radiation therapy, the most rapid decline in GH serum levels occurs within the first 2 years; monitor GH levels at the second year and annually thereafter.[6] Patients who receive single-dose radiation therapy should be evaluated at 6-month intervals because response is observed earlier.
- For patients receiving concurrent pharmacologic therapy with radiation therapy, withdraw therapies every 6 to 12 months to evaluate endogenous GH secretion and assess the development of hypopituitarism.[6]

❺ *Prolonged exposure to elevated GH and IGF-Is can lead to serious complications in patients with acromegaly. Aggressively manage comorbid conditions such as hypertension, diabetes, arrhythmias, coronary artery disease and heart failure to prevent vascular and neuropathic complications.* It is critical to monitor patients indefinitely for management of the comorbidities associated with acromegaly[8] (Table 43–4).

TABLE 43–4. Assessment of Acromegaly Complications at Diagnosis and Follow-Up[8]

At Diagnosis	During Long-Term Follow-Up
Glucose tolerance testing (samples for blood glucose and GH only)	Fasting blood glucose, HbA_{1c} if diabetes present (as appropriate)
Serum cholesterol and lipid profile	Annually
Echocardiography	Annually
Electrocardiogram (ECG)	Annually
Exercise ECG	If angina present
Colonoscopy	Every 2–3 years
DEXA (hypogonadal only)	Every 2–3 years
Sleep assessment	Annually (if altered at diagnosis)
Blood pressure monitoring	Annually or change of treatment (if hypertensive)
Echo-Doppler of carotid artery	As indicated by clinical features

DEXA, dual-energy x-ray absorptiometry; ECG, electrocardiogram; GH, growth hormone; HbA_{1c}, glycosylated hemoglobin A_{1c}.
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Acromegaly: Patient Care and Monitoring

1. Assess patient's clinical signs and symptoms to determine severity of acromegaly.
2. Review the biochemical disease markers to assess severity of acromegaly.
3. Review the available diagnostic data to determine pituitary tumor size and location. Determine if the patient has a coexisting prolactin-secreting tumor. Determine if the tumor extends toward the optic chiasm or if it is continuous on the optic tracts.
4. Assess presence of acromegaly complications. Identify any significant comorbidities associated with acromegaly that require immediate treatment or early diagnosis.
5. Determine what treatment options the patient has tried in the past.
6. Evaluate the patient for the presence of surgical contraindications to transsphenoidal microsurgery. Determine if the patient is able or willing to undergo surgical intervention.
7. Develop a formal plan to assess patient's response to and complications of surgical intervention. Measure both GH and IGF-I levels.
8. If surgical intervention does not achieve satisfactory disease control, select subsequent appropriate pharmacologic therapy based on patient-specific factors. In selecting therapy, be sure to consider if the patient has any contraindications or allergies to therapies.
9. Evaluate patient for presence of adverse drug reactions, drug allergies, and drug interactions.
10. Develop a plan to assess efficacy of pharmacologic therapy. Also consider if the patient's therapy requires any dose adjustments.
11. Assess biochemical markers annually once disease control is achieved.
12. Routinely assess acromegaly complications, including blood pressure, glucose tolerance, fasting lipid profile, cardiac evaluations (if clinically indicated), colonoscopy, dual-energy x-ray absorptiometry (DEXA) scan (hypogonadal only), evaluation of residual pituitary function, and evaluation of sleep apnea.
13. Provide patient education with regard to disease state and non-drug and drug therapy. Discuss with the patient:
    - Possible complications of acromegaly
    - How to reduce the modifiable cardiovascular and metabolic risk factors
    - Potential disadvantages and effectiveness of existing treatment options
    - Importance of adherence to therapy
    - The potential for adverse effects to occur

Growth Hormone Deficiency

Epidemiology and Etiology

In the United States, GH deficiency affects 50,000 adults, with 6,000 new cases diagnosed annually.[34] Approximately 10,000 to 15,000 children have growth failure owing to GH deficiency. Children may present with GH deficiency at any time during their developmental stages. The evaluation for GH deficiency in a short child should be deferred until appropriate exclusion of other identifiable causes of growth failure, such as hypothyroidism, chronic illness, malnutrition, genetic syndromes, and skeletal disorders.[39] Several medications, such as methoxamine, isoproterenol, glucocorticoids, cimetidine, methylphenidate, and amphetamines, also may induce GH insufficiency.[32]

Pathophysiology

GH deficiency exists when GH is absent or produced in inadequate amounts. GH deficiency may be congenital, acquired, or result from disruption of the hypothalamus-pituitary axis. The diagnosis of GH deficiency remains a clinical challenge because no "gold standard" currently exists. Because GH is frequently undetectable with random sampling, a stimulation or provocative test usually is performed to confirm the diagnosis in both adults and children in whom GH deficiency is suspected. Numerous pharmacologic agents such as insulin-induced hypoglycemia, levodopa, arginine, arginine plus levodopa, arginine plus GHRH, clonidine, and glucagon have been used to stimulate the pituitary to produce GH. However, no single test perfectly predicts GH deficiency or displays 100% sensitivity and specificity.[33] Additionally, administration of each of these tests is associated with adverse effects requiring close medical supervision. Further, current abnormal cutoffs to determine diagnosis are arbitrarily defined and lack universal consensus.[33] With further studies, these diagnostic criteria are likely to evolve and become more accurate.[34]

In children, the diagnosis of GH deficiency is further supported if height is more than two standard deviations (SD) below the population mean (age- and sex-matched).[35] Failure of linear growth is an almost universal presenting feature of childhood GH deficiency.

Childhood GH deficiency may or may not continue into adulthood. Most adults with GH deficiency have overt pituitary disease and present with nonspecific clinical disorders distinct from pediatric GH deficiency, thereby making diagnosis of GH deficiency in adults more difficult than in children. Additionally, adult GH deficiency presumably is associated with increased risk of death from cardiovascular diseases.[34]

Treatment Goals for GH Deficiency

The goal of treatment for GH deficiency is to correct associated clinical symptoms.[34,35] In children, prompt diagnosis and early initiation of treatment are important to maximize final adult height. In adults, efforts should be made to achieve normal physiologic GH levels in an attempt to reverse the metabolic abnormalities associated with increased cardiovascular risks and decreased quality of life.



Clinical Presentation and Diagnosis of GH Deficiency in Children[7,34,35]

General

The patient will have a physical height that is greater than two standard deviations below the population mean for a given age and gender.

Signs

- The patient will present with reduced growth velocity and delayed skeletal maturation.
- Children with GH-deficient or GH-insufficient short stature also may present with abdominal obesity, prominence of the forehead, and immaturity of the face.

Laboratory Tests

- The patient will exhibit a peak GH level of less than 10 ng/mL (10 mcg/L) following a GH stimulation test.
- Reduced IGF-I and IGFBP-3 concentrations also may be present.
- Because GH deficiency may be accompanied by the loss of other pituitary hormones, hypoglycemia and hypothyroidism also may be noted.

Other Diagnostic Tests

- Perform MRI or CT of the hypothalamic-pituitary region to detect structural or developmental anomaly.
- Perform x-ray of left wrist and hand for children over 1 year of age to estimate bone age (knee and ankle for children younger than 1 year of age).

Source: Adapted, with permission, from Heck AM, Yanovski JA, Calis KA. Pituitary Gland Disorders. In: DiPiro JT, Talbert RL, Yee GC, et al. (eds.) *Pharmacotherapy. A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill, 2005: 1407–1423.

Pharmacologic Therapy

Growth Hormone Therapy

❻ *Recombinant GH therapy is the main pharmacologic treatment for GH deficiency in both children and adults.* It promotes skeletal, visceral, and general body growth; stimulates protein anabolism; and affects bone, fat, and mineral metabolism[2] (Table 43–1). GH therapy requires daily subcutaneous or intramuscular administrations. Since two-thirds of GH secretion normally occurs during sleep, it is recommended to administer subcutaneous injections in the evening.[37] Many preparations of synthetic GH are available with a variety of injection devices to make administration more appealing and easier. Protropin® (somatrem) and Tev-Tropin™ (somatropin) are approved by the Food and Drug Administration (FDA) for use in children, whereas other somatropin products such as Nutropin®, Nutropin AQ®, Humatrope®, Norditropin®, Genotropin®, and Saizen® are FDA approved in both children and adults.



Clinical Presentation and Diagnosis of GH Deficiency in Adults[34,36,37]

General

The patient likely will have a history of childhood-onset GH deficiency, hypothalamic or pituitary disorder, or the presence of three or four other pituitary hormone deficiencies caused by head trauma, tumor, infiltrative diseases, surgery, or radiation therapy.

Symptoms

- Reduced strength and exercise capacity
- Defective sweating
- Psychological problems
  - Low self-esteem
  - Depression
  - Fatigue/listlessness
  - Sleep disturbance
  - Anxiety
  - Social isolation
  - Emotional lability and impaired self-control
  - Poor marital and socioeconomic performance

Signs

- Increased fat mass (especially abdominal obesity)
- Reduced lean body mass
- Reduced muscle strength
- Reduced exercise performance
- Thin, dry skin; cool peripheries; poor venous access
- Depressed affect, labile emotions
- Impaired cardiac function

Laboratory Tests

- The patient will exhibit a peak GH level of less than 5 ng/mL (5 mcg/L) following a GH stimulation test.
- Low or low-normal IGF-I level also may be present.
- Increased low-density lipoprotein cholesterol, total cholesterol, triglycerides; decreased high-density lipoprotein cholesterol.
- Reduced bone mineral density associated with an increased risk of fracture.
- Increased insulin resistance and increased prevalence of impaired glucose tolerance.
- GH deficiency may be accompanied by the loss of other pituitary hormones.

❼ *Although comparative trials have not been conducted to date, recombinant GH products appear to have similar efficacy for treating GH deficiency as long as the regimen follows currently approved guidelines.* Adults with GH deficiency often require substantially lower replacement doses (6–25 mcg/kg per day) than prepubertal children (25–50 mcg/kg per day).[38] The conversion of international units (IU or mU) to milligrams is a 3:1 ratio.[34] Selection of an injection device depends on patient preference because there is currently no difference in clinical outcomes among the various injection systems.[38]

Over the last four decades, evidence has suggested that GH treatment in GH-deficient children can increase short-term growth and improve final adult height.[39] Beneficial effects of GH therapy in adults with GH deficiency have been demonstrated in subsequent studies to normalize body composition and metabolic process; improve cardiac risk profile, bone mineral density, quality of life and psychological well-being; and increase muscle strength and exercise capacity.[40,41] Nonetheless, long-term efficacy in improving cardiovascular risks and reducing mortality in adults treated with GH therapy remains to be established.

Begin GH therapy as soon as possible to optimize long-term growth, especially for young children in whom GH deficiency is complicated by fasting hypoglycemia.[35] Selection of the optimal GH replacement dose will need to be individualized depending on response, financial resources, and product availability. Although the appropriate time to discontinue therapy remains controversial in childhood GH deficiency, it is reasonable to continue GH replacement until either the child has reached satisfactory adult height, achieved documented epiphyseal closure, or failed to respond to therapy.[34] Management of the transition between pediatric and adult GH replacement remains a challenge because there are no current data to indicate the correct approach. Starting GH therapy at a low dose and gradually titrating upward may decrease the potential for adverse effects. The need for GH replacement therapy may be lifelong.

Children treated with GH replacement therapy rarely experience significant adverse effects, whereas adults are more susceptible to dose-related adverse effects. Treatment with GH may mask underlying hypothyroidism. GH-induced symptoms, such as edema, arthralgia, myalgia, and carpal tunnel syndrome, are common and necessitate dose reductions in up to 40% of adults. Benign increases in intracranial pressure may occur with GH therapy and generally are reversible with discontinuation of treatment. Often, GH therapy can be restarted with smaller doses without symptom recurrence.

In rapidly growing children, a slipped capital femoral epiphysis may occur when the head of the femur shifts in a backward direction.[38] There is no evidence that this problem is caused by GH therapy, but any child who experiences a change in gait during treatment should be evaluated by an orthopedic surgeon.[38] Treatment with GH may induce insulin resistance and lead to the development of glucose intolerance in patients with preexisting risk factors. Presently, there is no compelling evidence that GH replacement therapy is associated with an increased risk of leukemia, solid tumor, or tumor recurrence.[34,35,37] However, in children with a history of malignancies, it would be prudent to wait for a 1-year tumor-free period (5 years for adults) before initiating GH therapy.[34] Any patients treated for a prior malignancy may be at risk for a second malignancy and should be monitored carefully for tumor recurrence.[34] Other rare findings associated with GH replacement therapy include breast development, pancreatitis, juvenile osteochondritis (inflammation of a bone and its cartilage), worsening of **scoliosis,** and increased pigmentation.[38]



Growth Hormone Deficiency in Children: Patient Care and Monitoring

1. Assess the child's growth characteristics, and compare physical height with a population standard.
2. Obtain a thorough history and physical examination that may indicate the possible presence of GH deficiency. Exclude other identifiable causes of growth failure, such as hypothyroidism, chronic illness, malnutrition, genetic syndromes, and skeletal disorders.
3. Perform imaging tests of the hypothalamic-pituitary region to detect structural or developmental anomalies. Perform x-ray to estimate bone age.
4. Perform a provocative test to measure GH, IGF-I, and/or IGFBP-3 levels.
5. Initiate GH replacement therapy based on patient preference. Make sure that the child does not have any contraindications to GH therapy.
6. Develop a formal plan to assess response (increase in height and change in height velocity) and adverse effects of GH replacement therapy. Make dosage adjustments when appropriate.
7. May continue GH replacement therapy until a child reaches satisfactory adult height, achieves documented epiphyseal closure, or fails to respond to treatment.
8. Review and retest the child using adult GH deficiency diagnostic criteria once the child reaches final adult height.
9. Provide patient education in regard to disease state and drug therapy. Discuss with the child and parents:
   - GH deficiency
   - Potential disadvantages and effectiveness of existing GH replacement therapy
   - Importance of adherence to therapy
   - Potential for adverse effects or need for lifelong replacement

Insulin-Like Growth Factor I Therapy

Mecasermin rinfibate (Iplex™ and Increlex™) is the only recombinant once-daily IGF-I replacement therapy for the treatment of growth failure in children with severe primary IGF-I deficiency or with GH gene deletions who have developed neutralizing antibodies to GH. This product has not been evaluated in patients with GH deficiency aside from the genetic abnormalities.

Outcome Evaluation

- Children with GH deficiency should be evaluated by a pediatric endocrinologist every 3 to 6 months. Monitor for an increase in height and change in height velocity to assess response to GH therapy.[35] Every effort should be made to maximize height before the onset of puberty. Once final adult height is reached and GH is discontinued for at least 1 month, retest and reevaluate the patient using the adult GH-deficiency diagnostic criteria.[35]
- Assess patients with scoliosis for further curvature of the spine.
- Although GH and IGF-I levels do not always correlate with growth response, measure IGF-I levels yearly to assess adherence to therapy and patient response. If the IGF-I levels are substantially above the normal range 2 years after GH replacement therapy, the dose should be reduced.[38] IGF-I level may be used as a guide to gradually reduce replacement dose after epiphyseal closure.
- Routine monitoring of fasting lipid profile, bone mineral density, and body composition in children is not typically required during GH replacement but should be done before and after discontinuation of therapy.[35]
- In adults, measurement of serum IGF-I, along with careful clinical evaluation, appears to be the most reliable way to assess the appropriateness of the GH dose.
- Continuously monitor for dose-related adverse effects such as edema, arthralgia, myalgia, and carpal tunnel syndrome.
- Assess patient's body composition, psychological well-being, fasting lipid profile, bone mineral density, and metabolic status.
- Patients with a history of cancer or those at risk for malignancy should be monitored closely.
- Measure a free thyroxine serum concentration at baseline and at 6- to 12-month intervals thereafter.[34]
- Measure blood glucose levels at baseline and every 3 months to assess for glucose intolerance and insulin resistance. Periodic measurement of glycosylated hemoglobin (HbA_{1c}) also may be useful.[34]



Growth Hormone Deficiency in Adults: Patient Care and Monitoring

1. Assess patient's clinical signs and symptoms to determine severity of GH deficiency.
2. Perform a provocative test to measure GH and IGF-I levels.
3. Evaluate the patient for the presence of metabolic abnormalities and cardiovascular and fracture risks.
4. Initiate GH replacement therapy based on patient preference. Make sure that the patient does not have any contraindications to GH therapy.
5. Develop a plan to assess the efficacy and adverse effects of GH therapy, and consider if the patient's therapy requires any dose adjustments based on IGF-I level, patient response, and adverse effects.
6. Provide patient education in regard to disease state and drug therapy. Discuss with the patient:
   - Possible complications of GH deficiency
   - How to reduce the modifiable cardiovascular and metabolic risk factors
   - Potential disadvantages and effectiveness of existing GH replacement therapy
   - Importance of adherence to therapy
   - Potential for adverse effects or need for lifelong replacement

PROLACTIN

Prolactin is an essential hormone for normal production of breast milk following childbirth. It also plays a pivotal role in a variety of reproductive functions. Prolactin is regulated primarily by the hypothalamus-pituitary axis and secreted solely by the lactotroph cells of the anterior pituitary gland. Under normal conditions, secretion of prolactin is predominantly under inhibitory control by dopamine and acts on the D_2 receptors located on the lactotroph cells. Increase of hypothalamic thyrotropin-releasing hormone (TRH) in primary hypothyroidism can stimulate the release of prolactin.

Hyperprolactinemia

Epidemiology and Etiology

Hyperprolactinemia commonly affects women of reproductive age more than men. Although this disorder occurs in less than 1% of the general population, the estimated prevalence in women with reproductive disorders (e.g., amenorrhea) is as high as 9% to 17%.[43] Numerous etiologies of hyperprolactinemia are presented in Table 43–5.[43,44] Any medications that block dopamine or increase the release of dopamine can induce hyperprolactinemia[7,32,43,45] (Table 43–6). Therefore, it is important to exclude medication-induced hyperprolactinemia from other common causes such as pregnancy, primary hypothyroidism, benign prolactin-secreting pituitary adenoma (prolactinoma), and renal insufficiency. Prolactinomas are the most common pituitary tumors. They are classified as microprolactinomas if they are less than 10 mm in diameter and as macroprolactinomas if they are 10 mm or greater in diameter.[46] In general, microprolactinomas rarely increase in size, whereas macroprolactinomas have the potential to enlarge and invade the surrounding tissues.[46]

TABLE 43–5. Causes of Hyperprolactinemia[43,44]

Physiologic Causes
Pregnancy
Stress (including exercise and hypoglycemia)
Orgasm
Sleep
Meal
Increased Prolactin Production
Ovarian: polycystic ovarian syndrome
Pituitary tumors:
Adenomas
Microprolactinoma (less than 10 mm diameter)
Macroprolactinoma (greater than or equal to 10 mm diameter)
Hypothalamic stalk interruption (prevent dopamine from reaching the pituitary)
Hypophysitis (inflammation)
Ectopic tumors
Hypothalamic Prolactin Stimulation
Primary hypothyroidism
Adrenal insufficiency
Reduced Prolactin Elimination
Chronic renal failure
Hepatic cirrhosis
Neurogenic Causes
Breast stimulation
Breast-feeding
Chest-wall injury (e.g., surgery, herpes zoster)
Abnormal Molecules
Macroprolactinemia
Medications (Table 43–6)[7,32,43,45]
Seizures
Idiopathic (Unknown)

TABLE 43–6. Medication-Induced Hyperprolactinemia[7,32,43,45]

Dopamine Antagonists
Antipsychotics[a]
Phenothiazines
Metoclopramide
Domperidone
Dopamine-Depleting Agents
Reserpine
α-Methyldopa
Prolactin Stimulators
Serotonin reuptake inhibitors (SSRIs)
Dexfenfluramine
Estrogens
Progestins
Antiandrogens
Gonadotropin-releasing hormone analogs
Benzodiazepines
Tricyclic antidepressants (TCAs)
Monoamine oxidase inhibitors (MAOIs)
Protease inhibitors
Histamine$_2$ receptor antagonists
Other
Isoniazid
Cocaine
Opioids
Verapamil

[a]Atypicals (olanzapine and clozapine) other than risperidone may cause an early but transient elevation in prolactin.[32]
Adapted, with permission, from McGraw-Hill Companies.

Pathophysiology

Hyperprolactinemia is a condition of elevated serum prolactin.[43] It is the most common endocrine disorder of the hypothalamic-pituitary axis. High prolactin levels inhibit the release of gonadotropin-releasing hormone (GnRH) by the hypothalamus and subsequently suppress secretion of LH and FSH from the anterior pituitary. High prolactin levels result in reduced gonadal hormone levels, often leading to reproductive dysfunction and **galactorrhea** (inappropriate breast milk production).

In combination with clinical symptoms, at least three repeated measures of serum prolactin levels greater than 20 ng/mL (20 mcg/L) are needed to confirm the diagnosis because prolactin,



Clinical Presentation and Diagnosis of Hyperprolactinemia[7,43,44]

General

Hyperprolactinemia most commonly affects women of reproductive age and is very rare in men.

Signs and Symptoms

Pre-menopausal women

- Headache and compromised or loss of vision caused by the prolactin-secreting tumor and its close proximity to the optic structures.
- Clinical presentation is associated with the degree of prolactin elevation:
  - Prolactin greater than 100 ng/mL (100 mcg/L): hypogonadism, galactorrhea, and amenorrhea
  - Prolactin 51 to 75 ng/mL (51–75 mcg/L): **oligomenorrhea** (infrequent menstruation).
  - Prolactin 31 to 50 ng/mL (31–50 mcg/L): decreased libido and infertility.
  - Increased body weight may be associated with prolactin-secreting pituitary tumor.
  - The degree of hypogonadism generally is proportionate to the degree of prolactin elevation.
  - Excessive hair growth (**hirsutism**) and acne also may be present owing to relative androgen excess compared with low estrogen levels.

Men

- Decreased libido, decreased energy, erectile dysfunction, impotence, decreased sperm production, infertility, gynecomastia, and rarely, galactorrhea.
- Impotence is unresponsive to treatment and is associated with reduced muscle mass, loss of pubic hair, and osteoporosis.

Laboratory Tests

- Prolactin serum concentrations at rest will be greater than 20 ng/mL (20 mcg/L) in men or 25 ng/mL (25 mcg/L) in women with at least three measurements.
- Obtain β-human chorionic gonadotropin (β-hCG) level to exclude pregnancy.
- Obtain TSH level to exclude primary hypothyroidism.
- Obtain blood urea nitrogen and serum creatinine tests to exclude renal failure.

Other Diagnostic Tests

- Perform MRI to locate the tumor, exclude a pseudoprolactinoma, and validate the diagnosis.
- Consider a bone mineral density test in patients with long-term hypogonadism.

Additional Clinical Sequelae

- The prolonged suppression of estrogen in pre-menopausal women with hyperprolactinemia leads to decreases in bone mineral density and significant risk for the development of osteoporosis.
- Risk for ischemic heart disease may be increased with untreated hyperprolactinemia.

Source: Adapted, with permission, from Heck AM, Yanovski JA, Calis KA. Pituitary Gland Disorders. In: Dipiro JT, Talbert RL, Yee GC, et al (eds.) *Pharmacotherapy. A Pathophysiologic Approach.* 6th ed. New York: McGraw Hill; 2005: 1407–1423.

similar to GH, is released in a pulsatile manner. To make an accurate diagnosis, obtain the prolactin measurements in a fasting state, before breast stimulation, and at rest. If an intravenous line is present or planned, it is prudent to wait at least 2 hours after line insertion before measuring serum prolactin to decrease detecting transient physiologic increases in prolactin level[43,44] (Table 43–5). Medication-induced hyperprolactinemia typically is associated with prolactin levels of less than 150 ng/mL (150 mcg/L), whereas prolactin levels greater than 250 ng/mL (250 mcg/L) are almost always associated with macroprolactinoma.[46]

Treatment Goals for Hyperprolactinemia

Because hyperprolactinemia is often associated with hypogonadism, the goals for management of hyperprolactinemia are to restore the clinical consequences of hypogonadism and reduce its associated risk for osteoporosis[44] (Table 43–7).

TABLE 43–7. Goals for Management of Hyperprolactinemia[44]

1. Normalize prolactin level
2. Improve clinical symptoms
3. Restore normal fertility
4. Restore and maintain normal gonadal function
5. Protect against development of osteoporosis
6. Prevent disease recurrence

If a pituitary tumor is present:

- Ablate or reduce tumor size to relieve tumor mass effect.
- Preserve normal pituitary function.
- Prevent progression of pituitary tumor or hypothalamic disease.

General Approaches to Treatment

Management of drug-induced hyperprolactinemia is to discontinue the offending agent, if possible, and start an appropriate therapeutic alternative. In situations where the offending agent cannot be discontinued, cautious use of hormone replacement, biphosphonate therapy, and/or dopamine agonists may be considered depending on the patient's clinical circumstances.[45] Treatment options for the management of hyperprolactinemia include (1) clinical observation, (2) pharmacologic therapy with dopamine agonists, (3) transsphenoidal pituitary adenomectomy, and (4) radiation therapy. Figure 43–4 demonstrates the approach to management of hyperprolactinemia.[44] Clinical observation and close monitoring are justifiable in patients with asymptomatic elevation of prolactin.[43] ❽ *Dopamine agonists are the first-line treatment of choice for all patients with hyperprolactinemia; transsphenoidal surgery and radiation therapy are reserved for patients who are resistant to or severely intolerant of pharmacologic therapy.*[43,47,48]

Pharmacologic Therapy

Dopamine is the principal neurotransmitter responsible for the inhibition of prolactin secretion from the anterior pituitary. Thus, dopamine agonists are the main pharmacologic therapy used for management of hyperprolactinemia.[47] Treatment with dopamine agonists has proven to be extremely effective in normalizing serum prolactin level, restoring gonadal function, decreasing tumor size, and improving visual fields.[47] Patients with macroprolactinomas generally require a higher dose to normalize prolactin levels compared with patients with microprolactinomas.[46]

Three dopamine agonists are used for the management of hyperprolactinemia, bromocriptine, cabergoline, and pergolide[47] (Table 43–8). Because these three dopamine agonists are ergot derivatives, they are contraindicated in combination with potent cytochrome P-450 subfamily IIIA polypeptide 4 (CYP3A4) inhibitors, including protease inhibitors (e.g., ritonavir and indinavir), azole antifungals (e.g., ketoconazole and itraconazole), and some macrolide antibiotics (e.g., erythromycin and clarithromycin). Furthermore, ergot derivatives can cause constriction of peripheral and cranial blood vessels. These medications are also contraindicated in patients with uncontrolled hypertension, severe ischemic heart disease, or peripheral vascular disorders. Caution should be exercised with concomitant use of other ergot derivates and in patients with impaired renal or hepatic function, dementia, concurrent antihypertensive therapy, or a history of psychosis, peptic ulcer disease, or cardiovascular disease.



Patient Encounter 2: The Medical History, Physical Examination, and Diagnostic Tests

WB, a 27-year-old woman, presents to the Women's Health Clinic. Her chief complaint is milky fluid discharge from both breasts. WB also mentions that her menstrual periods have stopped since she stopped taking her oral contraceptive 8 months ago with the hope of conceiving. Her menstrual cycle was regular before starting the oral contraceptive. WB has no recent weight change, excessive hair growth, or acne. She does not exercise excessively and is otherwise healthy.

PMH
None

FM
Both parents are still alive and healthy.

SH
Married, a high school teacher, and physically active (walks 3 miles twice a week)

Meds
NuvaRing® use as directed (discontinued 8 months ago)
Acetaminophen 325 mg 2 tablets every 4 to 6 hours as needed for mild headaches

ROS
Ophthalmic examination reveals normal visual acuity and fields.

PE
HEENT: (–) goiter
VS: 100/62 mm Hg, P 82 beats per minute, RR 18 breaths/minute, T 37.1°C (98.8°F)
CV: RRR, normal S_1, S_2; no murmurs, rubs, or gallops
Breasts: (+) bilateral expressible galactorrhea with no other abnormality
Abd: Soft, non-tender, non-distended; (+) bowel sounds; no hepatosplenomegaly; heme (–) stool

Labs
Electrolytes, renal and thyroid function, FSH, LH, and testosterone are within normal limits. Elevated prolactin at 115 ng/mL (115 mcg/L). Pregnancy test is negative.

MRI
Reveals a pituitary tumor approximately 9 mm in diameter.

- Given this information, what signs and symptoms does WB have for hyperprolactinemia?
- Identify your treatment goals for WB.
- What nonpharmacologic and pharmacologic treatment options are available for WB?

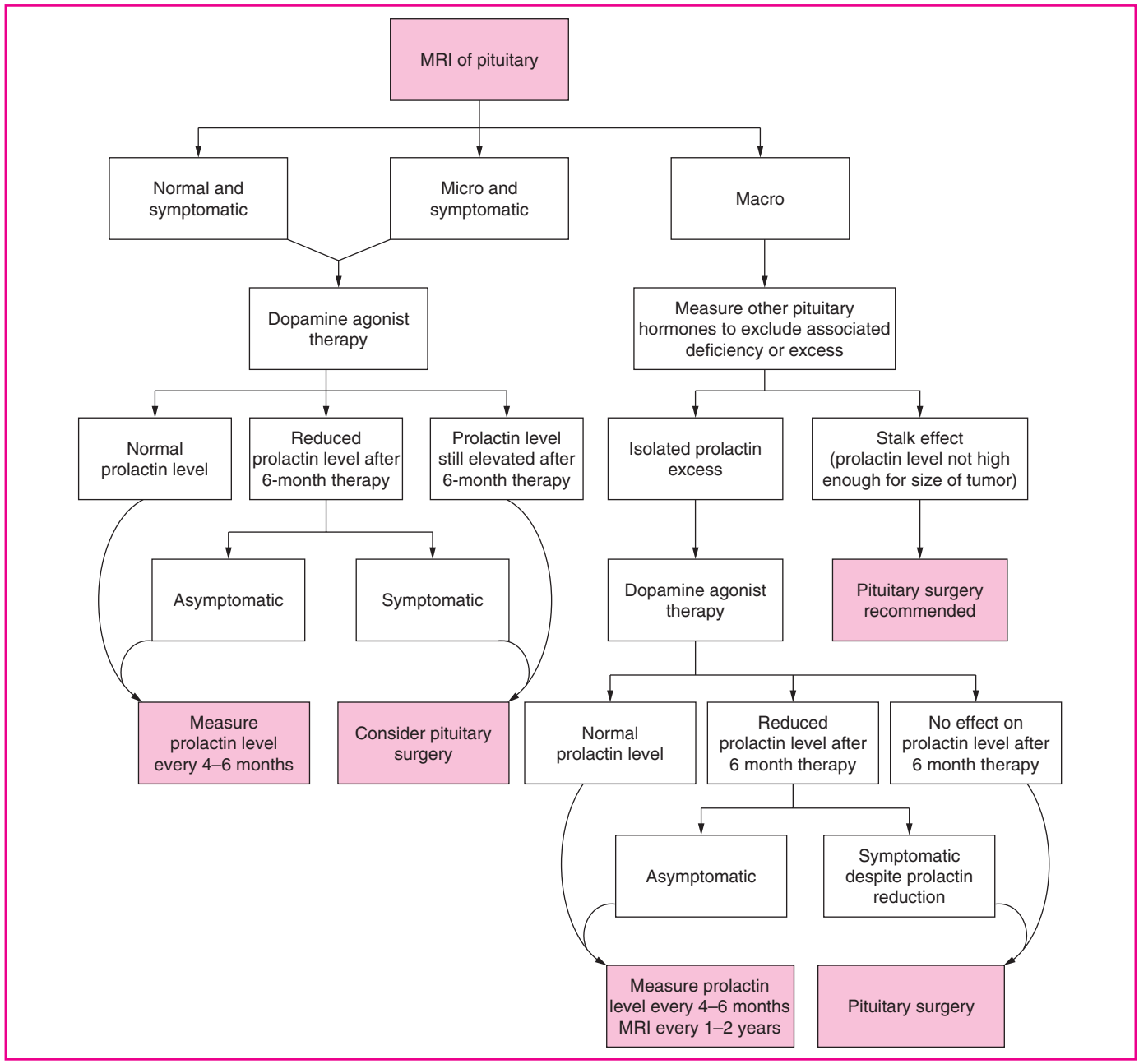


FIGURE 43–4. Approach to management of hyperprolactinemia.[44] MRI = magnetic resonance imaging. (Reprinted, with permission, from Serri O, Chik CL, Ezzat S. Diagnosis and management of hyperprolactinemia. Can Med Assoc J 2003; 169(9): 575–581. © 2003 by CMA Media, Inc.)

Bromocriptine

Bromocriptine directly binds to the D_2 receptors on the lactotroph cells to exert its effect. Bromocriptine normalizes prolactin level, restores menstrual cycles, and reduces tumor size in approximately 90% of patients.[49] Adverse effects such as nausea, dizziness, and orthostatic hypotension often limit 5% to 10% of patients from continuing treatment. Thus, start bromocriptine at a low dose (e.g., 0.625–1.25 mg) at bedtime (taken with a snack) to decrease adverse effects. Slowly titrate up to the optimal therapeutic dose (2.5–15 mg/day) because most adverse effects subside with continual treatment.[46] If the adverse GI effects are not tolerable, bromocriptine can be administered vaginally at a reduced dose (2.5 mg/day).[47] Owing to its short half-life of only 6 hours, bromocriptine must be administered in divided doses, which may compromise patient adherence.

TABLE 43–8. Comparison of Dopamine Agonists for Treatment of Hyperprolactemia[47]

Generic Name (Brand)	Starting Dose	Titrating Dose	Usually Effective Dose	Maximal Dose	Dosing Frequency	Adverse Effects	Cost
Bromocriptine (Parlodel®)	0.625–1.25 mg/day at bedtime	1.25 mg increments at 1-week interval	2.5–15 mg/day	40 mg/day	2 to 3 divided doses per day	Dizziness, headache, syncope, nausea, vomiting, GI cramps, orthostatic hypotension	$$
Cabergoline (Dostinex®)	0.5 mg/week or 0.25 mg twice/week	0.5 mg increment at 4-week intervals	1–2 mg/week	4.5 mg/week	Once or twice weekly	Similar but orthostatic hypotension less common	$$$
Pergolide[a] (Permax®)	25 mcg/day at bedtime	25 mcg increment at 1-week interval	50 mcg/day at bedtime	100 mcg/day	Once daily	Similar but somnolence and hypotension more common	$

[a]Withdrawn from United States market in 2007.
GI, gastrointestinal; $, relatively inexpensive; $$, moderately expensive; $$$, more expensive.

Cabergoline

Cabergoline was developed with a higher affinity for dopamine D_2 receptors than bromocriptine. It is a long-acting dopamine agonist capable of inhibiting pituitary prolactin secretion for at least 7 days after a single oral dose.[47] The prolonged duration of action allows for once- or twice-weekly administration. Adverse effects of cabergoline appear to be significantly better tolerated than those of bromocriptine.[47] However, transient elevations of serum alkaline phosphatase, bilirubin, and aminotransferases have been reported in a few patients treated with cabergoline. Cabergoline is also more effective in normalizing prolactin levels and restoring menses than bromocriptine.[47] It also may be effective in treating hyperprolactinemia in patients who are resistant or intolerant to bromocriptine and in men and women with micro- and macroprolactinomas.[47,50] Given the favorable safety, efficacy, and administration profile of cabergoline, it has replaced bromocriptine as first-line treatment for the management of hyperprolactinemia.

Pergolide

Pergolide is a dopamine agonist with affinity for D_1 and D_2 receptors. It is 10 to 1000 times more potent than bromocriptine on a milligram-per-milligram basis. This agent has a duration of action longer than 24 hours and offers the advantage of once-daily administration. Trials outside the United States have demonstrated pergolide to be as safe and effective as bromocriptine for lowering prolactin level and reducing tumor size.[47] Because pergolide has been associated with daytime sedation, carefully advise patients to use caution in performing activities that require alertness. Monitor and report daytime sedation or any episodes of falling asleep while engaged in the activities of daily living. In 2007, pergolide was withdrawn from the United States market due to reports of serious heart valve damage in patients receiving the drug for Parkinson's disease.

Nonpharmacologic Therapy

In a small number of patients who have failed or are intolerant of dopamine agonists, transsphenoidal adenomectomy may be necessary. Surgical treatment is also considered in patients with non-prolactin-secreting tumors or macroprolactinomas that jeopardize the optic chiasm.[43] Nonetheless, surgical intervention does not reliably lead to long-term cure and may cause permanent complications.[44] Radiation therapy is reserved for failures of both pharmacologic therapy and surgery.[48] However, normalization of prolactin levels with radiation therapy may take 10 years to show full benefit, and radiation-induced hypopituitarism may require lifelong hormone replacement.

Management of Hyperprolactinemia in Pregnancy

Most women with hyperprolactinemia require dopamine agonist therapy to achieve regular ovulatory cycles and pregnancy. Since restoration of the ovulatory cycle may occur within 1 week of initiating therapy, caution patients regarding their potential to become pregnant.[51]

Overall, there is reassuring worldwide experience that bromocriptine use during pregnancy does not increase fetal malformations, spontaneous miscarriage, ectopic pregnancy, or multiple births.[47,48] Furthermore, no teratogenic effects have been reported in women who received cabergoline during the

first and second trimesters of pregnancy.[47] Despite these data, ❾ *women who become pregnant while on a dopamine agonist should discontinue treatment immediately to minimize fetal exposure. Because cabergoline has a prolonged half-life, women who plan to become pregnant should discontinue the drug at least 1 month before planned conception.*[47,48]

Microadenomas rarely cause complications during pregnancy. However, untreated macroprolactinomas carry about 15% to 35% risk of tumor enlargement and potentially can jeopardize vision.[46] Therefore, monitor women with macroprolactinomas closely for the development of headache and visual impairments. Baseline and routine visual field examinations are essential. Evidence of abnormal visual fields may indicate tumor growth and should be followed by an MRI. Should tumors enlarge, bromocriptine is the preferred choice over cabergoline because of greater experience with this drug during pregnancy.[51]

Outcome Evaluation

- Assess patients for tolerability to dopamine agonists.
- Monitor clinical symptoms associated with hyperprolactinemia every month for the first 3 months to assess therapeutic efficacy and assist with dose titration.
- Evaluate the patient for symptoms, such as headache, visual disturbances, menstrual cycles in women, and sexual function in men, to assess clinical response to therapy.
- Once the prolactin level is normalized and clinical symptoms of hyperprolactinemia have resolved, monitor prolactin level every 6 to 12 months.[43,44,46]
- Evaluate pregnant patients every 2 months.[44]
- If the prolactin level is well controlled with dopamine agonist therapy for 2 to 3 years, gradually taper therapy to the lowest effective dose. Check prolactin levels after each dose reduction.[46]
- If the prolactin levels remain unchanged for 1 year at the reduced dose, dopamine agonist therapy may be discontinued.
- It is essential to monitor prolactin levels every 6 months or annually to detect the possibility of permanent remission of pituitary disease.[43,44]
- The need to continue dopamine agonists in postmenopausal women must be reassessed because these patients have a higher probability of maintaining normal prolactin levels after treatment is discontinued.[52]
- In patients with macroprolactinomas, monitor visual field at baseline and repeat the test 1 month after initiation of a dopamine agonist.
- Repeat the MRI 6 months after initiating therapy or if an increase in symptoms or rise in prolactin levels suggests the presence of tumor growth.[43,46]
- Discontinuation of therapy in patients with macroprolactinomas usually leads to tumor regrowth and recurrence of hyperprolactinemia. This decision warrants careful consideration.



Hyperprolactinemia: Patient Care and Monitoring

1. Assess patient's clinical signs and symptoms of hyperprolactinemia.
2. Review the available diagnostic data to determine severity and exclude other common causes of hyperprolactinemia.
3. Obtain a thorough medication history to exclude medication-induced hyperprolactinemia.
4. Determine patient's plan regarding pregnancy because this influences treatment.
5. Educate patient about safety and efficacy of dopamine agonists. Make sure that the patient does not have any contraindications or allergies to drug therapies.
6. Develop a formal plan to assess response and adverse effects of dopamine agonists. When appropriate, be sure to make dose adjustments.
7. If the prolactin level remains normal for 2 years, reassess the need to continue treatment. Make sure that the patient is taking the lowest effective dose for management of hyperprolactinemia.
8. Provide patient education in regard to disease state and non-drug and drug therapy. Discuss with the patient:
   - Risk factors associated with hyperprolactinemia
   - Potential disadvantages and effectiveness of existing dopamine agonist therapy
   - Potential disadvantages and effectiveness of surgery and radiation treatment
   - Importance of adherence to therapy
   - Potential for adverse effects or long-term complications

ABBREVIATIONS

AACE:	American Association of Clinical Endocrinologists
ACTH:	adrenocorticotropic hormone or corticotropin
ADH:	antidiuretic hormone
β-hCG:	β-human chorionic gonadotropin
CRH:	corticotropin-releasing hormone
CT:	computed tomography
CYP3A4:	cytochrome P-450 subfamily IIIA polypeptide 4
DEXA:	dual energy x-ray absorptiometry
ECG:	electrocardiogram
FDA:	Food and Drug Administration
FSH:	follicle-stimulating hormone
GABA:	γ-aminobutyric acid
GH:	growth hormone or somatotropin
GHIH:	growth hormone-inhibiting hormone or somatostatin
GHRH:	growth hormone-releasing hormone
GI:	gastrointestinal
GnRH:	gonadotropin-releasing hormone
HbA_{1c}:	glycosylated hemoglobin A_{1c}
IGF:	insulin-like growth factor

IGFBP-3: insulin-like growth factor binding protein 3
IGFBPs: insulin-like growth factor binding proteins
IGF-I: insulin-like growth factor I
IGF-II: insulin-like growth factor II
IM: intramuscularly
LAR: long-acting release
LH: luteinizing hormone
LHRH: luteinizing hormone–releasing hormone
MAOI: monoamine oxidase inhibitor
MRI: magnetic resonance imaging
MSH: melanocyte-stimulating hormone
OGTT: oral glucose tolerance test
PIH: prolactin-inhibiting hormone
PRH: prolactin-releasing hormone
PRL: prolactin
SD: standard deviation
SQ: subcutaneously
SSRI: selective serotonin reuptake inhibitor
T_3: triiodothyronine
T_4: thyroxine
TCA: tricyclic antidepressant
TRH: thyrotropin-releasing hormone
TSH: thyroid-stimulating hormone or thyrotropin

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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44 Pregnancy and Lactation: Therapeutic Considerations

Deborah Sturpe and Kari Alperovitz-Bichell



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Identify the stages of fetal development when birth defects are most likely to occur.
2. Describe hormonal regulation of lactation.
3. Determine trimesters and a due date for a pregnancy based on the last menstrual period.
4. List routine pregnancy care and screenings that should be provided for women with uncomplicated pregnancies.
5. Discuss characteristics that affect drug transfer across the placental barrier and into breast milk.
6. Discuss general methods by which teratogenic risk and drug exposure during pregnancy and lactation can be minimized.
7. Identify drugs whose use should be strictly avoided in pregnancy or lactation.
8. Recommend nonpharmacologic therapy for the following disorders when they occur during pregnancy or lactation: nausea and vomiting, constipation, heartburn, pain, and cough and cold.
9. Recommend an appropriate dose and formulation of folic acid to a woman desiring to become pregnant.
10. Recommend a pharmacotherapy regimen that is likely to minimize risk to the fetus or baby for the following disorders that are commonly experienced during pregnancy: nausea and vomiting, constipation, hemorrhoids, heartburn, pain, and upper respiratory symptoms.
11. Recommend a pharmacotherapy regimen for asymptomatic bacteriuria in a pregnant female that is likely to be safe and effective.
12. Recommend treatment (including drug selection, dosing, monitoring, and alternative treatments) for bacterial vaginosis, vulvovaginal candidiasis, and sexually transmitted diseases in a pregnant female based on guidelines from the Centers for Disease Control and Prevention.
13. Recommend a pharmacotherapy regimen for preterm labor that will prolong time to delivery and enhance fetal lung development while minimizing maternal side effects.
14. Recommend treatment (including drug selection, dosing, monitoring, and alternative treatments) for group B *Streptococcus* based on guidelines of the Centers for Disease Control and Prevention.
15. Recommend treatment (including drug selection, dosing, monitoring, and alternative treatments) for induction of labor.
16. Recommend a pharmacotherapy regimen that is likely to minimize risk to the infant for the following disorders experienced during lactation: acute mastitis, nipple candidiasis, and insufficient milk production.

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Key Concepts

❶ Although the risk of drug-induced teratogenicity is of concern, actual risk of birth defects from most drug exposures is small. Choose agents with the longest safety record in pregnancy or lactation first.
❷ The critical time for organogenesis is during the first eight weeks of pregnancy; thus, the risk for birth defects is highest during the first trimester.
❸ While unnecessary medication clearly should be avoided during pregnancy or lactation, clinicians also should avoid undertreating conditions that can lead to adverse maternal, fetal, or neonatal outcomes.
❹ Treat most benign pregnancy conditions with nonpharmacologic therapy prior to using drug therapy.
❺ Advise most women of childbearing potential to take a multivitamin containing 400 mcg folic acid.

Clinicians often must weigh the risks and benefits of drug therapy during pregnancy or lactation. Owing to fear of adverse effects on the developing fetus or newborn infant, a common solution is avoidance of therapy. However, many chronic medical conditions, acute medical conditions, and pregnancy- and lactation-related disorders necessitate therapy to preserve the health of the mother or the baby. Since few prospective clinical trials enroll pregnant or lactating women, clinicians must make decisions based largely on case reports and surveillance data. This chapter discusses available resources that help to guide therapy choices, general strategies that reduce risks of drug use in this population, and specific treatment recommendations for some conditions commonly experienced during pregnancy and lactation.

EPIDEMIOLOGY AND ETIOLOGY

Medication use in pregnancy is a common phenomenon. In North America, up to 50% of pregnancies are unplanned,[1] and up to 82% of women of childbearing age use a medication on a routine basis.[2] Consequently, many women unknowingly expose the fetus to a medication before discovering the pregnancy. Some pregnant women may be unaware of their condition and will continue use of medications for acute and chronic conditions. Overall, up to 86% of women are reported to use some type of prescription medication during pregnancy at an average of 2.9 medications per patient.[3]

Based on these usage patterns, it may be inevitable that some drugs will act as **teratogens**. ❶ *But actual risk of birth defects from most drug exposures is small. Congenital defects are found in approximately 5% of all live births, but only 10% of these events are due to external factors (e.g., chemical, physical, or biologic).*[4] *Of this 10%, only 1% is estimated to be due to medication use.*[4] Despite this low risk, many women unnecessarily terminate pregnancies due to fear of drug-induced malformations.[1]

There are fewer data on the frequency of medication use during lactation. Use does appear to be common. A recent Dutch study reported that 53% of all breast-feeding mothers had taken a medication, herb, or supplement (exclusive of iron, vitamins, and homeopathic remedies).[5] Furthermore, more women in the United States are now abiding by the recommendation to breast-feed. It is now estimated that up to 50% of United States women breast-feed for at least a short time.[6]

PATHOPHYSIOLOGY

Teratogenic risk is determined largely by timing of drug exposure. Establishment of full implantation of the fertilized egg takes 1 to 2 weeks. Thus, negative effects of drug exposure during this time typically result in spontaneous abortion.[3,7] ❷ *The critical time for organogenesis is during the first 8 weeks of pregnancy; thus, the risk for birth defects is highest during the first trimester*[3,7] (Fig. 44–1). After 8 weeks, most teratogenic effects are related to **fetal growth restriction** or functional deficits such as mental retardation.[3]

Multiple physical and hormonal changes take place during pregnancy that may cause related problems. Anemia is common due to a 30% to 50% increase in plasma volume with a disproportionate increase in red blood cell mass.[3] Increased levels of progesterone slow gastrointestinal motility, relax esophageal sphincter pressure, and increase mucosal edema.[8] This leads to constipation, heartburn, and rhinitis. Increased venous pressure and constipation often result in hemorrhoids.[9] ***Human chorionic gonadotropin*** produced by the placenta is thought to induce nausea and vomiting of pregnancy (commonly termed *morning sickness*).[10] Increasing abdominal girth and posture changes commonly cause back pain.[11] ❸ *Finally, preterm labor and fetal growth restriction often are caused by infection during pregnancy (e.g., chlamydia, bacterial vaginosis, and bacteriuria) or untreated maternal chronic disease (e.g., diabetes mellitus).*

After birth, a rapid drop in progesterone level initially triggers lactation through reversal of inhibitory effects on prolactin (Fig. 44–2). Nipple stimulation then enables lactation to continue once established. During lactation, ineffective removal of milk from the breast, trauma, and skin breaks may lead to problems such as milk stasis, nipple pain, and mastitis.[12] Additionally, some women have difficultly initiating lactation due to improper technique and/or activity of inhibitors such as dopamine (Fig. 44–2).

TREATMENT

Desired Outcomes

The primary goal for drug use during pregnancy and lactation is to treat maternal or fetal conditions as necessary while minimizing risk to the developing fetus or neonate. Numerous situations may necessitate drug therapy, including maternal

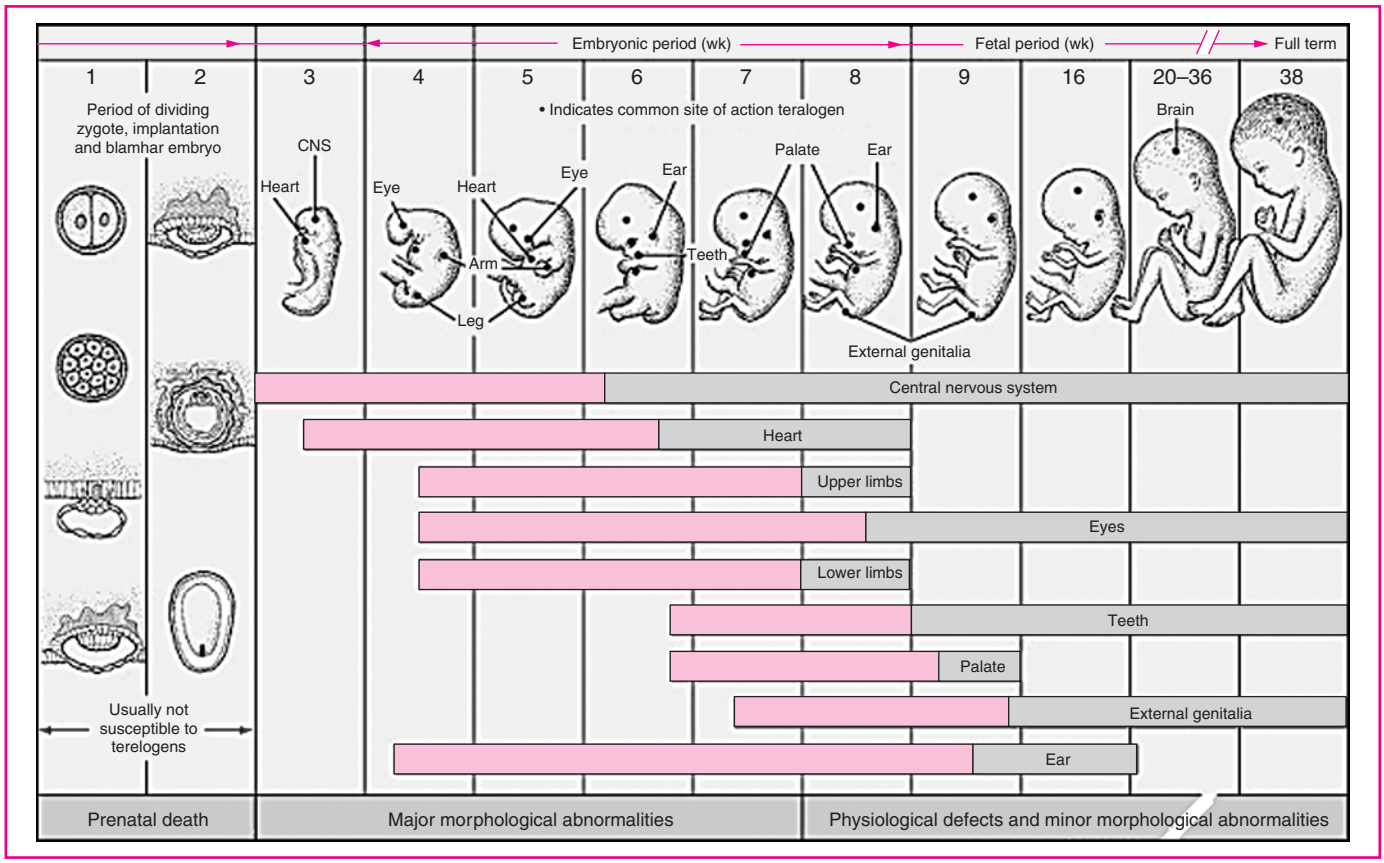


FIGURE 44–1. Embryonic development. (Reprinted, with permission, from Moore KL, *The Developing Human*. New York: Elsevier, 1874; p 96; copyright 1974.) The horizontal bars represent potential sensitivity to teratogens. The pink areas represent the more critical times.

chronic disease, symptomatic conditions associated with pregnancy or lactation, and conditions associated with adverse fetal or neonatal outcomes.

General Approach to Treatment

Sources of Information for Drug Use during Pregnancy or Lactation

The Food and Drug Administration (FDA) pregnancy labeling system is the most commonly used source for information regarding safety of drug use during pregnancy (Table 44–1). This system has several faults that include lack of data regarding drug use in lactation, reliance on animal studies for categorization, and lack of consideration for altered maternal pharmacokinetics and timing of exposure.[13] Furthermore, many older drugs have no FDA pregnancy category, and categorization may not be updated when new data prove that a medication is safer than originally believed. Consequently, the FDA pregnancy labeling system is currently under review.

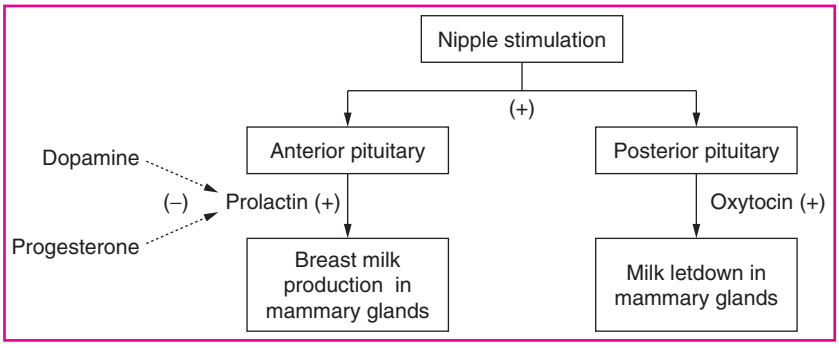


FIGURE 44–2. A simplistic schematic of the hormonal control of lactation. During pregnancy, high levels of progesterone block the effect of prolactin. After delivery, nipple stimulation enhances prolactin and oxytocin release from the pituitary gland, allowing for milk production and letdown in the mammary glands. Data from references 48 and 50.



Clinical Presentation and Diagnosis

Confirmation of Pregnancy

Positive urine human chorionic gonadotropin followed by positive ultrasound, fetal heart sounds, and/or fetal movement.

Pregnancy Dating and Gestational Age

Calculated from the first day of the last menstrual period. Due dates typically are estimated at 40 weeks' gestation; however, infants delivered at between 38 and 42 weeks are considered full term.

Pregnancy Symptoms

First trimester: Menstrual spotting, missed menses, fatigue, breast tenderness, increased urination, mood swings, nausea/vomiting, headache, heartburn, constipation
Second trimester: Frequent urination, heartburn, constipation, dry skin, edema, **linea nigra, melasma**
Third trimester: Backache, edema, shortness of breath

Routine Pregnancy Visits

In a normal, uncomplicated pregnancy, visits should occur monthly until 28 weeks' gestation, every 2 to 3 weeks from 28 to 36 weeks' gestation, and then weekly until birth. Examination for each of the following is performed at each visit:

- Blood pressure
- Weight
- Urine for protein and glucose
- Uterine size
- Fetal heart rate
- Fetal movement

Routine Lab Testing for Normal Pregnancies (First Trimester Unless Otherwise Indicated)

- Human immunodeficiency virus
- Purified protein derivative (PPD) test for tuberculosis
- Venereal Disease Research Laboratory slide test (VDRL) for syphilis
- Rubella immunity
- Cervical cytology
- Blood and Rh type
- Hepatitis B surface antigen
- Hepatitis C antibodies (if high risk)
- Bacterial vaginosis testing if symptomatic or at high risk (previous preterm labor)
- Antibody screen for Rh antibodies
- Hemoglobin and hematocrit for anemia (repeated at 26–32 weeks)
- Urinalysis with culture for asymptomatic bacteriuria
- Gonorrhea and chlamydia
- Screens for Down's syndrome and neural tube defects (at 15–20 weeks)
- Gestational diabetes screening (at 24–28 weeks)
- Group B *Streptococcus* screening (at 35–37 weeks)

Assessing Suitability of the Cervix for Labor Induction

Suitability is based on cervical dilation, length, consistency, and position. These findings are translated to a numerical rating called the *Bishop score*. A Bishop score of less than 6 indicates that pharmacologic therapy is needed to ripen the cervix prior to delivery.

Select Problems Experienced During Pregnancy or Lactation

Hyperemesis gravidarum. Severe, persistent nausea and vomiting during pregnancy accompanied by dehydration, electrolyte disturbance, ketonuria, and/or weight loss.
Bacteriuria. Often asymptomatic in pregnancy. Diagnosed by positive urine culture.
Bacterial vaginosis. Clinically diagnosed by presence of three of the following:

- White, non-inflammatory discharge
- **Clue cells** on microscopic examination
- Vaginal pH greater than 4.5
- A fishy odor before or after addition of 10% potassium hydroxide (i.e., "whiff" test)

Vulvovaginal candidiasis. Typical symptoms include vaginal itching and discharge. Clinical characteristics include:

- Vaginal pH less than 4.5
- Observation of yeast on Gram stain or wet preparation
- Thick, white, "cottage cheese–like" discharge

Chlamydia and gonorrhea. Typically asymptomatic. Diagnosed by positive culture.
Genital herpes simplex virus. Characterized by vesicular or ulcerative lesions. Diagnosis confirmed by virologic or serologic testing. Prodrome manifests as pain, burning, or itching at the site where lesions will develop.
Pelvic inflammatory disease. Difficult to diagnose in pregnancy. Symptoms may include:

- Uterine/ovarian tenderness
- Cervical motion tenderness
- Fever
- Abnormal cervical or vaginal discharge
- Presence of white blood cells in vaginal secretions
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein

Syphilis. Early disease may be characterized by a single genital lesion. Diagnosed by positive serologic testing [e.g., VDRL or rapid plasma reagin (RPR) test].
Trichomoniasis. Symptoms may include vulvar irritation and yellow-green discharge. Diagnosed after microscopic visualization of the organism.
Preterm labor. Onset of labor prior to 37 weeks' gestation.
Group B Streptococcus. Diagnosed by positive culture on vaginal or rectal swab.
Mastitis. Characterized by localized redness, tenderness, and warmth on one breast accompanied by fever and flulike symptoms. Although uncommon, symptoms also may be bilateral.
Nipple candidiasis. Typical symptoms include nipple pain, itching, burning, and/or breast pain that persist after feeding.
Gestational diabetes. See Chapter 40.
Hypertension in pregnancy. Categorized as one of the following:

- Chronic hypertension (blood pressure greater than or equal to 140/90 mm Hg prior to pregnancy or prior to 20 weeks' gestation that lasts more than 12 weeks postpartum)
- Preeclampsia (blood pressure greater than or equal to 140/90 mm Hg after 20 weeks' gestation accompanied by proteinuria)
- Chronic hypertension with superimposed preeclampsia (onset of proteinuria after 20 weeks' gestation in a woman with chronic hypertension)
- Gestational hypertension (hypertension without proteinuria after 20 weeks' gestation)
- Transient hypertension (diagnosis made retrospectively when blood pressure returns to normal before 12 weeks postpartum)



Patient Encounter, Part 1

LC is a 28-year-old woman who comes to your practice because she thinks that she is pregnant. She reports that she has not had a period in 9 weeks. When she first missed her period just over 1 month ago, she was not concerned because her cycle had become very light. However, when she missed her cycle again, she took a home pregnancy test. That test was positive. In your practice, a repeat urine pregnancy test confirms that the patient is pregnant.

- What additional medical history do you need to gather from this patient?
- What is the estimated gestational age of the fetus?
- What physical examination, laboratory testing, or other testing would you perform at this time?

Data regarding safety of drug use during lactation are also lacking. Most resources list only milk to plasma ratios for drugs secreted into breast milk. Unfortunately, this ratio gives no information regarding the amount of drug ingested by an infant or the effects of that drug on the infant.

Sources of information other than FDA pregnancy labeling exist that may provide more useful information to the clinician (Table 44–2). It still should be noted that these resources share the limitation of deriving recommendations largely from data from case reports and surveillance data. Consequently, clinicians often are forced to advise patients based on limited evidence.

TABLE 44–1. FDA Pregnancy Categories

Category A: Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.

Category B: Animal studies have revealed no evidence of harm to the fetus, however, there are no adequate and well-controlled studies in pregnant women, *or* animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.

Category C: Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women, *or* no animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.

Category D: Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.

Category X: Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.

TABLE 44–2. Sources of Information for Drug Use in Pregnancy and Lactation

- Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation*. 7th ed. Philadelphia: Lippincott Williams & Wilkins, 2005. (*Considered an authoritative text; contains alphabetical list of drugs with monographs and references.*)
- Hale TW. *Medications and Mother's Milk*. 11th ed. Amarillo, TX: Pharmacoft, 2004. (*Provides alphabetical list of drugs with references; calculates theoretical infant dose received after maternal use.*)
- American Academy of Pediatrics Committee on Drugs. The transfer of drugs and other chemicals into breast milk. *Pediatrics*. 2001; 108(3):776–789. (*Lists drugs that are considered "compatible with breast-feeding"; list is periodically updated.*)
- Motherisk (www.motherisk.org) (*Includes online information, fact-sheets, and has a "warm-line" phone number for advice for patients and clinicians during normal business hours.*)
- Organization of Teratology Information Services (www.otispregnancy.org) (*Lists and links to teratology information services by locale; many have telephone "warm-lines."*)

General Principles of Drug Use in Pregnancy and Lactation

❸ *While unnecessary medications clearly should be avoided during pregnancy or lactation, clinicians also should avoid undertreating conditions that can lead to adverse maternal, fetal, or infant outcomes. Additionally, clinicians should avoid unnecessarily discouraging breast-feeding because breast milk provides nutritional and immunologic benefit to the infant.*

Several general strategies may be employed to minimize drug exposure to the fetus or neonate. First, avoid drugs with known teratogenic effects and infant complications (Tables 44–3 and 44–4). Second, choose single-drug, short-acting therapy with agents having the longest safety record in pregnancy or lactation. Third, choose drugs with characteristics such as high molecular weights, strong ionization, high protein binding, and high water solubility to limit entry into the placental circulation or breast milk through passive diffusion.[3] Finally, counsel women to take agents immediately after breast-feeding to allow milk concentrations to fall prior to the next feeding.[14]

Preconception Planning

Planning prior to pregnancy is an important strategy for reducing the risks of birth defects and fetal or neonatal complications. Clinicians should consider childbearing potential when selecting therapy for chronic medical conditions and follow the same general principles of drug selection described earlier. This is especially important for the treatment of conditions such as hypertension or epilepsy because many medications used for these conditions are known teratogens. Engage women in discussions regarding the potential risks to an exposed fetus prior to starting therapy.[1] Further information regarding treatment of chronic medical conditions such as hypertension, human immunodeficiency virus, epilepsy and diabetes may be found in Chapters 2, 84, 27, and 40.

TABLE 44–3. Drugs with Known Teratogenic Effects[1,3,4]

Drug or Class	Teratogenic Effect
Angiotensin-converting enzyme inhibitors	Renal damage, growth restriction
Barbiturates	Neonatal withdrawal syndrome
Benzodiazepines	Neonatal withdrawal syndrome
Carbamazepine	Neural tube defects
Chemotherapeutic agents	Multiple malformations (including central nervous system, facial, and limb)
Isotretinoin	Central nervous system, ear, and heart malformations
Lithium	Cardiovascular malformations
Misoprostol	Limb and central nervous system malformations
Non-steroidal anti-inflammatory agents	Premature closing of the patent ductus arteriosus (late second and third trimesters), hemorrhage, necrotizing enterocolitis
Opioids	Neonatal withdrawal syndrome
Phenytoin	Central nervous system malformations, fetal growth restriction
Tetracyclines	Tooth and bone malformations
Thalidomide	Limb and internal organ malformations
Valproic acid	Neural tube defects
Warfarin	Growth restriction, fetal hemorrhage, skeletal and central nervous system malformations

TABLE 44–4. Contraindicated Drugs and Drugs of Concern During Lactation[3,14,25]

Drug or Class	Effect
Contraindicated Drugs and Drug Classes	
Amiodarone	Neonatal hypothyroidism and pulmonary toxicity
Bromocriptine	Lactation suppression
Chemotherapeutics	Neonatal immune suppression and neutropenia
Ergotamine	Neonatal diarrhea, vomiting, convulsions; lactation suppression
Isotretinoin	Possible neonatal tumors
Lithium	Neonatal central nervous system and cardiovascular disturbances
Drugs and Drug Classes of Concern	
Acebutolol	Neonatal hypotension, bradycardia, tachypnea
Aluminum-containing antacids	Developmental retardation
Antidepressants	Unknown, but possibly of concern
Antipsychotics	Unknown, but possibly of concern
Atenolol	Neonatal bradycardia, cyanosis
Benzodiazepines	Unknown, but possibly of concern
Clemastine	Neonatal drowsiness, irritability
Metronidazole	In vitro mutagen
Phenobarbital	Infantile spasms, neonatal sedation
Primodone	Neonatal sedation
Radioactive drugs	Transfer of radioactivity

Counsel all women of childbearing potential regarding lifestyle modifications that may improve pregnancy outcome. These include healthy eating habits, multivitamin use, cessation of tobacco use, cessation of illicit substance use, and moderation of alcohol intake.[15]

Nonpharmacologic Therapy

❹ *Treat most benign pregnancy conditions with nonpharmacologic therapy prior to using drug therapy.* These conditions include nausea and vomiting of pregnancy, constipation, hemorrhoids, heartburn, pain, and upper respiratory symptoms.

Nausea and Vomiting

Nonpharmacologic measures recommended for nausea and vomiting of pregnancy (e.g., morning sickness) include lifestyle and dietary changes, acupuncture, and acupressure. Counsel women to avoid or minimize nausea triggers such as objectionable odors and food textures, rapid positional changes, and car rides.[10] Advise administration of the prenatal vitamin at bedtime because the iron content often triggers nausea. Counsel women to eat small, frequent meals that are bland, high in carbohydrates, and low in fat.[10] Clinicians also may advise women to keep saltine crackers, water, or ginger ale (small sips only) at the bedside so that they can ingest a small snack immediately before getting out of bed. If nausea occurs, advise the patient to lie down because this strategy has been shown to relieve symptoms.[10]

Effectiveness of acupuncture and acupressure for nausea and vomiting of pregnancy has not been clearly proven in clinical studies, but both methods are safe to recommend.[10,16] Benefits may include a reduction in nausea and dry heaving but not in vomiting.[10]

Constipation and Hemorrhoids

Nonpharmacologic treatment is the mainstay of treatment for constipation and hemorrhoids in pregnant patients.[9,17] Advise women to eat a high-fiber diet, drink plenty of fluids, and avoid foods such as white rice and cheese that often exacerbate constipation. Patients should avoid prolonged time on the toilet, which increases pressure within hemorrhoids. Soaking in warm sitz baths also may help hemorrhoids by relaxing the anal sphincter. Icing the area may decrease pain and inflammation. If hemorrhoids are severe, surgical resection or banding can be performed. However, it is generally preferable to delay even minor surgery until after delivery.

Heartburn

Nonpharmacologic recommendations for the treatment of heartburn in a pregnant patient do not differ from those given

to non-pregnant patients. Primary recommendations include eating small, frequent meals, remaining upright after eating, elevating the head of the bed, and avoiding foods known to decrease lower esophageal sphincter tone (such as chocolate, coffee, fatty foods, and peppermint).

Pain

Women often experience pelvic and back pain during pregnancy. Systematic review suggests that water aerobics, pillows that support the abdomen, physiotherapy, and acupuncture offer back-pain relief.[18]

Common Cold

Rest, fluids, humidified air, and nasal saline are the mainstays of nonpharmacologic therapy for the common cold. Pregnant women experiencing cold symptoms should be advised of these strategies and reminded that cold symptoms typically last only 7 to 10 days.

Pharmacologic Therapy

Preconception Care

❺ *Advise most women of childbearing potential to take a multivitamin containing 400 mcg folic acid.* Folic acid deficiency is a major cause of **neural tube defects** because dietary intake alone is seldom sufficient to prevent the occurrence.[19] Neural tube defects are the second most common major congenital defect and occur in approximately 1.4 to 2 per 1000 pregnancies.[19] Defects usually develop during the first 2 weeks of pregnancy, prior to the woman knowing she has conceived; thus, preconception counseling regarding folic acid intake is especially important. For most women, over-the-counter multivitamins provide an adequate amount of supplementation (Table 44–5). Women at increased risk of delivering a child with neural tube defects, e.g., those with a personal or family history of neural tube defects and/or women taking medications known to cause neural tube defects, require higher doses (Table 44–5). In such instances, clinicians should recommend specific folic acid supplementation rather than extra doses of multivitamins because increasing the number of multivitamins may cause vitamin A toxicity.[19] Additional benefits of multivitamin intake include the calcium and iron components (Table 44–5).

Gastrointestinal Disturbances

Nausea and Vomiting

The combination of pyridoxine (vitamin B_6) and doxylamine appears to offer the most favorable benefit-to-risk ratio for the treatment of nausea and vomiting in pregnancy[10,16] (Table 44–5). Long-term usage data show no fetal risk with the regimen.[10] The combination was once marketed in the United States under the brand name Bendectin®, but the drug was withdrawn from the United States market in 1984. Women can approximate the dosage by taking each component separately.

Data also support that ginger is safe and effective when used as an antinausea agent in pregnancy[16] (Table 44–5). However, it may be difficult for most women to reproduce the type and dose of ginger used in clinical trials.

Second-line agents for nausea and vomiting include first-generation antihistamines such as diphenhydramine, dopamine agonists such as metoclopramide, and the serotonin agent ondansetron[10] (Table 44–5). Limited data address their safety, and maternal side effects may be experienced more commonly with these drugs than with first-line agents. Antihistamine use often is associated with drowsiness, and metoclopramide may cause **extrapyramidal symptoms.** Hyperemesis gravidarum often requires hospitalization and administration of intravenous therapy with 5-hydroxytryptamine type 3 receptor antagonists such as ondansetron.

Constipation

Bulk-forming laxatives such as psyllium and calcium polycarbophil are safe for use in pregnancy and lactation[17] (Table 44–5). If these methods fail, then stimulant laxatives such as bisacodyl and senna are acceptable second-line agents for short-term or intermittent use, but side effects of diarrhea and abdominal pain may limit use[17] (Table 44–5). Stool softeners such as docusate are recommended commonly but have shown little efficacy for the treatment of chronic constipation.[9] Avoid magnesium-containing laxatives or phosphosoda owing to the potential for electrolyte disturbances and fluid retention. During lactation, bulk-forming laxatives and the stimulant laxative senna are likely safe for use.[14]

Hemorrhoids

Studies are lacking regarding the safety and efficacy of hemorrhoid treatment during pregnancy.[20] At this time, recommend only topical anti-inflammatory agents such as witch hazel (Tucks® pads). Although prospective studies in pregnancy are lacking, witch hazel is used commonly during pregnancy and lactation without adverse incidence.

Heartburn

A recent consensus panel recommends calcium- or magnesium-containing antacids as first-line therapies for heartburn in pregnancy.[21] This recommendation was based on the added benefit of calcium and magnesium supplementation. Avoid antacids containing aluminum hydroxide owing to associations with fetal neurotoxicity.[22]

If antacids fail to improve symptoms, recommend ranitidine (Table 44–5). Although most H_2 blockers are thought to be safe in pregnancy, ranitidine is the only agent with double-blind, randomized trials evaluating its use in this population.[23]

Other agents that appear to be safe for use in pregnancy include the proton pump inhibitors, sucralfate, and metoclopromide (Table 44–5). The proton pump inhibitor with the largest body of human safety data during pregnancy is omeprazole.[24]

TABLE 44–5. Summary of Medication Dosing Recommendations[9,10,12,14,23,27,38,41,43,44, 48]

Drug	Dose	Comments
Preconception and Routine Pregnancy Care		
Calcium (Tums, Os-cal, Maalox, Citracal)	1300 mg orally per day (age 14–18) 1000 mg orally per day (age 19–50)	
Folic acid	400 mcg orally daily 4 mg orally daily if high risk	High risk = personal or family history of neural tube defects or on medication known to cause neural tube defects
Iron (Feosol, FeroSul)	27 mg elemental iron daily	Increase to 60–120 mg daily if iron-deficiency anemia present
Nausea and Vomiting of Pregnancy		
Diphenhydramine (Benadryl, Genahist)	12.5–25 mg orally four times daily	Second-line agent
Ginger	250 mg orally four times daily	First-line agent
Metoclopramide (Reglan)	5–10 mg orally three to four times daily	Second-line agent
Ondansetron (Zofran)	20 mg intravenously every 8 hours	Second-line agent, may be preferred for hyperemesis
Pyridoxine/doxylamine (Vitamin B_6/Unisom)	25 mg/12.5 mg orally three times daily	First-line agent
Constipation		
Bisacodyl (Dulcolax, Correctol)	5–10 mg orally (tabs) or rectally (suppositories) as needed	Second-line agent after bulk laxatives
Polycarbophil (Fiberlax, Fibercon)	2 tabs one to four times daily	First-line agent
Psyllium (Metamucil, Genfiber)	Product specific dosing, usually 1 packet/scoopful in water up to three times daily	First-line agent
Senna (ExLax, Senokot)	17.2 mg orally as needed	Second-line agent after bulk laxatives
Heartburn		
Antacids (various) (Tums, Maalox, Rolaids, GasEx)	15–30 mL or 250 mg–1.5 g up to four times daily	First-line agent (avoid aluminum-containing preparations)
Metoclopramide (Reglan)	5–10 mg orally three to four times daily	Third-line agent
Omeprazole (Prilosex)	20 mg orally daily	Third-line agent
Ranitidine (Zantac)	150 mg orally twice daily	Second-line agent after antacids
Sucralfate (Carafate)	1 g orally four times daily	Third-line agent (pregnancy); first-line agent (lactation)
Pain		
Acetaminophen (Tylenol)	500–650 mg orally four times daily	First-line agent
Codeine	15 mg every 4 to 6 hours	Third-line agent
Ibuprofen (Advil, Motrin)	200–400 mg orally four times daily	Second-line agent in first trimester only. Do not use in second or third trimester.
Naproxen (Aleve)	200–400 mg orally twice daily	Second-line agent in first trimester only. Do not use in second or third trimester.
Upper Respiratory Symptoms		
Budesonide (Rhinocort)	32 mcg spray, 1–4 sprays in each nostril daily	Preferred corticosteroid for allergic rhinitis.
Cetirizine (Zyrtec)	10 mg orally daily	Second-line agent for allergic rhinitis during second and third trimesters only.
Chlorpheniramine (Chlortrimeton)	4 mg every 4–6 hours	Preferred agent if first-generation antihistamines are to be used for allergic rhinitis.
Dextromethorphan (Robitussin Cough Gels, Vicks 44, Simply Cough, Delsym)	30 mg orally every 6–8 hours	First-line agent for cough/cold.
Guaifenesin (Hytuss, Mucinex, Robitussin)	200–400 mg orally every 4 hours	First-line agent for cough/cold.
Loratadine (Claritin, Alavert)	10 mg orally daily	Second-line agent for allergic rhinitis during second and third trimesters only.
Oxymetazoline (Afrin, Neo-Synephrine 12-hour)	0.05% spray, 2–3 sprays in each nostril twice daily for 3 to 5 days	First-line agent for cough/cold. Limit use to 3 to 5 days to avoid rebound congestion.
Pseudoephedrine (Sudafed)	60 mg every 4–6 hours	Second and third trimesters only.

TABLE 44–5. Summary of Medication Dosing Recommendations[9,10,12,14,23,27,38,41,43,44, 48] (*Continued*)

Drug	Dose	Comments
Bacteriuria		
Amoxicillin (Trimox, Amoxil)	500 mg three times daily for 3 days	
Cephalexin (Keflex)	250–500 mg four times daily for 3 days	
Nitrofurantoin macrocrystals (Macrobid)	100 mg twice daily for 3 days	
Bacterial Vaginosis		
Clindamycin (Cleocin)	300 mg orally twice daily for 7 days 100 mg cream or suppository intravaginally at bedtime for 3 days	Oral administration is second-line agent in pregnancy; vaginal administration is first-line agent in lactation, but contraindicated in pregnancy
Metronidazole (Flagyl)	250 mg three times daily for 7 days	First-line agent in pregnancy; avoid during lactation
Vulvovaginal Candidiasis		
Clotrimazole (Mycelex, Gyne-Lotrimin)	1% cream, 5 g intravaginally for 7 days 100-mg vaginal tablet daily for 7 days	
Miconazole (Monistat)	2% cream, 5 g intravaginally for 7 days 100-mg vaginal suppository daily for 7 days	
Terconazole (Terazol)	0.4% cream, 5 g intravaginally for 7 days	
Chlamydia		
Amoxicillin (Trimox, Amoxil)	500 mg orally three times daily for 7 days	First-line agent in pregnancy; third-line agent in lactation
Azithromycin (Zithromax)	1 g orally once	Third-line agent in pregnancy; first-line agent in lactation
Doxycycline (Vibramycin)	100 mg orally twice daily for 7 days	Avoid during pregnancy; first-line agent in lactation
Erythromycin base (Ery-tab)	500 mg orally four times daily for 7 days	Second-line agent in pregnancy
Gonorrhea		
Cefixime (Suprax)	400 mg orally once	First-line agent in pregnancy or lactation
Ceftriaxone (Rocephin)	125 mg intramuscularly once	First-line agent in pregnancy or lactation
Ciprofloxacin (Cipro)	500 mg orally once	Contraindicated in pregnancy; first-line agent in lactation, except for residents of California or Hawaii.
Ofloxacin (Floxin)	400 mg orally once	Both ofloxacin: levofloxacin should have description given for cipro.
Levofloxacin (Levaquin)	250 mg orally once	
Spectinomycin (Trobicin)	2 g intramuscularly once	Second-line agent in pregnancy for cephalosporin-allergic patients
Herpes Simplex Virus		
Acyclovir (Zovirax)	400 mg orally three times daily for 7–10 days, or 800 mg orally twice daily for 5 days	7–10-day therapy for initial episode; 5-day therapy for recurrent episodes
Pelvic Inflammatory Disease		
Clindamycin *plus* gentamicin (Cleocin/Garamycin)	Clindamycin 900 mg intravenously every 8 hours; gentamicin dosed based on pharmacokinetics × 14 days	
Syphilis		
Benzathine penicillin G (Bicillin)	2.4 million units intramuscularly once	Desensitize penicillin-allergic patients during pregnancy; also first-line agent during lactation.
Doxycycline (Vibramycin)	100 mg twice daily for 14 days	Alternative during lactation (but not pregnancy) for penicillin-allergic patients
Tetracycline (Sumycin)	500 mg four times daily for 14 days	Alternative during lactation (but not pregnancy) for penicillin-allergic patients
Trichomoniasis		
Metronidazole (Flagyl)	2 g orally once	Safe during pregnancy. During lactation, temporarily stop breast-feeding for 12–24 hours.
Antenatal Steroids		
Betamethasone (Celestone)	12 mg intramuscularly every 24 hours for two doses	
Dexamethasone (Decadron, Dexasone, Cortastat)	6 mg intramuscularly every 12 hours for two doses	
Tocolytics		
Indomethacin (Indocin)	50–100 mg oral load, then 25–50 mg orally every 6 hours × 48 hours	
Magnesium sulfate	4–6 mg intravenous bolus over 20 minutes, then 2–3 g per hour intravenous drip	Generally not favored

(Continued)

TABLE 44–5. Summary of Medication Dosing Recommendations[9,10,12,14,23,27,38,41,43,44,48] (*Continued*)

Drug	Dose	Comments
Nifedipine (immediate release) (Procardia)	30 mg oral load, then 10–20 mg every 4–6 hours	First-line agent
Terbutaline (Brethine)	0.25 mg subcutaneously every 20 minutes to 3 hours	
Group B *Streptococcus*		
Ampicillin (Principen)	2 g intravenously initially, then 1 g intravenously every 4 hours until delivery	See Fig. 44–3
Cefazolin (Ancef)	2 g intravenously initially, then 1 g intravenously every 8 hours until delivery	
Clindamycin (Cleocin)	900 mg intravenously every 8 hours until delivery	
Erythromycin (Erythocin)	500 mg intravenously every 6 hours until delivery	
Penicillin G (Pfizerpen)	5 million units intravenously initially, then 2.5 million units intravenously every 4 hours until delivery	
Vancomycin (Vancocin, Vancoled)	1 g intravenously every 12 hours until delivery	
Labor Induction		
Oxytocin	2–6 milliunits per minute intravenous infusion (high dose) 1–2 milliunits per minute intravenous infusion (low dose)	
Cervical Ripening		
Dinoprostone gel (Prepidil)	1 application (0.5 mg) every 6 hours to maximum of 3 doses in 24 hours	Store in refrigerator and bring to room temperature before use
Dinoprostone vaginal insert (Cervidil)	Insert once (releases 0.3 mg per hour) for up to 12 hours	
Misoprostol (Cytotec)	25 mcg intravaginally every 3–6 hours	Contraindicated if previous cesarean section
Mastitis		
Cephalexin (Keflex)	250 mg orally four times daily × 10–14 days	First-line agent
Dicloxacillin	125 mg orally four times daily × 10–14 days	First-line agent
Erythromycin (Ery-tab)	333 mg orally three times daily × 10–14 days	Second-line agent in penicillin-allergic patients
Nipple Candidiasis		
Fluconazole (Diflucan)	100 mg orally daily	Second-line agent when topical azoles fail
Ketoconazole (Nizoral)	2% cream—apply to affected areas after each feeding	First-line agent
Miconazole (Micatin, Monistat-Derm)	2% cream—apply to affected areas after each feeding	First-line agent
Nystatin drops (Mycostatin)	200,000 units (2 mL) orally four times daily	For concurrent treatment of the neonate/infant regardless of maternal drug choice
Nystatin topical (Mycostatin)	100,000 units/g—apply to affected areas after each feeding	
Enhancement of Lactation		
Metoclopramide	10 mg orally three times daily for 7–10 days	

During lactation, sucralfate may be the best choice for treatment of heartburn because it is not absorbed systemically.[25] If symptoms are not controlled, the H_2 blockers are acceptable alternatives.[14,25] Avoid aluminum-containing antacids during lactation owing to reports of aluminum toxicity in otherwise healthy infants.[22]

Pain

Acetaminophen generally is considered the drug of choice for the treatment of pain during pregnancy (Table 44–5). If acetaminophen does not relieve pain, non-steroidal anti-inflammatory drugs (NSAIDs) may be used cautiously during the first trimester only in women who do not have a history of gastrointestinal bleed, peptic ulcer, or aspirin allergy (Table 44–5). Also avoid NSAID use in women who have had difficulty conceiving or have experienced miscarriage.[26] Use of NSAIDs in the late second or third trimester has been associated with multiple fetal and neonatal complications (Table 44–3).

Avoid opioid use during pregnancy owing to reports of fetal growth restriction, neonatal dependence, and neonatal



Patient Encounter, Part 2

During your first encounter with LC, you collect the following data:

PMH
Seasonal allergic rhinitis

FH
Mother delivered two preterm infants.

SH
Works as a librarian. Denies use of alcohol, tobacco, or illicit substances.

Meds
- Loratadine 10 mg daily
- Ibuprofen 400 mg prn headache (uses approximately once weekly)
- Ortho-Tri-Cyclen Lo® daily
- Multivitamin (generic for Centrum®) daily

ROS
(+) Nausea with occasional vomiting on awakening each morning × 2 weeks. Lasts for 1 to 2 hours. Has missed 3 days of work owing to symptoms. Remainder of ROS within normal limits.

VS: Blood pressure 118/62, pulse 72 beats per minute, respiratory rate 12, temperature 37°C (98.6°F)
The patient states that she wants to have this baby but expresses concern over the medications she has been using over the last 9 weeks. She states that neither she nor her husband could handle having a "deformed" baby, and she asks you if she should consider terminating the pregnancy.

- What resources can you use to help determine the risk of her drug exposures?
- Based on that information, what advice would you give her regarding the risk to her baby?
- What do you recommended for her morning sickness?

respiratory depression. However, brief treatment with small doses of codeine is acceptable for severe pain unresponsive to acetaminophen or NSAIDs.[1] For lactating women, acetaminophen, NSAIDs, and most opioids are considered compatible with breast-feeding by the American Academy of Pediatrics.[14]

Upper Respiratory Symptoms

For common cold symptoms such as congestion and cough, recommend nasal oxymetazoline, oral guaifenesin, and dextromethorphan according to joint guidelines from the American College of Obstetricians and Gynecologists and the American College of Allergy, Asthma, and Immunology[27] (Table 44–5). Counsel patients using oxymetazoline to limit use to 3 to 5 days in order to minimize the incidence of rebound congestion. Oral pseudoephedrine is also acceptable for treatment of congestion during the second and third trimesters, but avoid use in the first trimester owing to the risk of fetal gastroschisis (incidence 20 per 10,000 treated women).[28] Codeine is not a preferred therapy for cough in this population.[27]

Treat allergy symptoms with nasal corticosteroids during pregnancy.[28] Budesonide has extensive safety data in pregnant women and may be the drug of choice in the treatment of naive patients. If antihistamines are indicated, chlorpheniramine is preferred owing to its record of safe use during pregnancy. Fewer data are available regarding the safety of second-generation antihistamines during pregnancy. Animal and human studies seem to suggest overall safety for cetirizine and loratadine.[28–30] However, guidelines recommend their use only in women on topical corticosteroid therapy who are unable to tolerate chlorpheniramine.[28] Avoid fexofenadine owing to reports of teratogenic effects in animals.[28]

During lactation, oral or nasal decongestants, nasal steroids, and loratadine are acceptable for treatment of upper respiratory symptoms.[14] However, one case of adverse neonatal outcome has been reported with the first-generation antihistamine clemastine.[14] Few data are available regarding the safety of other first-generation antihistamines during lactation. Therefore, avoid use of this drug class during lactation.

Bacteriuria

❸ *Bacteriuria during pregnancy, including asymptomatic disease, is associated with pyelonephritis, low birth weight, and preterm delivery. Treatment improves these risks; thus, treat all women testing positive for bacteriuria empirically with antimicrobial therapy targeted at* Escherichia coli *infection.*[31] Safe agents for empirical therapy include amoxicillin, cephalexin, and nitrofurantoin[32,33] (Table 44–5). Sulfonamides and ampicillin also have been used, but increasing bacterial resistance to these agents renders them second-line choices.[32] Avoid quinolones owing to the possible risk of bone and cartilage malformations. Once culture and sensitivity results are available, change the antimicrobial regimen if necessary. Recommend standard 3-day antimicrobial therapy because there is insufficient evidence among pregnant women to support 1-day regimens.[32,34]

Bacterial Vaginosis

Bacterial vaginosis is associated with preterm delivery, but treating asymptomatic disease does not appear to decrease this risk.[35–37] Consequently, treat only symptomatic disease (Table 44–5).

The Centers for Disease Control and Prevention (CDC) recommend oral metronidazole for the treatment of bacterial vaginosis in pregnant women.[38] Metronidazole is deemed safe for use by the CDC during all stages of pregnancy despite package labeling listing a contraindication in the first trimester.[38] Oral clindamycin is an option for women not tolerating metronidazole.[38]

It is not a first-line agent owing to lower efficacy compared with oral metronidazole in non-pregnant populations.[38] Avoid clindamycin vaginal cream due to associations with premature labor and neonatal infection.[38]

Counsel women taking metronidazole regarding potential for nausea, vomiting, and abdominal pain. Counsel patients to avoid alcohol or alcohol-containing substances during therapy with metronidazole owing to the risk of **disulfuram-like reactions**.

Clindamycin vaginal cream is the preferred therapy for bacterial vaginosis during lactation because metronidazole is listed as a drug of concern by the American Academy of Pediatrics (AAP)[14] (Tables 44–4 and 44–5). Counsel patients that clindamycin cream weakens latex condoms and diaphragms, potentially rendering them ineffective.

Vulvovaginal Candidiasis

Treat symptomatic vulvovaginal candidiasis in pregnant women with topical azole therapy according to CDC guidelines.[38] Oral fluconazole is not recommended. Asymptomatic disease does not require treatment. Vulvovaginal candidiasis during pregnancy is considered a "complicated" case; thus, 7-day therapy (instead of 1- to 3-day therapy) is recommended[38] (Table 44–5).

During lactation, topical azoles remain the drug of choice for vulvovaginal candidiasis.[38] Oral fluconazole is not recommended in order to minimize the development of fluconazole-resistant *Candida* species in the general population. Counsel women using topical azoles that the medication weakens latex condoms and diaphragms, potentially rendering them ineffective for preventing pregnancy and transmission of sexually transmitted infections.

Sexually Transmitted Infections

Chlamydia

❸ *Treat chlamydia infections during pregnancy, including those that are asymptomatic, with erythromycin or amoxicillin in order to reduce risk of preterm labor*[38] (Table 44–5). Systematic review suggests that amoxicillin is better tolerated than erythromycin and has fewer discontinuations owing to adverse drug reactions than erythromycin.[39] Azithromycin may be a safe alternative in women unable to take, tolerate, or adhere to these first-line recommendations.[38] However, azithromycin is a third-line therapy because there are longer safety records for erythromycin and amoxicillin in pregnancy. Avoid doxycycline in pregnant women owing to known teratogenic effects (Table 44–3).

During lactation, azithromycin and doxycycline are first-line choices for chlamydia[38] (Table 44–5). Both are deemed compatible with breast-feeding by the AAP and generally are more effective and better tolerated than erythromycin or amoxicillin.[14,38]

Gonorrhea

❸ *Treat gonorrheal infections during pregnancy, including those that are asymptomatic, with cefixime or ceftriaxone in order to reduce the risk of preterm labor*[38] (Table 44–5). Spectinomycin is an alternative choice for penicillin- or cephalosporin-allergic women.[38] Avoid tetracyclines during pregnancy owing to known teratogenic effects (Table 44–3). Also avoid quinolones owing to the possible risk of bone or cartilage malformations.

During lactation, all CDC first-line recommended therapies for gonorrhea (Table 44–5) are deemed compatible with breast-feeding by the AAP.[14] Quinolone therapy is not recommended for women residing in California or Hawaii due to the increasing numbers of quinolone-resistant species.[38]

Herpes Simplex

Herpes simplex virus may be transmitted to the neonate if active vaginal lesions or the prodrome is present at the time of birth. Consequently, cesarean section often is recommended for these women. Vaginal delivery is indicated if vaginal lesions or the prodrome are not present.

Recommend oral acyclovir for treatment of genital herpes simplex episodes during pregnancy in order to help reduce the need for cesarean section[38] (Table 44–5). Intravenous therapy may be indicated for very severe episodes. Safety of acyclovir has not been firmly established, but surveillance data do not suggest an increased risk of teratogenic effects. Acyclovir is preferred over valacyclovir or famcyclovir because experience with the latter agents in pregnancy is limited.

During lactation, acyclovir is deemed compatible with breast-feeding by the AAP even though the drug does concentrate in milk.[14] No recommendation has been made regarding the safety of valacyclovir or famcyclovir during lactation.

Pelvic Inflammatory Disease

❸ *Treat pelvic inflammatory disease during pregnancy with intravenous clindamycin plus gentamicin in order to reduce maternal morbidity, preterm delivery, and fetal death*[38] (Table 44–5). Avoid regimens using doxycycline owing to known teratogenic effects (Table 44–3), and avoid quinolones owing to the possible risk of bone and cartilage malformations.

Syphilis

❸ *Treat syphilis during pregnancy with benzathine penicillin G in order to prevent transmission of syphilis to the fetus and to cure the disease in the fetus*[38] (Table 44–5). Penicillin-allergic women must undergo desensitization to the drug.[38] Alternative therapies used in non-pregnant patients are either teratogenic (e.g., tetracycline and doxycycline) or will not cure disease in the fetus (e.g., erythromycin).[38]

Treat syphilis during lactation with benzathine penicillin G or any of the CDC-recommended alternatives for penicillin-allergic patients (Table 44–5). All choices are deemed compatible with breast-feeding by the AAP.[14]

Trichomoniasis

Treat symptomatic trichomoniasis with oral metronidazole in order to alleviate maternal symptoms (Table 44–5). Do not treat asymptomatic disease. There is no evidence suggesting that treatment of asymptomatic disease will reduce the incidence of preterm labor or low birth weight, and systematic review suggests that this practice may even increase the incidence of preterm birth.[40]

Advise women requiring treatment for trichomoniasis during lactation to discontinue breast-feeding for 12 to 24 hours after receiving single-dose metronidazole therapy in order to minimize risk to the infant.[14] During this time, advise women to pump and discard breast milk in order to avoid engorgement.

Counsel women taking metronidazole to avoid drinking alcohol or using alcohol-containing substances during therapy.

Preterm Labor

❸ *Administration of **antenatal** corticosteroids during preterm labor having an onset prior to 34 weeks' gestation has been proven to decrease the risk of neonatal respiratory distress, intraventricular hemorrhage, necrotizing enterocolitis, and death*[15,41] (Table 44–5). No benefit from antenatal corticosteroids is gained if labor starts after 34 weeks' gestation. In order to allow for administration of antenatal steroids, **tocolytic** therapy often is used to prolong time to delivery by 2 to 7 days.[36] Agents commonly used as tocolytics in the United States include magnesium sulfate, terbutaline, indomethacin, and nifidepine (Table 44–5).

Systemic review concludes that tocolytic therapy with the calcium channel blockers offers the best benefit-to-risk ratio.[42] However, few head-to-head comparisons have been made between agents. Guidelines from the American College of Obstetricians and Gynecologists (ACOG) therefore recommend selecting an agent based on maternal status and potential adverse drug reactions.[41] Do not recommend combination tocolytic therapy, maintenance tocolytic therapy, or repeated courses of acute tocolytic therapy owing to increased fetal risk and lack of efficacy.[41]

Data proving that magnesium sulfate prolongs pregnancy is lacking.[36] It is contraindicated for use in women with myasthenia gravis, and serious complications such as maternal pulmonary edema and cardiac arrest have been reported.[41] More benign side effects such as flushing, headache, and nausea often cause discontinuation of therapy.[36]

Terbutaline has been shown to prolong pregnancy but has not been associated with decreased neonatal morbidity.[36] It is contraindicated for use in women with preexisting cardiac arrhythmia. Potentially serious adverse effects include pulmonary edema, cardiac arrhythmia, or myocardial ischemia in the mother. Reported fetal and neonatal adverse effects include tachycardia, hyperglycemia, and hyperinsulinemia.[41]

Indomethacin prolongs pregnancy but has not been independently associated with decreased neonatal morbidity.[36] It may be of particular benefit in women with **hydramnios.**[36] Avoid use in women with a history of severe renal or hepatic impairment, aspirin allergy, or a history of peptic ulcer disease or other bleeding disorders. Although typically well tolerated by the mother, reports of increased risk of postpartum hemorrhage and **patent ductus arteriosus** is worrisome.[36]

The calcium channel blockers have been associated with both prolonged pregnancy and decreased neonatal morbidity.[36,42] When compared with β-mimetics (e.g., terbutaline) and magnesium, they show better neonatal outcome and a lower incidence of serious maternal side effects.[42] Potential minor maternal adverse effects include headache, flushing, dizziness, and transient hypotension.[41]

Group B *Streptococcus*

❸ *Maternal transmission of group B* Streptococcus *during the **intrapartum** period is a cause of neonatal sepsis and death. All pregnant women should be screened for group B* Streptococcus *disease using vaginal and rectal swabs between 35 and 37 weeks' gestation. Antibiotic therapy has been proven to reduce the incidence of early-onset neonatal disease in high-risk groups of women*[43] (Table 44–6). Start treatment at the time of membrane rupture and continue until delivery. If women receive therapy owing to unknown group B *Streptococcus* status and no growth is seen 48 hours after culture, discontinue therapy. Therapy is not required in women undergoing planned cesarean section who have not experienced membrane rupture.

The antibiotic of choice for group B streptococcal disease is penicillin G, although ampicillin is an alternative.[43] No resistance to either agent has been reported, and their narrow spectrum of activity makes them ideal choices.[43] Resistance has developed with the use of alternative choices for penicillin-allergic patients. A treatment algorithm for group B *Streptococcus* is shown in Fig. 44–3, and dosing recommendations are shown in Table 44–5.

Labor Induction

Up to 33.7% of pregnancies are delivered through labor induction.[44] Prior to pharmacologically inducing contractions, the cervix must be favorable for labor. Two drugs have proven efficacy for cervical ripening: the prostaglandin E analog dinoprostone (available as a gel or a vaginal insert) and misoprostol (Table 44–5). Guidelines from the ACOG recommend using either drug and give no clear guidance on choosing one over the other.[45]

TABLE 44–6. Characteristics of Women Who Should Receive Intrapartum Treatment for Group B *Streptococcus* per CDC Guidelines[43]

- Previous delivery of a group B *Streptococcus*–positive infant
- Positive group B *Streptococcus* screen
- Group B *Streptococcus* bacteriuria
- Unknown group B *Streptococcus* status plus one or more of the following:
  - Less than 37 weeks' gestation
  - Membrane rupture of greater than 18 hours
  - Intrapartum body temperature greater than or equal to 38°C (100.4°F)

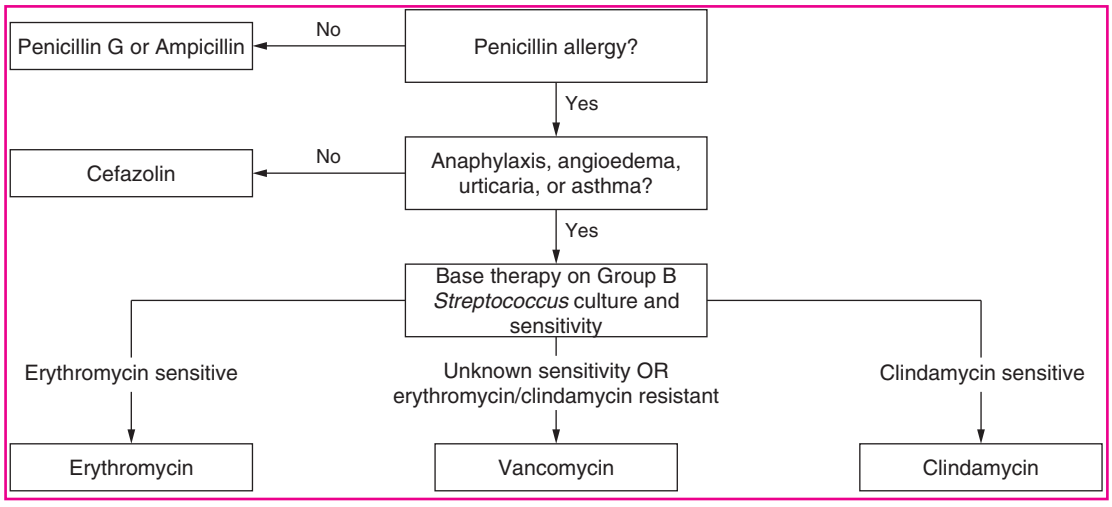


FIGURE 44–3. Algorithm for intrapartum antibiotic therapy against group B *Streptococcus*.[43]

Systematic review concludes that misoprostol shows greater efficacy versus dinoprostone, but this benefit is offset by a greater incidence of side effects.[46] Compared with dinoprostone, misoprostol is associated with a higher incidence of uterine hyperstimulation, alterations in fetal heart rate, and fetal distress.[46] Misoprostol also has been associated with uterine rupture in patients with previous delivery by cesarean section and should be avoided in this population.[44]

Despite these limitations to misoprostol's use, it is much cheaper than the dinoprostone products. The average cost of misoprostol is less than $1 per dose versus a cost of $65 to $75 for dinoprostone gel.[45] At $165, the dinoprostone insert is more expensive than the dinoprostone gel but offers the advantage of quick removal should adverse events occur.[45]

Pharmacologic agents used for cervical ripening often induce contractions. However, if contractions do not begin within 6 to 12 hours of dinoprostone use or within 3 hours of misoprostol use, oxytocin may be administered.[44] Both high- and low-dose oxytocin regimens have been studied (Table 44–5). Both regimens appear to have equal efficacy and are recommended by the ACOG.[44,45] High-dose oxytocin may shorten the time to delivery, but this advantage is offset by a higher incidence of uterine hyperstimulation and fetal heart rate changes.[47]

Breast Infections

Acute Mastitis

Treat acute mastitis with antistaphylococcal antibiotics such as dicloxacillin or cephalexin for 10 to 14 days in order to prevent recurrent disease and breast abscess[12] (Table 44–5). Penicillin-allergic women alternatively may be treated with erythromycin.[12] Occasionally, intravenous antibiotics are needed for resistant, recurrent, or chronic cases. Encourage women to continue breast-feeding through acute mastitis and to empty all leftover milk from the affected breast.[12]

Nipple Candidiasis

Treat nipple candidiasis by applying topical ketoconazole, nystatin, or miconazole to the nipples after each feeding and by administering oral nystatin drops to the breast-feeding infant[12] (Table 44–5). In severe or recurrent cases, the mother may be treated with oral fluconazole.[12,14] Although messy, gentian violet applied topically to both the nipples and the infant's mouth is also effective for resistant cases.[12]

Enhancement of Lactation

Metoclopramide is the drug of choice for enhancement of lactation when improved feeding technique fails to increase milk flow[48] (Table 44–5). Metoclopramide exerts its effect through dopamine antagonism. Increases in milk production should be noted within 2 to 5 days of metoclopramide initiation. Monitor patients for extrapyrimidal symptoms.

Other agents used for lactation enhancement include domperidone and fenugreek. Like metoclopramide, domperidone is a dopamine antagonist. Risk of extrapyramidal effects is lower with domperidone because it does not cross the blood-brain barrier. However, the FDA issued a warning against domperidone use owing to reports of cardiac arrhythmia, myocardial infarction, and sudden death associated with the intravenous formulation.[49] Data regarding fenugreek's efficacy are anecdotal, and the herb should not be recommended unless other efforts fail.[48]



Patient Encounter, Part 3

LC had an uneventful pregnancy before arriving at the hospital in labor at 31 weeks' gestation.

- What do you recommend at this time?

OUTCOME EVALUATION

Report birth defects that are believed to be teratogenic effects. At a minimum, complete an FDA Medwatch Form (available at www.fda.gov/medwatch). Additionally, clinicians may report events to local teratology information services (links available at www.otispregnancy.org). Some pharmaceutical companies have developed pregnancy registries for their drugs. In such instances, report both positive and negative outcomes of drug exposure during pregnancy to those companies.

Monitor the mother for efficacy and adverse effects of drug therapy used during pregnancy or lactation. Monitor all parameters that would be followed in a non-pregnant or lactating population. At times, additional monitoring is required owing to pregnancy, and these exceptions are discussed below. Some conditions also require monitoring of the fetus or neonate.

Conditions Requiring Only Monitoring for Symptomatic Improvement

Little special monitoring is required for the treatment of gastrointestinal disturbances, upper respiratory symptoms, and pain experienced during pregnancy or lactation. Response to therapy is judged by maternal symptomatic relief. Change therapy if no relief is obtained within 1 to 2 weeks after initiating therapy. In the case of severe, persistent nausea and vomiting, monitor maternal weight, orthostatic blood pressure, and electrolytes to diagnose possible hyperemesis gravidarum.

Infections during Pregnancy

Owing to the risk of preterm labor that is associated with gynecologic infections during pregnancy, pregnant women require follow-up objective testing for most of these infections. This includes:[38]

- Repeat urine culture 10 days after completion of therapy for bacteriuria
- Repeat culture for bacterial vaginosis 1 month after completion of therapy
- Repeat culture for gonorrhea or chlamydia 3 weeks after completion of therapy

Some pregnancy infections can be passed to the neonate. In such instances, monitor the baby for signs and symptoms of disease. This includes the following:

- Group B *Streptococcus*. Observe the neonate for signs and symptoms of sepsis until 48 hours after birth. If present, start a full diagnostic work-up (including complete blood cell count and blood culture) and empirical antibiotic therapy.[43]
- Genital herpes simplex virus. Infants born to mothers with active disease at birth should be monitored for signs and symptoms of disease. Surveillance culture of mucosal surfaces is optional.[38]

Monitor mothers suffering from breast infections during lactation for clinical improvement as judged by physical examination and pain relief. Improvement should be noted within 1 week of initiating therapy.

Preterm Labor

Many tocolytic drugs require special monitoring of both mother and fetus. Monitor cardiac status by electrocardiogram and pulmonary status by physical examination in mothers receiving terbutaline or magnesium sulfate owing to the risk of cardiac arrhythmia, cardiac ischemia, and pulmonary edema. Monitor blood pressure and heart rate in mothers receiving terbutaline, magnesium sulfate, or nifedipine owing to the risk of hypotension. Check fetal heart rate during therapy and neonatal heart rate, respiratory rate, and oxygen saturations after delivery.

Labor Induction

Continuously monitor uterine activity and fetal heart rate when giving drug therapy for cervical ripening or oxytocin. Total duration of monitoring depends on the agent used, and current guidelines recommend the following[44,45]:

- Dinoprostone gel. Start monitoring 15 minutes prior to gel insertion and continue for 30 to 120 minutes after administration.
- Dinoprostone insert. Start monitoring 15 minutes prior to insertion and continue for 15 minutes after removal.
- Misoprostol. Start monitoring 15 minutes prior to insertion and continue for 3 hours after administration.
- Oxytocin. Monitor until delivery.



Patient Care and Monitoring

1. Provide prenatal counseling regarding appropriate medication use during pregnancy. If possible, alter the drug regimen for chronic medical conditions to one that is least likely to cause fetal harm. Obtain good control of maternal conditions prior to conception.
2. Recommend appropriate folic acid, calcium, and iron intake prior to conception.
3. After pregnancy is achieved, encourage routine pregnancy monitoring and care.
4. Treat conditions during pregnancy that pose a risk to the fetus or neonate. Choose therapy as recommended by guidelines or those with the longest history of safe use in pregnancy.
5. Treat conditions that cause bothersome maternal symptoms during pregnancy with drug therapy only after nonpharmacologic methods fail. Choose therapy with the longest history of safe use in pregnancy.
6. Encourage breast-feeding. If drug therapy is required during breast-feeding, try to choose short-acting agents with the longest history of safe use in lactation and administer immediately after feedings.
7. Monitor infants for birth defects and/or unusual reactions that may be due to maternal drug use. Report suspected drug-related reactions to the FDA and other appropriate registries.

ABBREVIATIONS

AAP:	American Academy of Pediatrics
ACOG:	American College of Obstetricians and Gynecologists
CDC:	Centers for Disease Control and Prevention
FDA:	Food and Drug Administration
NSAID:	non-steroidal anti-inflammatory drug
PPD:	purified protein derivative
RPR:	rapid plasma reagin
VDRL:	Venereal Disease Research Laboratory slide test

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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45 Contraception

Julie M. Koehler and Kathleen B. Haynes



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Discuss the physiology of the normal female reproductive system.
2. Compare the efficacy of oral contraceptives with that of other methods of contraception.
3. State the mechanism of action of hormonal contraceptives.
4. Discuss the risks associated with the use of contraceptives, and state absolute and relative contraindications to their use.
5. List side effects associated with the use of various contraceptives, and recommend strategies for minimizing or eliminating such side effects.
6. Describe advantages and disadvantages of various contraceptives, including both oral and non-oral formulations.
7. Cite important drug interactions with oral contraceptives.
8. Provide appropriate patient education regarding the important differences between various barrier contraceptives.
9. Discuss how emergency contraception may be employed to prevent accidental pregnancy.
10. Provide appropriate patient education regarding the use of oral contraceptives, and recommend and discuss the use of non-oral contraceptives when appropriate.

Key Concepts

❶ Heavy smokers (greater than or equal to 15 cigarettes per day) over the age of 35, as well as patients with a history of thromboembolic disease, stroke, coronary artery disease, any estrogen-dependent neoplasm, or undiagnosed abnormal uterine bleeding, should not take estrogen-containing contraceptives.

❷ Side effects associated with the use of combined oral contraceptives may be minimized by appropriately adjusting either the total estrogen or progestin content.

❸ Antibiotic administration during contraceptive use may decrease the efficacy of many combined contraceptives.

❹ Non-oral forms of contraceptives, such as the transdermal patch and the transvaginal ring, avoid the need for daily administration and, as such, may enhance convenience of use for the patient.

❺ Oral, transdermal, and transvaginal contraceptives, as well as intrauterine devices and most barrier contraceptives, do not protect against sexually transmitted diseases.

❻ When a contraceptive dose is missed, the risk of accidental pregnancy may be increased. Depending on how many doses were missed, the contraceptive formulation being used, and the phase of the cycle during which doses were missed, counseling regarding the use of additional methods of contraception may be warranted.

Historically, the 1950s represented an important time in the control of human fertility. It was during that decade that the first combined oral contraceptives were developed. Shortly after the discovery that the exogenous administration of hormones such as progesterone successfully blocked ovulation, the use of hormonal steroids quickly became the most popular method of contraception worldwide. Specifically, combined oral contraceptives represent the most commonly used reversible form of contraception today, and it is estimated that nearly 100 million women worldwide take oral contraceptives.[1] Further, in the United States, it is estimated that at some time during their lives, more than 80% of women born since 1945 have used oral

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contraceptives.[1,2] Since the introduction of oral contraceptives, many newer forms of contraceptives have been developed and are available for use in the United States. New hormone delivery systems, such as transdermal systems, transvaginal systems, and intrauterine devices (IUDs), offer women effective and more convenient alternatives to oral contraceptives.

EPIDEMIOLOGY

According to the National Survey of Family Growth, approximately 6.3 million pregnancies occur annually in the United States.[3] Of these pregnancies, it is estimated that nearly 3.15 million are unintended.[3,4] Contributing to the risk of unintended pregnancy is the fact that approximately 7.5% of all women who are at risk of becoming pregnant do not use any form of contraception.[3,4] In addition, many women who do use contraceptives use their chosen method of contraception imperfectly, and this also increases the risk of undesired pregnancy. Given these statistics, the provision of appropriate and adequate instruction to patients regarding how to use contraceptive methods effectively is essential in order to reduce the risk of unwanted pregnancy.

Exposure to sexually transmitted diseases (STDs) is also a concern for women who are sexually active. It is estimated that 15 million people in the United States become newly infected annually with an STD.[5] Given that not all methods of contraception protect the user adequately against STDs, the provision of proper patient education by health care professionals regarding this risk is absolutely essential.

PHYSIOLOGY

The female menstrual cycle is divided into four functional phases: follicular, ovulatory, luteal, and menstrual.[6] The follicular phase starts the cycle, and ovulation generally occurs on day 14. The luteal phase then begins and continues until menstruation occurs.[6] The menstrual cycle is regulated by a negative-feedback hormone loop between the hypothalamus, anterior pituitary gland, and ovaries[6] (Fig. 45–1).

Initially, the hypothalamus releases gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary to produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH). The levels of FSH and LH released vary depending on the phase of the menstrual cycle. Just prior to ovulation, FSH and LH both are at their peak levels. The FSH helps to promote growth of the follicle in preparation for ovulation by causing granulose cells lining the follicle to grow and produce estrogen. The LH promotes androgen production by theca cells in the follicle, promotes ovulation and oocyte maturation, and converts granulose cells to cells that secrete progesterone after ovulation.

Conception is most likely to occur when viable sperm are present in the upper region of the reproductive tract at the time of ovulation. Fertilization occurs when a spermatozoan penetrates an ovum. Approximately 6 to 8 days after ovulation, attachment of the early embryo to the lining of the uterine cavity, or implantation, occurs.

PREVENTION OF PREGNANCY: CONTRACEPTIVES AND DEVICES

Goals of Contraception/Desired Outcome

As to be expected, the most common goal of contraception is the prevention of pregnancy. However, some patients may use contraceptive methods for other benefits, such as menstrual cycle regulation, reduction of premenstrual symptoms, or treatment of acne.

Choice of Contraceptives: Important Considerations

When helping a patient decide on a contraceptive, the most important goal is to find an option that the patient is comfortable with and that the clinician feels will be beneficial for the patient. It is imperative to explain the side effects, safety concerns, and non-contraceptive benefits of each alternative to the patient so that she may make an informed decision. Fertility goals can be different for each patient. It must be determined if the goal is to postpone contraception, space out the next pregnancy, or avoid further pregnancy altogether. Also, a clinician must understand the patient's desire to have or not have a regular bleeding pattern because many contraceptives will affect menses.

As discussed later in this chapter, contraindications exist for various forms of contraception. Patients must be evaluated completely by a health care professional to rule out any medical contraindications to certain contraceptives. The physical examination also will allow health care professionals to determine if there are other medical concerns, such as hypertension, diabetes, or liver disease, that need to be considered when determining the appropriate contraceptive agent. Clinicians also should review family history for potential risks with certain forms of birth control.

Sexual behavior of the female must be determined to understand the risk for STDs. Women who are not in a monogamous relationship must consider their risk of STDs as a factor in their contraceptive decision. Some barrier methods protect against STDs, but agents such as hormonal contraceptives are not capable of preventing STDs if used alone.

Personal preference plays a large role when determining the best contraceptive option. For instance, if a woman is not interested in using a method that will interrupt sexual activity, then a diaphragm would not be appropriate. Preference of the sexual partner may be important as well. Certain agents such as male condoms require the male partner to play an active role in contraception.

Cost is also another related issue for patients. Insurance may not cover all forms of contraception, and patients may have to bear the entire cost for certain options.

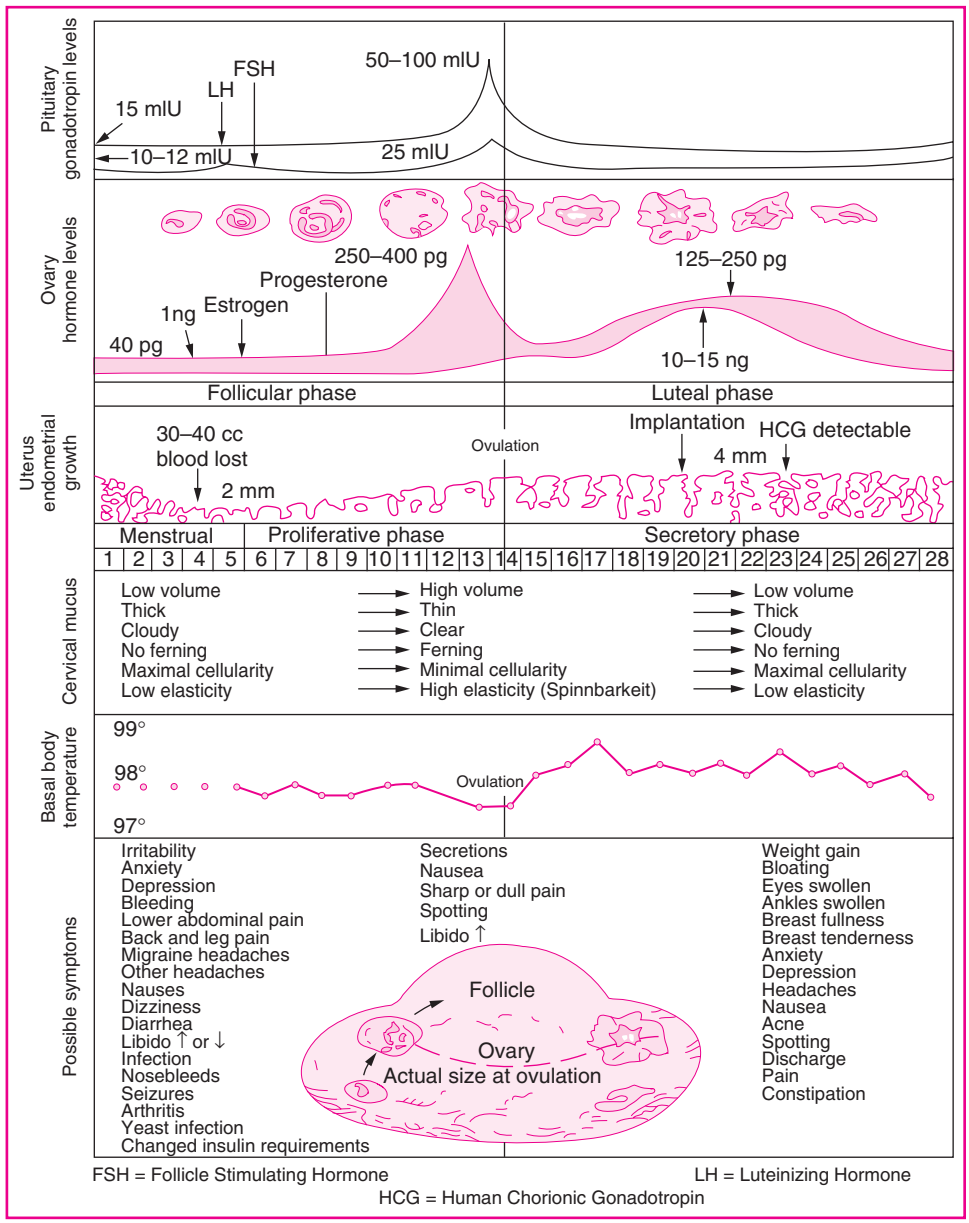


FIGURE 45–1. Menstrual cycle events.[6] (Reprinted, with permission, from Hatcher RA, Namnoum AB. The menstrual cycle. In: Hatcher RA, Trussel J, Stewart F, et al, (eds.) *Contraceptive Technology*. 18th revised ed. New York: Ardent Media; 2004: 63–72.)

Efficacy of Contraceptives

The accidental pregnancy rate for women who do not use any form of contraception is unknown. Therefore, it is difficult to determine the true efficacy of contraceptives in preventing unwanted pregnancy. Table 45–1 shows the percentage of women who experience unintended pregnancy within 1 year of use of a contraceptive.[7]

Oral Contraceptives (Combined)

Combined oral contraceptives contain a combination of a synthetic estrogen and one of several steroids with progestational activity. Most oral contraceptives contain one of two types of estrogen: ethinyl estradiol, which is pharmacologically active, or mestranol, which must be converted by the liver to ethinyl estradiol. Many different progestins are found in the various oral contraceptives. These include norethindrone, norethindrone acetate, ethynodiol diacetate, norgestrel, levonorgestrel, desogestrel, norgestimate, and drospirenone.

The primary mechanism by which combined oral contraceptives prevent pregnancy is through inhibition of ovulation. FSH and LH regulate the production of estrogen and progesterone by the ovaries. Secretion of estrogen and progesterone by the ovaries occurs in a cyclic manner, which, in turn, determines the regular hormonal changes that occur in the uterus, vagina, and cervix associated with the menstrual cycle. Cyclic changes in the levels of estrogen and progesterone in the

TABLE 45–1. Unintended Pregnancy Rates[7]

Method	Percent of Women Experiencing an Unintended Pregnancy within the First Year of Use		Percent of Women Continuing Use at 1 Year[c]
	Typical Use[a]	Perfect Use[b]	
No method	85	85	
Spermicides	29	18	42
Withdrawal	27	4	43
Periodic abstinence	25		51
Calendar		9	
Ovulation method		3	
Symptothermal		2	
Postovulation		1	
Cap			
Parous women	32	20	46
Nulliparous women	16	9	57
Diaphragm	16	6	57
Condom			
Female (Reality)	21	5	49
Male	15	2	53
Combined pill and minipill	8	0.3	68
Ortho Evra patch	8	0.3	68
NuvaRing	8	0.3	68
Depo-Provera	3	0.3	56
IUD			
ParaGard (copper T)	0.8	0.6	78
Mirena (LNG-IUS)	0.1	0.1	81
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.1	100

[a]Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason. Estimates of the probability of pregnancy during the first year of typical use for spermicides, withdrawal, periodic abstinence, the diaphragm, the male condom, the pill, and Depo-Provera are taken from the 1995 National Survey of Family Growth corrected for underreporting of abortion.
[b]Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
[c]Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.
Adapted with permission.

blood, together with FSH and LH, modulate the development of ova and the occurrence of ovulation. The estrogen component of combined oral contraceptives is most active in inhibiting FSH release.[1] However, at high enough doses, estrogens also may cause inhibition of LH release. In low-dose combination oral contraceptives, the progestin component causes suppression of LH.[1] Ovulation is prevented by suppression of the mid-cycle surge of both FSH and LH,[1] and this suppression, which is induced by combined oral contraceptives, mimics the physiologic changes that occur during pregnancy.

Although suppression of FSH and LH is the primary mechanism by which combined oral contraceptives prevent ovulation, there are other mechanisms by which these hormones work to prevent pregnancy. Other mechanisms include reduced penetration of the egg by sperm, reduced implantation of fertilized eggs, thickening of cervical mucus to prevent sperm penetration into the upper genital tract, and slowed tubal motility, which may delay transport of sperm.[1] Thus, in addition to inhibition of ovulation, combined oral contraceptives induce changes in the cervical mucus and endometrium that make sperm transport and implantation of the embryo unlikely.[1]

Table 45–2 contains a partial listing of the many oral contraceptives available today.[8] Although the efficacy of combined oral contraceptives was quickly demonstrated following their introduction into the market, it took longer to determine their safety and acceptability for patients. Since the mid-1960s, ethinyl estradiol has been the primary estrogen used in most combined oral contraceptives. However, the amount of ethinyl estradiol used in combined oral contraceptives has decreased progressively since that time, and most pills now contain 35 mcg of ethinyl estradiol or less. In addition, to reduce side effects and improve tolerability associated with oral contraceptive use, new progestins and different routes of administration have been explored. In an attempt to minimize the undesirable androgenic side effects associated with

TABLE 45–2. Some Available Oral Contraceptives[8]

Brand Name	Estrogen (mcg/Tablet)	Progestin (mg/Tablet)
Monophasic Preparations		
Loestrin 21 1/20	EE (20)	Norethindrone (1)
Loestrin Fe 1/20	EE (20)	Norethindrone (1)
Alesse	EE (20)	Levonorgestrel (0.1)
Desogen	EE (30)	Desogestrel (0.15)
Ortho-Cept	EE (30)	Desogestrel (0.15)
Levlen	EE (30)	Levonorgestrel (0.15)
Nordette	EE (30)	Levonorgestrel (0.15)
Yasmin	EE (30)	Drospirenone (3)
Lo/Ovral	EE (30)	Norgestrel (0.3)
Loestrin 21 1.5/30	EE (30)	Norethindrone (1.5)
Loestrin Fe 1.5/30	EE (30)	Norethindrone (1.5)
Ortho-Cyclen	EE (35)	Norgestimate (0.25)
Ovcon-35	EE (35)	Norethindrone (0.4)
Brevicon	EE (35)	Norethindrone (0.5)
Necon 0.5/35	EE (35)	Norethindrone (0.5)
Necon 1/35	EE (35)	Norethindrone (1)
Ortho-Novum 1/35	EE (35)	Norethindrone (1)
Demulen 1/35	EE (35)	Ethynodiol diacetate (1)
Zovia 1/35E	EE (35)	Ethynodiol diacetate (1)
Ovral	EE (50)	Norgestrel (0.5)
Ovcon-50	EE (50)	Norethindrone (1)
Demulen 1/50	EE (50)	Ethynodiol diacetate (1)
Zovia 1/50E	EE (50)	Ethynodiol diacetate (1)
Necon 1/50	Mestranol (50)	Norethindrone (1)
Norinyl 1 + 50	Mestranol (50)	Norethindrone (1)
Ortho-Novum 1/50	Mestranol (50)	Norethindrone (1)
Biphasic Preparations		
Mircette	EE (20, 0,10)	Desogestrel (0.15)
Kariva	EE (20, 0, 10)	Desogestrel (0.15)
Ortho-Novum 10/11	EE (35)	Norethindrone (0.5,1)
Necon 10/11	EE (35)	Norethindrone (0.5,1)
Triphasic Preparations		
Estrostep Fe	EE (20, 30, 35)	Norethindrone (1)
Tri-Levlen	EE (30, 40, 30)	Levonorgestrel (0.05, 0.075, 0.125)
Triphasil	EE (30, 40, 30)	Levonorgestrel (0.05, 0.075, 0.125)
Ortho Tri-Cyclen	EE (35)	Noregestimate (0.18, 0.215, 0.25)
Tri-Norinyl	EE (35)	Norethindrone (0.5, 1, 0.5)
Ortho-Novum 7/7/7	EE (35)	Norethindrone (0.5, 0.75, 1)
Ortho Tri-Cyclen Lo	EE (25)	Norgestimate (0.18, 0.215, 0.25)
Velivet	EE (25)	Desogestrel (0.1, 0.125, 0.15)
Cyclessa	EE (25)	Desogestrel (0.1, 0.125, 0.15)

EE, ethinyl estradiol.

the progestins of combined oral contraceptives, the type of synthetic progestin was modified to create "third generation" progestins (e.g., desogestrel and norgestimate). These synthetic progestins are extremely potent in their ability to inhibit ovulation and prevent pregnancy.

Combined oral contraceptives are available in monophasic, biphasic, and triphasic preparations. Monophasic preparations contain fixed doses of estrogen and progestin in each active pill. Although all three preparations contain both estrogens and progestins, biphasic and triphasic preparations differ from monophasic preparations in that they contain varying proportions of one or both hormones during the pill cycle. These preparations were introduced to reduce the amount and total monthly dose of progestins, as well as to mimic more closely the hormonal changes of the menstrual cycle. However, there is no evidence to suggest that the biphasic and triphasic preparations offer any clinical advantage over the monophasic pills.[8]

Non-contraceptive Benefits of Combined Oral Contraceptives

In addition to preventing pregnancy, there are several non-contraceptive benefits associated with the use of combined oral contraceptive pills. Many of the potential non-contraceptive benefits are highlighted below.

Reduction in the Risk of Endometrial Cancer

The risk of endometrial cancer among women who have used oral contraceptives for at least 1 year is approximately 40% less than the risk in women who have never used oral contraceptives.[9] There is additional evidence to suggest that the benefit of reduced risk for endometrial cancer is detectable within 1 year of use[10–12] and that the benefit may persist for years following discontinuation of oral contraceptives.[9]

Reduction in the Risk of Ovarian Cancer

When compared with women who have never used oral contraceptives, women who have used oral contraceptives for 4 years or less are 30% less likely to develop ovarian cancer. There is also additional evidence to suggest that the longer the duration of oral contraceptive use, the greater the reduction in the risk of ovarian cancer. Women who have taken oral contraceptives for 5 to 11 years are 60% less likely to develop ovarian cancer, and women who have taken oral contraceptives for more than 12 years are 80% less likely to develop ovarian cancer. As with the reduced risk of endometrial cancer, there is evidence to suggest that the benefit of the reduced risk of ovarian cancer may persist for years following discontinuation of oral contraceptives.[10–12]

Improved Regulation of Menstruation

Women who take oral contraceptives typically experience more regular menstrual cycles. In general, oral contraceptive use is associated with less cramping and **dysmenorrhea.**[1,8] Also, women who take oral contraceptives experience fewer days of menstruation each month and as a result experience less blood loss with each menstrual period.[1,13] Some studies suggest that oral contraceptive use decreases overall monthly menstrual flow by 60% or more, which may be particularly beneficial in women who are anemic.[1]

Relief of Benign Breast Disease

Women who use oral contraceptives are less likely to develop benign breast cysts or **fibroadenomas.**[1,8]

Prevention of Ovarian Cysts

Because oral contraceptives suppress ovarian stimulation, women who take them are less likely to develop ovarian cysts.[8]

Reduction in the Risk of Symptomatic Pelvic Inflammatory Disease

The risk of hospitalization owing to symptomatic pelvic inflammatory disease caused by gonorrheal infection is reduced in oral contraceptive users.[14] While the exact protective mechanism is unknown, it is believed that thickening of the cervical mucus and/or reduction in the ability of pathogens to enter the fallopian tubes may contribute.[1]

Improvement in Acne Control

All combination oral contraceptives can improve acne by increasing sex hormone–binding globulin and decreasing free testosterone concentrations.[8] The newer progestins, such as desogestrel and norgestimate, are believed to have less androgenic activity.[8] However, it is not clear that combined oral contraceptives containing these progestins confer any advantage over other combined oral contraceptives with respect to their ability to improve acne control. Only Ortho Tri-Cyclen® (ethinyl estradiol and norgestimate) and Estrostep Fe® (ethinyl estradiol and norethindrone acetate) are approved by the Food and Drug Administration (FDA) for the treatment of acne.[1,8]

Potential Risks of Combined Oral Contraceptives

While there are many non-contraceptive benefits associated with the use of combined oral contraceptives, their use is not without risk or potential for adverse effects.

Sexually Transmitted Diseases

Since the use of combined oral contraceptives may decrease the use of selected barrier contraceptive methods that do protect against STDs (e.g., latex condoms), one of the most common risks associated with the use of oral contraceptives is the risk of acquiring an STD.[8]

Cardiovascular Events and Hypertension

A World Health Organization (WHO) collaborative study found that high-dose (50 mcg or more of ethinyl estradiol) oral contraceptive users with uncontrolled hypertension have an increased risk of experiencing a myocardial infarction or stroke.[8,15] In this study, women who had the lowest risk for experiencing a myocardial infarction or stroke were those who did not smoke, took low-dose oral contraceptives, and had their blood pressure checked prior to beginning oral contraceptives.[16–18] Hypertension secondary to oral contraceptive use is thought to occur in up to 1% to 3% of women, and this is believed to be attributed to the effect that estrogens and progestins can have on aldosterone activity.[1] Given this and the risk for cardiovascular events, women should have their blood pressure checked prior to initiating oral contraceptives, as well as periodically throughout oral contraceptive use. If significant elevations in blood pressure are noted, oral contraceptives should be discontinued. Estrogen-containing contraceptives are not recommended for smokers who are older than 35 years of age, for women with hypertension, or for women who experience migraine headaches (especially those with focal neurologic symptoms).[8,19]

Venous Thromboembolism

It is believed that the estrogen component of combined oral contraceptives stimulates the liver to produce higher levels of clotting factors. Lower-dose estrogen pills have been associated with a three- to four-fold increase in the risk of venous thromboembolism compared with women who do not use oral contraceptives.[8] Contraceptive users at greatest risk for the development of venous thromboembolism include those who are obese, those who smoke, those who have hypertension, and those with diabetes complicated by end-organ damage. It is important to note, however, that the increase in risk of venous thromboembolism in oral contraceptive users is lower than that of pregnant women.[8] Newer progestins, such as desogestrel, were reported initially to be associated with a higher risk of venous thromboembolism.[20,21] However, prospective studies validating this risk are lacking. In general, progestin-only contraceptives are preferred for women who are at increased risk of cardiovascular or thromboembolic complications, including women with a prior history of thromboembolic disease.[8]

Glucose Intolerance

Older oral contraceptive formulations containing higher doses of hormones were shown in some cases to induce hyperglycemia.[1] Because estrogens may inhibit the release of insulin from islet cells of the pancreas, low-dose estrogen formulations may be preferred in patients with diabetes. Progesterone competes with insulin for binding to its receptor. Although it is thought that progestins may increase insulin resistance, the newer progestins are thought to be less androgenic and have little effect on carbohydrate and lipid metabolism. In general, the use of combined oral contraceptives is relatively contraindicated in patients with diabetes.

Gallbladder Disease

In women with preexisting gallstones, low-dose estrogen-containing oral contraceptives may enhance the potential for the development of symptomatic gallbladder disease.[1] Although this risk has not been demonstrated with the use of higher-dose oral contraceptives, combined oral contraceptives containing estrogen should be used with caution in patients with a history of gallbladder disease.

Hepatic Tumors

Although the use of oral contraceptives is not associated with an increased risk for the development of hepatocellular

carcinoma, long-term use of high-dose oral contraceptives has been associated with the development of benign liver tumors.[1] Because even benign liver tumors may pose significant risk to the patient, oral contraceptives should be discontinued if liver enlargement is noted on physical examination.

Cervical Cancer

There appears to be an increased risk for the development of cervical cancer among long-term users of oral contraceptives.[1] Whether or not this increase in risk can be attributed directly to the use of oral contraceptives is uncertain, however. Data suggest that oral contraceptive users, on average, tend to have more sexual partners and use condoms less frequently, and as a result, this may increase their susceptibility to becoming infected with human papilloma virus (HPV), a known risk factor for cervical cancer.

Breast Cancer

While a history of breast cancer traditionally has been considered an absolute contraindication to the use of oral contraceptives, most recent studies evaluating the relationship between oral contraceptive use and the risk for breast cancer suggest little, if any, association between the two. A recent study illustrated that current or past use of oral contraceptives among women between the ages of 35 and 64 was not associated with an increased risk for the development of breast cancer.[22] In older studies that have suggested a link between oral contraceptive use and the diagnosis of breast cancer, the cancers diagnosed in those studies were found to be more localized.[23] Although the relationship between oral contraceptive use and the potential for breast cancer in older patients is becoming better understood, still the question of risk for breast cancer diagnosis in oral contraceptive users under age 35 is less clear.[1]



Patient Encounter, Part 1

RC, a 22-year-old woman, presents to your clinic requesting information on contraception. You begin to take a history and determine that the patient is currently sexually active and is not using any method of birth control. Her past medical history is significant only for acne, and she takes no medications except occasional ibuprofen for menstrual cramps. On further questioning, you discover that she has a positive family history for hypertension and coronary artery disease. As you begin to discuss various contraceptive options with the patient, it is clear that she has a preference for an oral contraceptive agent.

- What additional information do you need to know before recommending a contraceptive for this patient?
- Based on the information provided by the patient, what oral contraceptive agent would you recommend for the patient and why?
- What education would you provide to this patient regarding the risks associated with oral contraceptive use?

TABLE 45–3. ❶ Contraindications to the use of Combined Oral Contraceptives[1]

Absolute Contraindications
History of thromboembolic disease
History of stroke (or current cerebrovascular disease)
History of (or current) coronary artery disease
History of carcinoma of the breast (known or suspected)
History of any estrogen-dependent neoplasm
Undiagnosed abnormal uterine bleeding
Pregnancy (known or suspected)
Heavy smokers (greater than or equal to 15 cigarettes per day) who are greater than 35 years of age
History of hepatic tumors (benign or malignant)
Active liver disease
Relative Contraindications
Smoking (less than or equal to 15 cigarettes per day) at any age
History of migraine headache disorder
Hypertension
Fibroid tumors of the uterus
Breast-feeding
Diabetes

❶ Absolute and relative contraindications to the use of oral contraceptives are listed in Table 45–3.[1]

Adverse Effects of Oral Contraceptives and Their Management

As with all medications, there are potential adverse effects with combined oral contraceptives (COCs). ❷*Many side effects can be minimized or avoided by adjusting the estrogen and/or progestin content of the oral contraceptive.* It is also important to have proper patient selection for oral contraceptives because some women are at increased risk for potentially serious side effects.

Many women stop their oral contraceptives owing to side effects such as headaches, nausea, vomiting, or weight gain that occur during oral contraceptive use. Package labeling reports a higher incidence of these side effects, although it cannot be determined if they occurred because of the pill or just happened when the women were on the pill.[1] One double-blind trial compared women taking oral contraceptives with women taking placebo for 6 months. A similar percentage of patients in each group experienced headaches, nausea, vomiting, **mastalgia,** and weight gain, and there were no significant differences in the traditional "hormone-related" side effects.[24] Given that oral contraceptives often are discontinued owing to side effects, proper counseling before initiation of COCs is necessary.

Between 30% and 50% of women complain of breakthrough bleeding or spotting when initiated on oral contraceptives. These side effects tend to resolve by the third or fourth cycle.[1] Before changing formulations, other more serious causes of bleeding or spotting, such as pregnancy, infection, poor absorption of the oral contraceptive owing to drug interaction, or gastrointestinal problems should be ruled out. Once these causes

have been ruled out, the timing of the spotting must be determined in order to adjust the formulation appropriately.

Women who have spotting or bleeding before they finish their active pills need a higher progestin content to increase endometrial support. Either a monophasic formulation with a higher progestin or a triphasic formulation with an increasing dose of progestin would be appropriate. Women with continued bleeding after menses need more estrogen support. Either increasing the estrogen component or having a lower early progestin component (in triphasic pills) should be sufficient. If mid-cycle bleeding occurs, it is more difficult to ascertain the reasoning. It may be best to increase both the estrogen and progestin component for these women.[1]

Hormonal methods of contraception usually will decrease the amount of withdrawal bleeding quite significantly, and patients need to be made aware of this. Lower-dose estrogen formulations may increase the risk of breakthrough bleeding. Switching to a higher estrogen formulation or to a triphasic formulation will help to minimize breakthrough bleeding and will increase the amount of withdrawal bleeding if desired by the patient.

Acne, oily skin, and **hirsutism** are all side effects from progestins with increased androgenicity. Older progestins such as norgestrel and levonorgestrel have more androgenic effects, whereas agents containing norgestimate or desogestrel are less likely to have such side effects. If patients are complaining of such side effects, switching to a product with a lower risk of androgenic effects is appropriate.

Gastrointestinal complaints are seen often with oral contraceptives. Estrogen can induce nausea and vomiting via the central nervous system, whereas progesterone slows peristalsis, causing constipation and feelings of bloating and distention.[1] Most women will adjust to the symptoms, and the symptoms often will resolve within 1 to 3 months. If women are unable to tolerate the gastrointestinal side effects, then either a decrease in ethinyl estradiol to a low-dose 20 mcg formulation may minimize nausea or a decrease in progestin may minimize bloating and constipation. Progestin-only products may be considered if even low-dose ethinyl estradiol causes nausea. It also can be suggested to take the medication with food or at night to minimize gastrointestinal side effects.

Headaches are a common occurrence for women but must be evaluated because they are a major warning sign for stroke. If headaches begin or become worse after initiation of COCs, all differential diagnoses must be considered. A patient's blood pressure should be evaluated to rule out hypertension. If any neurologic symptoms or blurred vision occur with the headache, the oral contraceptive should be stopped immediately. Migraine headaches with aura showed a significant increase in the risk for ischemic stroke in one WHO study.[17] If the headaches are not serious but still are troublesome to the patient, the following changes are suggested: (1) discontinue the oral contraceptive, (2) lower the dose of estrogen, (3) lower the dose of progestin, and (4) eliminate the pill-free interval for two to three consecutive cycles (for women with headaches during the pill-free interval only).[1]

Although rare, some women may complain of a decrease in libido. This often is found to coincide with feelings of depression. Alterations to vaginal lubrication and free testosterone levels may occur with some COCs, and both can relate to decreased libido.[25] Low levels of estrogen can decrease vaginal lubrication as well and make intercourse painful. Use of the vaginal hormonal ring (NuvaRing®) may help with lubrication problems.[1]

Dyslipidemias can occur from hormone therapy. Estrogen is known to cause an increase in high-density lipoprotein cholesterol (HDL-C), triglycerides, and total cholesterol levels and to decrease low-density lipoprotein cholesterol (LDL-C). Androgenic progestins are more likely to decrease HDL-C and triglycerides and increase LDL-C. Depending on the ratio of estrogen to progestin content, the HDL-C, LDL-C, and triglyceride levels may fluctuate up or down. In women with no risk factors for dyslipidemias, it is not necessary to obtain a baseline lipid panel. However, if the lipid panel is monitored, and if dyslipidemia occurs, then it is recommended to go with a more estrogenic and less androgenic formulation. In women with a triglyceride level greater than 350 mg/dL (3.96 mmol/L) at baseline, estrogen-containing formulations should be used only with caution, and low doses of 20 to 25 mcg ethinyl estradiol or a progestin-only formulation might be preferred.[1]

Mastalgia can occur in up to 30% of women taking oral contraceptives and is most likely due to the estrogen component. The average woman has a 20% increase in breast volume in the luteal phase owing to venous and lymphatic engorgement. Estrogen also causes adipose cell hypertrophy in the breast.[1] Lower-dose pills (20 mcg) produce less mastalgia than those with 35 mcg of ethinyl estradiol.[26] If tenderness occurs prior to menses, switching to a contraceptive that offers extended cycle length (see "Unique Oral Contraceptives" below) can minimize problems as well.

Women often are concerned about using oral contraceptives for fear of gaining weight. It has been proven that low-dose oral contraceptives (less than or equal to 50 mcg ethinyl estradiol) do not increase the risk of weight gain in women compared with placebo.[24] Estrogen can cause hypertrophy of adipose cells, and therefore, women see an increase in measurement of their breasts, hips, and thighs.[1] Decreasing the estrogen content of the COCs will minimize this effect. Weight gain associated with premenstrual fluid retention may occur with the combination of estrogen and a higher androgenic progestin. Switching to a lower-dose estrogen and a progestin with less androgenic activity may be beneficial in this situation.[1]

Additional side effects have been noted in some women. Women with contact lenses may have visual changes and more disturbances with lenses. If normal saline eye drops do not help, referral to an ophthalmologist is recommended. **Melasma** and **chloasma** can occur secondary to estrogen stimulation of melanocyte production. Women with darker pigmentation are more susceptible. The melasma may not be

completely reversible on discontinuation. Progestin-only products may be preferable, and sunscreen use is highly recommended.[1]

As described earlier, many of the side effects of COCs may be minimized by adjusting the amount of hormones within the pill. However, while low- and ultra-low-dose COCs may cause fewer side effects, it is important to note that in the event that doses are missed, such COCs may be more likely to result in contraceptive failure.

Progestin-Only Pills

For women unable to take estrogen-containing oral contraceptives, there is an alternative—oral contraceptives containing only progestin. There are two active ingredients used in this form of contraception, norethindrone and norgestrel. These agents are slightly less effective than COCs but have other advantages over COCs. Progestin-only products have not shown the risk of thromboembolic events as products containing estrogen have. Therefore, women at increased risk for or with a history of thromboembolism may be good candidates for progestin-only oral contraceptives. Also, these products can minimize menses, and some women have **amenorrhea.** These products should be taken at the same time every day, and there is no pill-free or hormone-free period.

Unique Oral Contraceptives

Along with varying doses of ethinyl estradiol and different progestins, there are also formulation modifications that may benefit various patient situations. These formulations include products such as Seasonale®, Ortho Tri-Cyclen®, Estrostep Fe®, Yasmin®, Mircette®, and Ovcon 35®. Each of these products may show benefit in certain women owing to their unique characteristics.

Seasonale® (levonorgestrel/ethinyl estradiol) is a monophasic combination that has been marketed previously. This product is packaged as a 91-day treatment with 84 active tablets that are taken consecutively and then 7 placebo tablets. The extended cycle length of this product allows for one menstrual cycle per "season," or four per year. This formulation may be appealing to women with perimenstrual side effects or those at higher risk for anemia with menstrual bleeding. Seasonale® may improve anxiety, headache, fluid retention, dysmenorrhea, breast tenderness, bloating, and menstrual migraines. Although, in the SEA 301 clinical trial comparing the efficacy of Seasonale® with that of an equivalent-dosage 28-day cycle regimen, 7.7% versus 1.8% of women discontinued prematurely for unacceptable bleeding.[27] The risk of intermenstrual bleeding and/or spotting is higher for patients taking Seasonale® than for patients taking 28-day-regimen COCs.[27]

Ortho Tri-Cyclen® (norgestimate/ethinyl estradiol) and Estrostep Fe® (norethindrone acetate/ethinyl estradiol) both have an approved indication for treatment of moderate acne vulgaris in females 15 years of age or older desiring contraception who have failed topical antiacne medication. This can help clinicians to streamline medications by serving dual purposes.

Yasmin® (drospirenone/ethinyl estradiol) is the only oral contraceptive that uses the progestin drospirenone. This hormone not only has antiandrogenic properties but also showed antimineralcorticoid activity in preclinical trials. It has a unique application in young women who experience problems associated with producing too much androgen. Drospirenone is a spironolactone analog, and the 3 mg dose available in Yasmin® has antimineralcorticoid activity equal to 25 mg spironolactone. It can affect the sodium and water balance in the body, although it has not shown superior efficacy for side effects such as bloating compared with other oral contraceptives. Caution should be used in women with chronic conditions or other medications that may affect serum potassium.[28] It is advised to check a baseline potassium level in patients at risk for hyperkalemia, such as those taking angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.

Mircette® (desogestrel/ethinyl estradiol) has a unique dosing schedule. After the usual 21 active tablets, there are only 2 tablets with inert ingredients. The last 5 tablets in the package have 10 mcg of ethinyl estradiol. In theory, this may minimize bleeding during the menstrual cycle, although the clinical significance of this dosing schedule has not been established.[29] It is important to counsel patients to complete the entire pack and not to discard the last 7 days of medication.

Finally, another unique formulation is a chewable tablet available to women who have difficulty swallowing medications. Ovcon® 35 (norethindrone/ethinyl estradiol) has all 28 tablets in chewable form and has added spearmint flavoring.[30] Along with each of these unique oral contraceptives, there are preparations currently being studied that contain 24 active pills and 4 placebo pills per pack, shortening the hormone-free period.[1]



Patient Encounter, Part 2: Adverse Effects

After 10 weeks of taking Desogen, RC returns to your clinic complaining of breakthrough bleeding during her third week of active pills. The patient also reports a 3-lb weight gain since starting Desogen, and because she has heard that birth control pills cause weight gain, she expresses concern and wants to discuss other birth control options.

- What are some potential causes of the breakthrough bleeding that the patient has been experiencing?
- What information can you provide to the patient regarding the potential association between weight gain and oral contraceptive use?
- What strategy would you recommend to eliminate or minimize the potential adverse effects experienced by the patient?

Drug Interactions with Oral Contraceptives

Ethinyl estradiol is metabolized in the liver via the cytochrome P-450 system. It is metabolized primarily via CYP450 3A4. When reviewing drug interactions of oral contraceptives, ❸ *it is important to keep in mind that antibiotic administration during contraceptive use may decrease the efficacy of many combined contraceptives.* Refer to Table 45–4 for a list of common drug interactions seen with oral contraceptives.[1, 31]

Non-oral Hormonal Contraceptives

❹ *As an alternative to oral contraceptive pills, which must be taken daily in order to reliably prevent pregnancy, non-oral contraceptives in the form of transdermal, transvaginal, and injectable preparations are available and offer patients safe and effective alternatives to the pills for prevention of pregnancy. These formulations also do not require daily administration, making them more convenient than the pill formulations.*

Ortho-Evra® is a transdermal patch that contains both an estrogen (20 mcg of ethinyl estradiol) and a progestin (150 mcg of norelgestromin). A new patch is applied to the abdomen, buttocks, upper torso, or upper (outer) arm once weekly for 3 weeks, followed by 7 patch-free days.[8] Although some women have noted irregular bleeding more commonly during the first two cycles of patch use, the patch has been demonstrated to provide similar menstrual cycle control and contraceptive efficacy to that of combined oral contraceptives.[32] It is important to note, however, that higher contraceptive failure rates are seen when the patch is used in women weighing more than 90 kg.[8,32] Further, Ortho McNeil (the manufacturer of Ortho-Evra®) recently updated the prescriber information for the product to indicate that women who take Ortho-Evra® are exposed to approximately 60% more estrogen than women who take COCs with 35 mcg estrogen.[33] The clinical significance of this is unknown. With the exception of a slightly higher reported incidence of breast discomfort and local skin irritation, the side effects seen with the patch are very similar to those observed with COCs.[8,34]

The NuvaRing® is a unique transvaginal delivery system that provides 15 mcg ethinyl estradiol and 120 mcg etonogestrel for the prevention of ovulation. The NuvaRing® is inserted into the vagina on or before day 5 of the menstrual cycle and is removed

TABLE 45–4. Commonly Seen Drug Interactions with COCs[1,31]

Medication	Mechanism	Clinical Effect
Anticonvulsants (carbamazepine, oxcarbazepine, phenytoin, phenobarbital, primidone, topiramate, and felbamate)	Increase metabolism of COCs via induction of various cytochrome P-450 enzymes	Decrease efficacy of OCs (EE doses less than 35 mcg are not recommended in women on these medications)
Benzodiazepines (alprazolam)	COCs may inhibit oxidative metabolism	Increase side effects of benzodiazepines
Corticosteroids (hydrocortisone, methylprednisolone, prednisone)	COCs may inhibit metabolism of corticosteroids	Increase side effects of corticosteroids
Griseofulvin	Increase metabolism of COCs	Decrease efficacy of COCs; backup method of contraception is recommended
Modafinil	Increase metabolism of COCs	Decrease efficacy of COCs; alternative method of contraception is recommended
Penicillins (amoxicillin, ampicillin); tetracyclines (doxycycline, minocycline, tetracycline)	Broad-spectrum antibiotics may alter intestinal flora, reducing enterohepatic circulation of estrogen metabolites; although the drop in estrogen levels has been shown to be only statistically significant, rather than clinically significant	Decrease efficacy of COCs, although the recommendation of a backup method of contraception is controversial
Protease inhibitors (amprenavir, nelfinavir, lopinavir, saquinavir, ritonavir)	Increase or decrease serum levels of estrogen and progestins	Decrease efficacy of COCs or increase side effects of COCs
Rifampin, rifabutin	Increase metabolism of COCs	Decrease efficacy of COCs; backup method of contraception is recommended
Selegiline	COCs decrease metabolism of selegiline	Increase side effects of selegiline; may adjust dose of selegiline if needed
St. John's wort	Increase metabolism of COCs via induction of various cytochrome P-450 enzymes	Decrease efficacy of COCs; avoid use with COCs
Theophylline	COCs decrease theophylline clearance by 34% and increase the $t_{1/2}$ by 33%	Increase side effects of theophylline

from the vagina after 3 weeks.[8] Seven days after the ring is removed, a new ring is inserted. In clinical trials, the NuvaRing® demonstrated comparable efficacy and cycle control with that of COCs.[8] Side effects seen with NuvaRing® are also similar to those observed in women taking COCs.[8,35] NuvaRing® should not be removed during intercourse. If the ring falls out or is removed for more than 3 hours, efficacy could be compromised, and a backup method of contraception is recommended until a new ring has been in place for 7 days.

Depo-Provera® is a progestin-only injectable contraceptive that contains depot medroxyprogesterone acetate. Depo-Provera® is administered intramuscularly as a 150-mg injection once every 3 months. An advantage of Depo-Provera® is that it provides an estrogen-free method of contraception either for women in whom estrogens are contraindicated or for women who cannot tolerate estrogen-containing preparations. Depo-Provera® is extremely effective in preventing pregnancy. However, the incidence of menstrual irregularities (including amenorrhea) and weight gain appears to be much greater than that seen with COCs. The use of Depo-Provera® also has been demonstrated to result in significant loss of bone mineral density (BMD).[36] Although it is not known whether the use of Depo-Provera® will increase the risk for osteoporotic fracture, a black-box warning within the product labeling cautions against the risk of potentially irreversible BMD loss associated with long-term use (e.g., greater than 2 years) of the injectable product. While the extended duration of activity of this product may offer women the advantage of less frequent administration, it is important to note that on discontinuation of Depo-Provera®, the return of fertility can be delayed by approximately 10 to 12 months (range 4–31 months).[8]

Depo-SubQ Provera 104® is also an injectable contraceptive product that contains only a progestin (depot medroxyprogesterone acetate). This product, which was approved by the FDA in 2005, is different from Depo-Provera® in that it is given subcutaneously rather than intramuscularly, and it provides only 104 mg medroxyprogesterone acetate (approximately 30% less hormone) every 3 months for the prevention of pregnancy.[37] Clinical trials have demonstrated that the subcutaneous formulation of depot medroxyprogesterone acetate is as effective as the intramuscular formulation in the prevention of pregnancy.[38] Although this product carries the same warning in its package labeling regarding possible effects on BMD as Depo-Provera®,[37] it is not yet known if the lower progestin dose will lessen the potential for long-term side effects.

Implantable Devices

Although IUDs are the most common form of reversible contraception in the world, only 1% of women in the United States use IUDs.[39] There are currently two IUD products available, one containing a progestin and one non-hormonal device. Mirena® is a levonorgestrel-releasing intrauterine system, and Paragard® T 380A is a copper intrauterine device. Mirena® is inserted for up to 5 years, and Paragard® T 380A is inserted for up to 10 years. Surveys have shown that IUDs have the highest satisfaction rate among patients using reversible contraceptives.

Although the mechanism of action for IUDs is not completely understood, various theories have been considered. The original theory is that the presence of a foreign body in the uterus causes an inflammatory response that interferes with implantation. It is believed that copper-containing IUDs may have a direct toxic effect on spermatozoa. Progestin-containing IUDs can have direct effects on the uterus, such as thickening of cervical mucus and alterations to the endometrial lining. Mirena® can inhibit ovulation because it contains levonorgestrel, but Paragard® T 380A does not prevent ovulation.

It is important to evaluate a patient to determine if she is an appropriate candidate for an IUD. IUDs are recommended for women with at least one child, in a monogamous relationship, who have no history of pelvic inflammatory disease (PID) and no history or risk of **ectopic pregnancy.** There are also multiple contraindications to IUD use. Evaluation of the patient is essential because IUDs cannot be used in the following situations: (1) pregnancy or suspected pregnancy, (2) anatomically abnormal or distorted uterine cavity, (3) acute PID or history of PID, unless there has been a subsequent intrauterine pregnancy, (4) postpartum **endometritis** or infected abortion in the past 3 months, (5) known or suspected uterine or cervical neoplasia or unresolved abnormal Pap smear, (6) genital bleeding of unknown etiology, (7) untreated acute **cervicitis** or vaginitis, (8) acute liver disease or liver tumor, (9) woman or her partner has multiple sexual partners, (10) previously inserted IUD still in place, (11) conditions associated with increased susceptibility to infections (e.g., leukemia or acquired immune deficiency syndrome), (12) genital actinomycosis, (13) hypersensitivity to any component of the IUD, (14) known or suspected carcinoma of the breast, (15) history of ectopic pregnancy or a condition that would predispose to ectopic pregnancy, and (16) **Wilson's disease.**[40,41]

There are potential side effects of IUD use. The most common adverse effects are cramping, abnormal uterine bleeding, and expulsion of the device. Other side effects seen are ectopic pregnancy, sepsis, PID, embedment of the device, uterine or cervical perforation, and ovarian cysts.[40,41]

Nonpharmacologic Contraceptive Methods

Barrier Contraceptives

As an alternative to hormonal contraceptives, several barrier contraceptive options are available for the prevention of pregnancy. While barrier contraceptives are associated with far fewer adverse effects compared with hormonal contraceptives, their efficacy is highly user-dependent. Overall, compared with both hormonal contraceptives and IUDs, barrier contraceptives are

associated with much higher accidental pregnancy rates [8] (Table 45–1).

Diaphragms and Cervical Caps

Diaphragms and cervical caps are dome-shaped rubber caps that are placed over the cervix to provide barrier protection during intercourse. Both diaphragms and cervical caps require fitting by a health care professional, and they must be refitted for the patient in the event of weight gain or weight loss. Diaphragms or cervical caps typically can be placed over the cervix as much as 6 hours prior to intercourse. They must be left in place for at least 6 hours after intercourse before they can be removed. Diaphragms should not be left in place longer than 24 hours, and smaller cervical caps should not be left in place longer than 48 hours owing to the risk of toxic shock syndrome (TSS). Diaphragms and cervical caps are used along with spermicides to prevent pregnancy. When sexual intercourse is repeated with the diaphragm, reapplication of the spermicide is necessary. However, when sexual intercourse is repeated with a cervical cap, reapplication of the spermicide typically is not necessary.[8] Whether or not diaphragms or cervical caps provide adequate protection against STDs without concurrent use of a spermicide remains unclear.[42]

Spermicides

Nonoxynol-9, a surfactant that destroys the cell membranes of sperm, is the most commonly used spermicide in the United States.[8,43] Nonoxynol-9 is available in a variety of forms, including a cream, foam, film, gel, suppository, and tablet. Spermicides may be used alone, with a barrier method, or adjunctively with other forms of contraceptives to provide additional protection against unwanted pregnancy.[43] To be used most effectively, spermicides must be placed in the vagina not more than 1 hour prior to sexual intercourse, and they must come in contact with the cervix.[8] While the efficacy of spermicides depends largely on how consistently and correctly they are used, their efficacy is enhanced when they are used in combination with a barrier contraceptive device.[43] Clinical trials assessing the ability of spermicides to protect against STDs have failed to produce positive results.[43] Further, there exists some evidence to suggest that frequent use of spermicides actually may increase risk for transmission of human immunodeficiency virus (HIV) secondary to vaginal mucosal tissue breakdown, which may allow a portal of entry for the virus.[8]

Condoms

Condoms, which are available for both male and female use, act as physical barriers to prevent pregnancy.[44] Condoms are easy to use, available without a prescription, and inexpensive. Most condoms are made of latex. When used correctly, condoms can be very effective in prevention of unwanted pregnancy. Condoms should be stored in a cool, dry place, away from exposure to direct sunlight. When stored improperly or when used with oil-based lubricants, however, latex condoms can break during intercourse, increasing the risk of pregnancy.[8] For latex-sensitive individuals, condoms made from lamb intestine ("natural membrane" condoms) and synthetic polyurethane condoms are available. Unlike latex condoms, condoms made from lamb intestine contain small pores that may permit the passage of viruses and therefore do not provide adequate protection against STDs.[44] ❺ *Both latex and synthetic condoms do provide protection against many STDs. Data from one meta-analysis suggested that HIV transmission can be reduced by as much as 90% when condoms are consistently used.*[45] *This is in contrast to hormonal contraceptives (oral, transdermal, or vaginal), IUDs, and most other barrier contraceptives, which do not protect against STDs.* Relative to male condoms, female condoms may offer even better protection against STDs because they provide more extensive barrier coverage of external genitalia, including the labia and the base of the penis.[46] It is important to note that the male and female condoms are not recommended to be used together because they may adhere to one another, causing displacement of one or both condoms.[46]

Sponge

The Today® sponge is a small, pillow-shaped polyurethane sponge containing nonoxynol-9.[46] It is an over-the-counter barrier contraceptive that has been shown to be generally less effective at preventing pregnancy than diaphragms.[47] The sponge is moistened with water and then is inserted and placed over the cervix for up to 6 hours prior to sexual intercourse. The sponge then is left in place for at least 6 hours following intercourse.[46] Although the sponge maintains efficacy for 24 hours (even if intercourse is repeated), as with diaphragms, the sponge should be removed after 24 hours owing to the risk of TSS.[8]

Fertility Awareness and Periodic Abstinence

Periodic abstinence and fertility awareness–based methods represent another nonpharmacologic means of pregnancy prevention. Although failure rates of such methods can be high, some couples still prefer these types of approaches. Fertility awareness–based methods depend on the ability of the couple to identify the woman's "fertile window," or the period of time in which pregnancy is most likely to occur as a result of sexual intercourse.[48] During the fertile window, the couple practices abstinence, or avoidance of intercourse, in order to prevent pregnancy. In some cases, rather than practicing abstinence during the fertile period, some couples may prefer to employ barrier methods or spermicides as a means of preventing pregnancy rather than to avoid intercourse altogether.[8] In order to identify the fertile window, a number of different fertility awareness–based methods may be tried. The calendar (rhythm) method involves counting the days in the menstrual cycle and then using a mathematical

equation to determine the fertile window.[48] The temperature method involves monitoring changes in the woman's basal body temperature.[48] The cervical mucus (or ovulation) method involves observing changes in the characteristics of cervical secretions throughout the cycle.[48] The symptothermal method, which is considered to be the most difficult to learn but potentially the most effective, is a combination of both the temperature method and the cervical mucus method.[8] In general, fertility awareness–based methods are not recommended for women who have irregular menstrual cycles or who have difficulty interpreting their fertility signs correctly.[48]

Emergency Contraception

Emergency contraception (EC) is used to prevent pregnancy after known or suspected unprotected sexual intercourse. There are two hormonal forms of FDA-approved emergency contraception: combination products containing an estrogen and a progestin and a progestin-only formulation[49] (Table 45–5). PREVEN® is a combination of ethinyl estradiol 0.05 mg and levonorgestrel 0.25 mg, and patients should take two tablets within 72 hours of intercourse and then two tablets 12 hours later. This method of using two hormones is also known as the *Yuzpe regimen*, after Alfred Yuzpe, who discovered it in 1974. Other marketed products containing ethinyl estradiol and levonorgestrel or norgestrel can be used with the same efficacy. The second and more preferred regimen uses only levonorgestrel and is marketed as Plan B®. With this formulation, patients take one 0.75-mg tablet within 72 hours of intercourse and then a second dose 12 hours later. In August of 2006, the FDA approved Plan B® for non-prescription sale to patients 18 years of age and older. It is important to note that EC is more effective the earlier it is used after unprotected intercourse. This progestin-only formulation has shown decreased risk of side effects such as nausea and vomiting, which decreases the risk of emergency contraception failure. The only other approved form of emergency contraception is the placement of a copper IUD within 5 days of intercourse, although this is most commonly used in women who are appropriate candidates for long-term use of such a device.

TABLE 45–5. Emergency Contraception Methods Available in the United States[49]

Levonorgestrel Only	Dose × 2 (12 Hours Apart)	Color
Plan B®[a]	1 + 1 pill	White pills
Ovrette®	20 + 20 pills	Yellow pills
EE + Levonorgestrel or Norgestrel	**Dose × 2 (12 Hours Apart)**	**Color**
PREVEN®[a]	2 + 2 pills	Blue pills
Ogestrel®[a]		White pills
Ovral®[a]		White pills
Alesse®	5 + 5 pills	Pink pills
Levlite™		Pink pills
Aviane™		Orange pills
Lessina™		Pink pills
Cryselle™[a]	4 + 4 pills	White pills
Low-Ogestrel®[a]		White pills
Lo/Ovral®[a]		White pills
Levora®		White pills
Levlen®		Light orange pills
Nordette®		Light orange pills
Triphasil®		Yellow pills
Tri-Levlen®		Yellow pills
Trivora®		Pink pills

[a]FDA approved agent for EC.



Patient Encounter, Part 3: Missed Doses

RC calls your clinic in a panic today because she forgot to start a new package of oral contraceptives. Three days have elapsed since she took her last placebo pill, and she reports having had unprotected sexual intercourse last night. The patient is very concerned about her risk of pregnancy, and she would like to discuss her options for prevention of pregnancy. ❻ *When a contraceptive dose is missed, the risk of accidental pregnancy may be increased. Depending on how many doses were missed, the contraceptive formulation being used, and the phase of the cycle during which doses were missed, counseling regarding the use of additional methods of contraception may be warranted.*

- Given this patient's reported imperfect use of her oral contraceptive, what information can you provide to the patient regarding her risk of pregnancy?
- Compare and contrast the available emergency contraceptive (EC) options for this patient, and provide a recommendation for this patient.
- Provide appropriate patient education regarding the adverse effects associated with the option you have recommended.

OUTCOME EVALUATION/MONITORING

Side effects of contraceptives tend to occur in the first few months of therapy. Thus, schedule a follow-up visit 3 to 6 months after initiating a new contraceptive. Yearly checkups usually are sufficient for patients who are doing well on a particular product.[1] At each follow-up visit, assess blood pressure, headache frequency, and menstrual bleeding patterns, as well as compliance with the prescribed regimen.



Patient Care and Monitoring

1. Obtain a thorough medical and family history and carefully evaluate each patient's risk factors prior to prescribing contraceptives.
2. Educate all women taking hormonal contraceptives to prevent pregnancy regarding self-monitoring for early warning signs that may precede adverse events. Health care professionals can easily recall the major warning signs by using the two simple pneumonics highlighted below:
   ACHES—for women taking hormonal contraceptives
   A = Abdominal pain. This may be an early warning sign of the presence of an abdominal thromboembolism, liver adenoma, or gallbladder disease.
   C = Chest pain. The presence of chest pain may indicate pulmonary embolism, angina, or myocardial infarction.
   H = Headaches. Headaches (particularly those associated with focal neurologic symptoms, such as blurred vision, speech impairment, and/or weakness) may represent strokelike symptoms. Headaches also may indicate poorly controlled blood pressure.
   E = Eye problems. Blurred vision and/or ocular pain may be early warning signs for stroke and/or blood clots. In addition, visual changes may occur in patients wearing contact lenses (secondary to changes in corneal shape).
   S = Severe leg pain. Patients taking hormonal contraceptives who complain of severe leg pain should be evaluated for the presence of venous thromboembolism.
   PAINS—for women with an IUD
   P = Period late
   A = Abdominal pain, pain with intercourse
   I = Infection, abnormal or odorous vaginal discharge
   N = Not feeling well, fever, chills
   S = String (missing, shorter, longer)
3. In addition to the preceding, monitor patients taking hormonal contraceptives for missed periods, signs of pregnancy, appearance of jaundice, and/or severe mood changes. Instruct patients to consult a health care professional on noticing or experiencing any of these warning signs.[1]
4. Stress the importance of adherence to the patient's chosen method of contraception in order to reliably prevent pregnancy. Educate the patient on what to do in the event of missed doses with hormonal contraception.

ABBREVIATIONS

BMD:	bone mineral density
COC:	combined oral contraceptive
EC:	emergency contraception
EE:	ethinyl estradiol
FDA:	Food and Drug Administration
FSH:	follicle-stimulating hormone
GnRH:	gonadotropin-releasing hormone
HDL:	high-density lipoprotein
HIV:	human immunodeficiency virus
HPV:	human papilloma virus
IUD:	intrauterine device
LDL:	low-density lipoprotein
LH:	luteinizing hormone
PID:	pelvic inflammatory disease
STD:	sexually transmitted disease
TSS:	toxic shock syndrome
WHO:	World Health Organization

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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46 Menstruation-related Disorders

Elena M. Umland, Lara C. Weinstein, and Abby Morris



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Describe the underlying etiology and pathophysiology of amenorrhea, menorrhagia, anovulatory bleeding, and dysmenorrhea and how they relate to selection of effective treatment modalities.
2. Differentiate between premenstrual syndrome and premenstrual dysphoric disorder with respect to pathophysiology, clinical presentation, and treatment.
3. Describe the clinical presentation of amenorrhea, menorrhagia, anovulatory bleeding, dysmenorrhea, and premenstrual dysphoric disorder.
4. Recommend appropriate lifestyle and dietary modifications and pharmacotherapeutic interventions for patients with amenorrhea, menorrhagia, anovulatory bleeding, dysmenorrhea, premenstrual symptoms, and premenstrual dysphoric disorder.
5. Identify the desired therapeutic outcomes for patients with amenorrhea, menorrhagia, anovulatory bleeding, dysmenorrhea, premenstrual symptoms, and premenstrual dysphoric disorder.
6. Design a monitoring plan to assess the effectiveness and adverse effects of pharmacotherapy for amenorrhea, menorrhagia, anovulatory bleeding, premenstrual symptoms, and premenstrual dysphoric disorder.

Key Concepts

❶ Unrecognized pregnancy remains the most common cause of amenorrhea, and a urine pregnancy test should be one of the first steps in the evaluation of this disorder.

❷ Causes of menorrhagia can be divided into systemic disorders and specific uterine abnormalities.

❸ Intrauterine pregnancy, ectopic pregnancy, and miscarriage must be at the top of the differential diagnosis list for any woman presenting with heavy menses.

❹ Anovulatory bleeding, also referred to as dysfunctional uterine bleeding, is secondary to the effects of unopposed estrogen and does not include bleeding owing to an anatomic lesion of the uterus.

❺ For most conditions associated with primary and secondary amenorrhea, estrogen (along with a progestin to minimize the risk of endometrial hyperplasia) is provided.

❻ The reduction in menorrhagia-related blood loss with the use of non-steroidal anti-inflammatory drugs and oral contraceptives is directly proportional to the amount of pretreatment blood loss.

❼ The use of metformin and thiazolidinediones for anovulatory bleeding associated with polycystic ovary syndrome is beneficial for anovulatory bleeding and fertility and also improves glucose tolerance and decreases overall cardiovascular risk.

❽ Intrauterine devices (IUDs) are considered therapeutic options in a variety of menstrual-related disorders. Recent guidelines from the American College of Obstetricians and Gynecologists indicate that nulliparous and multiparous women at low risk of sexually transmitted diseases are good candidates for IUD use.

❾ First-line pharmacologic treatment options for premenstrual dysphoric disorder include the selective serotonin reuptake inhibitors (SSRIs).

Problems related to the menstrual cycle are exceedingly common in women of reproductive age. The issues considered in this chapter are the most frequently encountered menstrual-related difficulties and include amenorrhea, menorrhagia,

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dysfunctional uterine bleeding, dysmenorrhea, and premenstrual syndrome/premenstrual dysphoric disorder. The need for effective treatments for these disorders stems from their impact on any or all of the following: a reduced quality of life, negative effects on reproductive health, and the potential for long-term detrimental health effects, such as osteoporosis in the case of amenorrhea and cardiovascular disease in the case of polycystic ovary disease.

AMENORRHEA

Amenorrhea traditionally is described as either primary or secondary in nature. **Primary amenorrhea** is the absence of menses by age 16 in the presence of normal secondary sexual development or the absence of menses by age 14 in the absence of normal secondary sexual development. **Secondary amenorrhea** is the absence of menses for three cycles or 6 months in a previously menstruating woman. However, in clinical practice, there is a significant amount of overlap. The initial evaluation of amenorrhea is often the same regardless of age of onset, except in unusual clinical situations.[1]

Epidemiology and Etiology

❶ *Unrecognized pregnancy remains the most common cause of amenorrhea, and a urine pregnancy test should be one of the first steps in the evaluation of this disorder.* To help organize an approach to diagnosis and treatment, it is helpful to consider the organs involved in the menstrual cycle, which include the uterus, ovaries, anterior pituitary, and hypothalamus.

After pregnancy, the five most common causes of secondary amenorrhea, in descending order of prevalence, include:[2]

- Hypothalamic suppression (33%)
- Chronic anovulation (28%)
- Hyperprolactinemia (14%)
- Ovarian failure (12%)
- Uterine disorders (7%)

Pathophysiology

The physiology of the normal menstrual cycle depends on a coordinated system of hormonal interactions involving the hypothalamus, anterior pituitary gland, ovary, and endometrium. Figures 46–1 and 46–2 summarize these points. Pulsatile gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus stimulates the anterior pituitary to secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH). In the specialized cells of the ovarian follicle, FSH and LH stimulate the release of estradiol. Estradiol stimulates endometrial growth during the follicular phase of the cycle. Following the LH surge and ovulation, the follicle is transformed into the corpus luteum. Progesterone

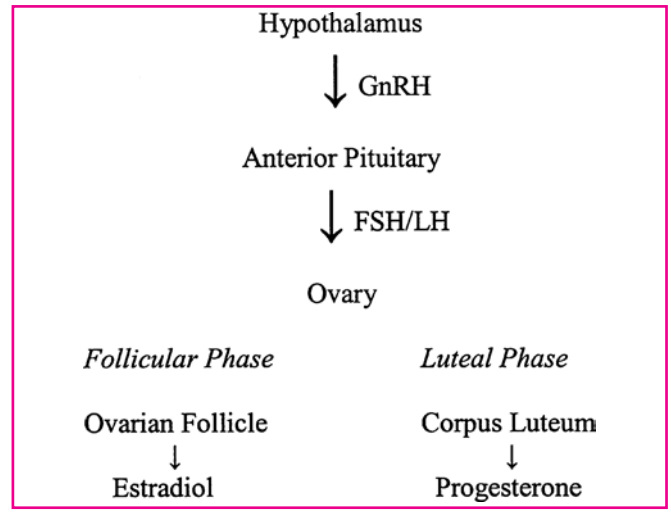


FIGURE 46–1. Summary of the normal menstrual cycle.

that is secreted by the corpus luteum during the luteal phase of the cycle causes endometrial "organization." If conception does not occur, the drop in estrogen and progesterone stimulates the shedding of the endometrium.[4]

Table 46–1 illustrates the pathophysiology of amenorrhea relative to the organ system(s) involved, as well as the specific condition that results in amenorrhea. Amenorrhea is also a normal side effect that may result from the use of low-dose oral contraceptives (OCs), extended-cycle OC pill use, or depot medroxyprogesterone acetate use.[5] Many women may experience delayed return of menses after discontinuation of OCs. Postpill amenorrhea usually is a self-limited condition. Further evaluation for other unrecognized conditions, such as polycystic ovary syndrome (PCOS), should be considered if spontaneous resolution of the amenorrhea does not occur within 3 to 6 months following discontinuation of the OCs.[6,7]

MENORRHAGIA

The traditional definition of **menorrhagia** is a menstrual blood loss of greater than 80 mL per cycle. This definition has been questioned for several reasons, including difficulty with quantifying menstrual blood loss in clinical practice. Many women with "heavy menses" but blood loss of less than 80 mL will merit consideration for treatment because of problems with containment of flow, unpredictable heavy flow days, and other associated symptoms.[8,9]

Epidemiology and Etiology

Rates of menorrhagia in healthy women range from 9% to 14%.[10] ❷ *Causes of menorrhagia can be divided into systemic*

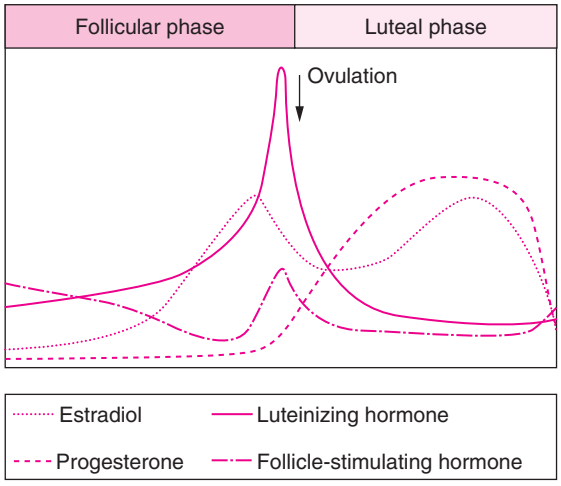


FIGURE 46–2. Hormonal fluctuations with the normal menstrual cycle. (Reprinted, with permission, from ref. 3.)



Clinical Presentation and Diagnosis of Amenorrhea

General
Patients may be concerned about cessation of menses and fertility implications but generally are not in acute distress.

Symptoms
- Cessation of menses
- Possible complaints of infertility, vaginal dryness, decreased libido

Signs
- Cessation of menses for longer than 6 months in women with established menstruation, or absence of menses by age 16 in the presence of normal secondary sexual development, or absence of menses by age 14 in the absence of normal secondary sexual development
- Recent significant weight loss or weight gain
- Presence of acne, hirsutism, hair loss, or **acanthosis nigricans** may suggest androgen excess.

Laboratory Tests
- Pregnancy test
- TSH
- Prolactin
- If suspect PCOS, consider free or total testosterone, 17-hydroxyprogesterone, fasting glucose, and fasting lipid panel.
- If suspect premature ovarian failure, consider FSH and LH.

Other Diagnostic Tests
- Progesterone challenge
- Pelvic ultrasound to evaluate for polycystic ovaries



Clinical Presentation and Diagnosis of Menorrhagia

General
Patient may or may not be in acute distress.

Symptoms
Complaints of heavy/prolonged menstrual flow and fatigue and light-headedness in the case of severe blood loss. These symptoms may or may not occur with dysmenorrhea.

Signs
Orthostasis, tachycardia, and pallor may be noted, especially in cases of significant acute blood loss.

Laboratory Tests
Complete blood count (CBC) and ferritin levels; hemoglobin and hematocrit results may be low.
If the history dictates, testing may be done to identify coagulation disorder(s) as a cause.

Other Diagnostic Tests
- Pelvic ultrasound
- Pelvic magnetic resonance imaging (MRI)
- Pap smear
- Endometrial biopsy
- Hysteroscopy
- Sonohysterogram

disorders and specific uterine abnormalities. ❸ *Pregnancy, including intrauterine pregnancy, ectopic pregnancy, and miscarriage, must be at the top of the differential diagnosis list for any woman presenting with heavy menses.* In several studies of adolescents with acute menorrhagia, underlying bleeding disorders accounted for 3% to 13% of emergency room visits. von Willebrand's disease has an incidence of 1% in the general population and may present initially as heavy menses in an adolescent.[5] Hypothyroidism also may be associated with heavy menses. Specific uterine causes of menorrhagia are more common in older childbearing women, and they include fibroids, adenomyosis, endometrial polyps, and gynecologic malignancies.

Pathophysiology

Table 46–1 illustrates the pathophysiology of menorrhagia relative to the organ system(s) involved, as well as the specific conditions that result in menorrhagia.

TABLE 46–1. Pathophysiology of Selected Menstrual Bleeding Disorders[1,10,11,13,15]

Organ System	Condition	Pathophysiology/Laboratory Findings
AMENORRHEA[1]		
Uterus	Asherman's syndrome	Postcurettage/postsurgical uterine adhesions
	Congenital uterine abnormalities	Abnormal uterine development
Ovaries	Turner's syndrome	Lack of ovarian follicles
	Gonadal dysgenesis	Other genetic anomalies
	Premature ovarian failure	Early loss of follicles
	Chemotherapy/radiation	Gonadal toxins
Anterior pituitary	Pituitary prolactin-secreting adenoma	↑ Prolactin suppresses HPO axis
	Hypothyroidism	TRH causing ↑ prolactin, other abnormalities
	Medications—antipsychotics, verapamil	↑ Prolactin suppresses HPO axis
Hypothalamus	"Functional" hypothalamic amenorrhea	↓ Pulsatile GnRH secretion in the absence of other abnormalities
	Disordered eating	↓ Pulsatile GnRH secretion, ↓ FSH and LH secondary to weight loss
	Exercise	↓ Pulsatile GnRH secretion, ↓ FSH and LH secondary to low body fat
	Anovulation/PCOS	Asynchronous gonadotropin and estrogen production, abnormal endometrial growth
ANOVULATORY BLEEDING		
Physiologic causes	Adolescence	Immaturity of the hypothalamic-pituitary-ovarian axis: no LH surge
	Perimenopause	Declining ovarian function
Pathologic causes	Hyperandrogenic anovulation—PCOS	Hyperandrogenism: high testosterone, high LH, hyperinsulinemia, and insulin resistance
	Hypothalamic dysfunction (physical or emotional stress, exercise, weight loss)	Suppression of pulsatile GnRH secretion and estrogen deficiency: low LH, low FSH
	Hyperprolactinemia (pituitary gland tumor, psychiatric medications)	High prolactin
	Hypothyroidism	High TSH
	Premature ovarian failure	High FSH
MENORRHAGIA		
Hematologic	von Willebrand disease	Factor VII defect causing impaired platelet adhesion and increased bleeding time
	Idiopathic thrombocytopenic purpura	Decrease in circulating platelets—can be acute or chronic
Hepatic	Cirrhosis	Decreased estrogen metabolism, underlying coagulopathy
Endocrine	Hypothyroidism	Alterations in HPO axis
Uterine	Fibroids	Alteration of endometrium, changes in uterine contractility
	Adenomyosis	Alteration of endometrium, changes in uterine contractility
	Endometrial polyps	Alteration of endometrium
	Gynecologic cancers	Various dysplastic alterations of endometrium, uterus, cervix

↑, high; ↓, low; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; HPO, hypothalamic-pituitary-ovarian axis; LH, luteinizing hormone; PCOS, polycystic ovary disease; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

ANOVULATORY BLEEDING

Anovulatory bleeding is irregular menstrual blood flow from the uterine endometrium that ranges from light spotting to heavy blood flow.[11] ❹ *Anovulatory bleeding, also referred to as dysfunctional uterine bleeding, is secondary to the effects of unopposed estrogen and does not include bleeding owing to an anatomic lesion of the uterus.* Anovulatory bleeding includes polycystic ovary syndrome (PCOS), which typically presents with irregular menstrual bleeding, **hirsutism,** obesity, or infertility.

Epidemiology

Anovulatory bleeding is the most common form of non-cyclic uterine bleeding.[11] Patients often seek medical care to regulate their menstrual cycle or improve fertility. All women of reproductive age should have a pregnancy test when presenting with irregular menstrual bleeding. Anovulation may be secondary to physiologic or pathologic causes. It is common at menarche and in the perimenopausal period. During adolescence, ovulatory menstrual cycles may not be regular for a year or more after menarche.[11] In the year following menarche, there may be an immature feedback mechanism in the hypothalamic-pituitary-ovarian (HPO) axis whereby the LH surge needed for ovulation does not occur. During perimenopause, anovulatory cycles may occur owing to a declining quality and quantity of ovarian follicles. As ovarian function declines, estrogen secretion continues, and progesterone secretion decreases. Chronic anovulatory cycles and unopposed estrogen secretion lead to endometrial proliferation and increased risk of polyps, endometrial hyperplasia, and carcinoma.



Patient Encounter, Part 1

TP, a 22 year-old woman, presents to your office for a routine gynecologic examination. She entered menarche at the age of 12. Her last menstrual period was 3 months ago. Her periods are often irregular and occur about every 2 to 3 months. She has had all normal Pap smears in the past and no history of sexually transmitted infections. She is currently in a monogamous relationship with a male partner. She has had a total of four sexual partners. She is not taking oral contraceptives and does not routinely use condoms. She has never been pregnant in the past, but she plans on starting a family in the near future. As you examine the patient, you note facial and chest acne, increased facial and abdominal hair, and obesity.

- What anovulatory disorder is most likely present, and what signs/symptoms support this conclusion?
- What diagnostic test should be done first in the office?

Anovulation also may occur at any time during the reproductive years due to a pathologic cause. The most common causes of non-physiologic ovulatory dysfunction and their prevalence rates[11] are:

- PCOS (70%)
- Hypothalamic amenorrhea (10%)
- Hyperprolactinemia (10%)
- Premature ovarian failure (10%)

PCOS, while responsible for 70% of the cases of ovulatory dysfunction, occurs in approximately 4% of women.[12]

Etiology

Anovulation may result from a problem at any level of the HPO axis. In addition to various physiologic life stages such as adolescence, perimenopause, pregnancy, and lactation, other causes of anovulation include:[11]

- Hyperandrogenic anovulation (PCOS, congenital adrenal hyperplasia, androgen-producing tumors)
- Hypothalamic dysfunction (anorexia nervosa, physical or emotional stress)
- Hyperprolactinemia
- Hypothyroidism
- Primary pituitary disease
- Premature ovarian failure

Pathophysiology

A normal ovulatory cycle consists of follicular development, ovulation, **corpus luteum** development, and **luteolysis.** During the cycle, the endometrium undergoes proliferation, secretory change, and desquamation. This cycle is influenced first by the effects of estrogen alone, then by estrogen and progesterone, and culminates with estrogen and progesterone withdrawal. Progesterone stops the growth of the endometrium and stimulates its differentiation. In patients with anovulation, a corpus luteum is not formed, and the ovary does not secrete progesterone. Without progesterone, there is no desquamation or differentiation of the endometrium. Chronic unopposed estrogen causes continuous endometrial proliferation, and the endometrium becomes vascular and fragile, resulting in non-cyclic menstrual bleeding. In addition, the endometrium may become hyperplastic and progress to a precancerous state, placing the patient at increased risk of endometrial cancer.[13] See Table 46–1 for the pathophysiology of anovulatory bleeding relative to the specific conditions that contribute to it.

The most common pathologic cause of anovulation is PCOS. It is a syndrome of ovarian dysfunction diagnosed by the presence of two of the following three characteristics: **oligoanovulation** or anovulation, clinical or laboratory evidence of hyperandrogenism, and polycystic ovary morphology on ultrasound.[14] No gene or environmental substance has been found to cause PCOS.[15] However, the observance of familial clustering of cases suggests that genetics plays a role.[16] It is thought that insulin resistance, hyperandrogenism, and changes in gonadotropins also influence the development of PCOS.[12] The underlying cause for increased androgens is unknown.[16]

PCOS is associated with a three to seven times increased risk of developing type 2 diabetes.[14] Patients diagnosed with PCOS should be screened for impaired glucose tolerance, diabetes, hypertension, and dyslipidemia.[12] If any of these conditions are present, there is an increased risk of cardiovascular events.



Clinical Presentation and Diagnosis of Anovulatory Bleeding

General
May or may not be in acute distress

Symptoms
Irregular, heavy, or prolonged vaginal bleeding, perimenopausal symptoms (hot flashes, etc.)

Signs
Acne, hirsutism, obesity

Laboratory Tests
- If suspect PCOS, consider free or total testosterone, fasting glucose, fasting lipid panel.
- If suspect perimenopause, FSH.

Other Diagnostic Tests
Pelvic ultrasound to evaluate for polycystic ovaries



Patient Encounter, Part 2: The Medical History, Physical Examination, and Diagnostic Tests

PMH
- Obesity
- Acne

FH
Father is living and has hypertension. Mother is living and has diabetes mellitus and hypercholesterolemia. Both parents are obese.

SH
The patient works as a secretary. She lives with her fiancée. She denies any tobacco or recreational drug use. She drinks about five alcoholic beverages per week. She is sedentary.

Meds
None

ROS
(+) acne, (+) hirsutism, (–) dysmenorrhea, (–) breast tenderness, (–) vaginal discharge

PE
- **VS:** blood pressure 128/82, pulse 80 beats per minute, respiratory rate 18, weight 270 lb (123 kg), height 5 ft, 3 in (160 cm), BMI 47.9 kg/m^2
- **Abd:** Obese, soft, non-tender, non-distended, (+) bowel sounds, no hepatosplenomegaly
- **Gyn:** Normal external appearance of labia minora and majora, vaginal walls within normal limits, cervix well visualized and without lesions, midposition uterus, no cervical motion tenderness, no adnexal masses palpated

Labs
Urine HCG negative, free testosterone 100 ng/dL (3.47 nmol/L) (elevated), TSH 2.1 mIU/L (2.1 mU/L) (within normal limits), prolactin 9 ng/mL (9 ug/L) (mcg/L) (within normal limits), fasting glucose 120 mg/dL (6.66 mmol/L). Fasting lipid panel: total cholesterol 181 mg/dL (4.69 mmol/L), HDL cholesterol 58 mg/dL (1.50 mmol/L), triglycerides 65 mg/dL (0.73 mmol/L), LDL cholesterol 110 mg/dL (2.85 mmol/L).

Pelvic ultrasound
15 follicles in right ovary, 14 follicles in left ovary, increased ovarian volume of 12 mL

- What treatment options are available for this patient?
- Will this patient have fertility problems in the future?
- Given this patient's fasting glucose results, what medication would you recommend?

DYSMENORRHEA

Dysmenorrhea is commonly defined as crampy pelvic pain occurring with or just prior to menses. Primary dysmenorrhea implies pain in the setting of normal pelvic anatomy and physiology, whereas secondary dysmenorrhea is associated with underlying pelvic pathology.[17]



Clinical Presentation and Diagnosis of Dysmenorrhea

General
Patient may or may not be in acute distress depending on the level of menstrual pain experienced.

Symptoms
Complaints of crampy pelvic pain beginning shortly before or at the onset of menses. Symptoms typically last from 1 to 3 days.

Laboratory Tests
- Sexually active females should have a pelvic examination to screen for sexually transmitted diseases.
- Gonorrhea, chlamydia cultures or PCR, wet mount.

Other Diagnostic Tests
Pelvic ultrasound may be used to identify anatomic abnormalities such as masses/lesions or to detect ovarian cysts and endometriomas.

Etiology and Epidemiology

Rates of dysmenorrhea range from 20% to 90%.[17–19] Dysmenorrhea can be associated with significant interference in attendance at work and school. Risk factors for dysmenorrhea include young age, heavy menses, and **nulliparity.**[17]

Pathophysiology

The most significant mechanism for primary dysmenorrhea is the release of prostaglandins in the menstrual fluid and possibly vasopressin-mediated vasoconstriction.[5,17] Causes of secondary dysmenorrhea may include cervical stenosis, endometriosis, pelvic infections, pelvic congestion syndrome, uterine or cervical polyps, and uterine fibroids.[20]

PREMENSTRUAL SYNDROME AND PREMENSTRUAL DYSPHORIC DISORDER

Epidemiology

Premenstrual syndrome (PMS) is a constellation of symptoms including mild mood disturbance and physical symptoms that occur prior to menses and resolve with initiation of menses. It is estimated that up to 70% of menstruating women experience symptoms of PMS. However, a spectrum of premenstrual mood disturbances exists and the most severe is **premenstrual dysphoric disorder (PMDD).** Approximately 4% to 7% of women have PMDD. A summary of the American Psychiatric Association's criteria for PMDD is as follows[1,21]:

- Symptoms are temporally associated with the last week of the luteal phase and remit with onset of menses.
- At least five of the following symptoms are present: markedly depressed mood, marked anxiety, marked affective lability,

marked anger or irritability, decreased interest in activities, fatigue, difficulty concentrating, changes in appetite, sleep disturbance, feeling overwhelmed, and physical symptoms such as breast tenderness or bloating.
- One of the symptoms must be marked depressed mood, anxiety, irritability, or affective lability.
- Symptoms interfere significantly with work or social relationships.
- Symptoms are not an exacerbation of another underlying psychiatric disorder.
- The criteria are confirmed prospectively by daily ratings over two menstrual cycles.

Etiology and Pathophysiology

PMDD is a complex psychiatric disorder with multiple biologic, psychological, and sociocultural determinants.[21] While cyclic hormonal changes are in some way related to PMS and PMDD, the association is neither linear nor simple. However, when ovulation is suppressed medically or surgically, symptoms do improve. There is some evidence to suggest that PMS and PMDD symptoms are related to low levels of the centrally active progesterone metabolite allopregnanolone in the luteal phase and/or lower cortical γ-aminobutyric acid (GABA) levels in the follicular phase.[21] Women with PMS and PMDD may have enhanced sensitivity to progesterone.[22] Studies of the relationship of PMS and PMDD to testosterone levels are conflicting.[21] A number of studies suggest a link between PMS and PMDD and low levels of serotonin.[21,22] A recent study suggests that despite similar affective symptoms, the function of the hypothalamic-pituitary-adrenal (HPA) axis in PMS and PMDD is distinct from that seen in major depressive disorder (MDD). Specifically, women with PMS show a decrease in stimulated HPA axis response, whereas this response is increased in MDD.[23]

Several cross-cultural studies suggest that while the physical symptoms of PMS are consistent across cultures, the negative affective symptoms are part of the negative "menstrual socialization" in Western culture.[1,21]

TREATMENT: AMENORRHEA

Desired Outcomes

Therapeutic modalities for amenorrhea are targeted at restoring the normal menstrual cycle. The goals of treatment are to preserve bone density, prevent bone loss, and restore ovulation, thus improving fertility as desired. Amenorrhea resulting from conditions contributing to hypoestrogenism also may affect quality of life via the induction of hot flashes (premature ovarian failure), dyspareunia, and in prepubertal females, lack of secondary sexual characteristics and absence of menarche.

Nonpharmacologic Therapy

Nonpharmacologic therapy for amenorrhea varies depending on its underlying cause. Amenorrhea secondary to anorexia may respond to weight gain. Such patients also would benefit from psychotherapy. In young women for whom excessive exercise is an underlying cause, a reduction in exercise is recommended.

Pharmacologic Therapy

Estrogen/Progestin Replacement Therapy

❺ *For most conditions associated with primary or secondary amenorrhea, a goal of therapy is to replace estrogen (along with a progestin to minimize the risk of endometrial hyperplasia) via an OC, conjugated equine estrogen (CEE), or an estradiol patch.* The purpose of estrogen therapy in this patient population is two-fold: to reduce the risk of osteoporosis and to improve quality of life.[24,25] Table 46–2 identifies a variety of therapeutic options for amenorrhea, including recommended doses. Figure 46–3 illustrates a treatment algorithm for the management of amenorrhea.

If hyperprolactinemia is identified as the cause of amenorrhea, the use of bromocriptine, a dopamine agonist, results in a reduction in prolactin concentrations and the resumption of menses.

Amenorrhea related to anovulation resulting from PCOS may respond to the use of agents that reduce insulin resistance. The use of metformin for this purpose will be discussed in the anovulatory bleeding section that follows.

Progestins have long been used to induce withdrawal bleeding in women with secondary amenorrhea. Several factors predict the efficacy of progesterone for this purpose.[27] These factors include estrogen concentrations greater than or equal to 35 pg/mL (128 pmol/L) and endometrial thickness (the greater it is, the greater is the amount of withdrawal bleeding).

The efficacy of progestins for secondary amenorrhea also varies depending on the formulation used. For example, progesterone in oil administered intramuscularly results in withdrawal bleeding in 70% of treated patients, whereas oral medroxyprogesterone acetate induces withdrawal bleeding in 95% of treated patients.[27] Table 46–2 identifies the types and doses of progesterones used for inducing withdrawal bleeding in women with secondary amenorrhea. Figure 46–3 illustrates when to consider the use of progesterone for the treatment of amenorrhea.

For all patients experiencing amenorrhea, owing to the negative impact this has on bone health, it is essential that a diet rich in calcium and vitamin D be followed.

Amenorrhea in Adolescents

Amenorrhea in the adolescent population is of great importance because this is the time in the female life cycle when peak bone mass is achieved. The cause of amenorrhea and appropriate treatment must be identified promptly in this population because hypoestrogenism contributes negatively to bone development. Estrogen replacement, typically via an OC, is important. In addition, ensuring that the patient is receiving adequate amounts of calcium and vitamin D is imperative.

TABLE 46–2. Therapeutic Agents for Select Menstrual Disorders[15,17,24–26,28,29]

Specific Menstrual Disorders(s)	Agent(s)	Dose Recommended	Common Adverse Effects
Amenorrhea (primary or secondary)	Conjugated equine estrogen (CEE)	0.625–1.25 mg by mouth daily on days 1–25 of the cycle[25]	Thromboembolism, breast enlargement, breast tenderness, bloating, nausea, gastrointestinal (GI) upset, headache, peripheral edema
	Ethinyl estradiol patch	50 mcg/24 hours[27]	
	Combination OC	30–40 mcg formulations[24]	
Amenorrhea (secondary)	Oral medroxyprogesterone acetate	5–10 mg by mouth on days 14–25 of the cycle[25]	Edema, anorexia, depression, insomnia, weight gain or loss, increase in serum total and LDL cholesterol, may reduce HDL cholesterol
Amenorrhea related to hyperprolactinemia	Bromocriptine	2.5 mg by mouth 2–3 times daily	Hypotension, nausea, constipation, anorexia, Raynaud's phenomenom
Anovulatory bleeding	Combination OC	Optimal dose unknown[15]	As noted above for CEE, ethinyl estradiol, and combination OC (progesterone side effects with the OC depend on agent chosen)
Dysmenorrhea	Combination OC	Less than 35 mcg formulations + norgestrel or levonorgestrel[28]; use of extended-cycle formulations are beneficial for this indication	As noted above for CEE, ethinyl estradiol, and combination OC (progesterone side effects with the OC depend on agent chosen)
	Depo-medroxyprogesterone acetate	150 mg intramuscularly every 12 weeks	Irregular menses, amenorrhea
	Levonorgestrel IUD[29]	20 mcg released daily	Irregular menses, amenorrhea
	NSAIDs—any are acceptable; the most commonly studied/cited are included in this table	Diclofenac 50 mg by mouth 3 times daily	GI upset, stomach ulcer, nausea, vomiting, heartburn, indigestion, rash, dizziness
		Ibuprofen 800 mg by mouth 3 times daily	
		Mefenamic acid 500 mg by mouth as a loading dose, then 250 mg by mouth up to 4 times daily as needed[17]	
		Naproxen 550-mg loading dose by mouth started 1–2 days prior to menses, followed by 275 mg by mouth every 6–12 hours as needed[28]	
		Treatment should begin 1–2 days prior to the suspected onset of menses[17]	
Menorrhagia	Combination OC	Optimal dose unknown	As noted above
	Levonorgestrel IUD	20 mcg released daily	As noted above
	Medroxyprogesterone acetate (oral)	5–10 mg by mouth on days 5–26 of the cycle ***or*** during the luteal phase[29]	As noted above
	NSAIDs	Doses as recommended for above; therapy should be initiated with the onset of menses[29]	As noted above
PCOS-related amenorrhea and/or anovulatory bleeding	Clomiphene[15]	50 mg by mouth daily × 5 days starting 3–5 days after the start of menses	Hot flashes, ovarian enlargement, thromboembolism, blurred vision, breast discomfort
	Depo-medroxyprogesterone acetate	150 mg intramuscularly every 12 weeks	As noted above
	Medroxyprogesterone acetate (oral)	10 mg by mouth × 10 days[15]	As noted above
	Metformin	1500–2000 mg by mouth daily in 2–3 divided doses[15]	Anorexia, nausea, vomiting, diarrhea, flatulence, lactic acidosis

TABLE 46–2. Therapeutic Agents for Select Menstrual Disorders[15,17,24–26,28,29] (*Continued*)

Specific Menstrual Disorders(s)	Agent(s)	Dose Recommended	Common Adverse Effects
	Thiazolidinediones[15]	Pioglitazone 15–45 mg by mouth daily; rosiglitazone 4–8 mg by mouth daily	Weight gain; increase in total, LDL, and HDL cholesterol; edema; headache; fatigue; hepatic injury (rare)
PMDD	Clomipramine[26]	25–75 mg by mouth daily taken continuously or only during the luteal phase	Dry mouth, fatigue, vertigo, sweating
	Drospirenone	3 mg (+30 mcg ethinyl estradiol) by mouth on days 1–21 of the menstrual cycle[31]	As noted with other OCs above; drospirenone may contribute to hyperkalemia in patients with reduced renal function
	Leuprolide	3.75 mg intramuscularly[26]	Hot flashes, night sweats, headache, nausea
	SSRIs	Citalopram 10–30 mg; fluoxetine 10–20 mg; fluvoxamine 50 mg; paroxetine 10–30; sertraline 25–150 mg; all agents are given by mouth daily and can be dosed continuously or during the luteal phase only[26]	Sexual dysfunction (reduced libido, anorgasmia), insomnia sedation, hypersomnia, nausea, diarrhea

TREATMENT: MENORRHAGIA

Desired Outcomes

Menorrhagia therapy should focus on reducing menstrual blood flow, improving the patient's quality of life, and deferring the need for surgical intervention. Table 46–2 identifies the various agents used in the management of menorrhagia. It also includes their dosing and common side effects. Figure 46–4 illustrates how to decide which treatment(s) to use and when.

Nonpharmacologic Therapy

Nonpharmacologic interventions for menorrhagia include surgical interventions that are reserved for patients not responding

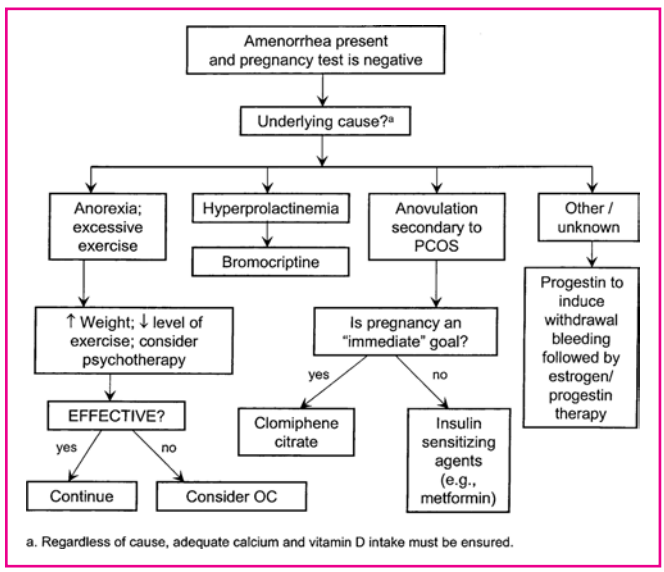


FIGURE 46–3. Treatment algorithm for amenorrhea.

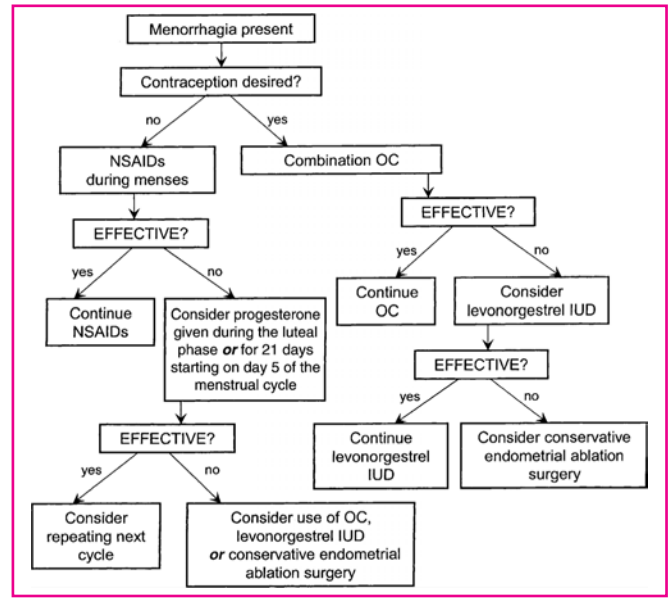


FIGURE 46–4. Treatment algorithm for menorrhagia.

to pharmacologic treatment. These interventions may vary from conservative endometrial ablation to hysterectomy.[32]

Pharmacologic Therapy

Non-steroidal anti-inflammatory drugs (NSAIDs) are first-line treatments for menorrhagia associated with ovulatory cycles.[33] They have the advantage of being taken only during menses, and their use is associated with a significant reduction in menstrual blood loss. A 20% to 50% reduction in blood loss has been observed in 75% of treated women.[29] In some patients, as much as an 80% reduction has been observed. ❻ *This reduction is directly proportional to the amount of pretreatment blood loss.*[29]

The use of OCs is beneficial in women with menorrhagia who do not desire pregnancy. A 43% to 53% reduction in menstrual blood loss has been observed in 68% of patients treated with OCs containing greater than or equal to 35 mcg estradiol for the treatment of menorrhagia.[29] As with the use of NSAIDs, ❻ *the reduction in blood loss is proportional to pretreatment blood loss.*

Menorrhagia also may be treated with the levonorgestrel-releasing intrauterine device (IUD). This is a very effective treatment that consistently reduces menstrual flow by 90% or greater.[29,30] Its use has resulted in the postponement or cancellation of scheduled endometrial resection surgery or hysterectomy. Specifically, 60% of treated patients have been able to avoid hysterectomy.[30,34,35]

Progesterone therapy either during the luteal phase of the menstrual cycle or for 21 days starting on day 5 after the onset of menses results in a 32% to 50% reduction in menstrual blood loss.[29] Its use has not been shown to be superior to other medical treatments, including NSAIDs.[29] In addition, it is not associated with any contraceptive benefit.[33]

TREATMENT: ANOVULATORY BLEEDING

Desired Outcomes

In the short term, the desired outcome is to stop acute bleeding. The long-term goals of therapy include preventing future episodes of non-cyclic bleeding, decreasing the long-term complications of anovulation (e.g., osteopenia and infertility), and improving overall quality of life.[11] Table 46–2 identifies the agents used in the management of anovulatory bleeding, their doses, and common side effects.

Nonpharmacologic Therapy

Nonpharmacologic treatment options for anovulatory bleeding depend on the underlying cause. In a woman of reproductive age with PCOS, weight loss may be beneficial. In women who have completed childbearing or who have failed medical management, endometrial ablation or resection and hysterectomy are surgical options. It is unclear as to which procedure is preferred. Short term, it appears that ablation or resection results in less morbidity and shorter recovery periods. However, a significant number of these women eventually undergo hysterectomy in the 5 years that follow.[11]

Pharmacologic Therapy

Estrogen is the recommended treatment for managing acute bleeding episodes because it promotes endometrial growth and stabilization.[11] Following its initial use for controlling acute bleeding episodes, it is necessary to continue therapy to prevent future occurrences. The use of OCs fulfills this role.

The role of OCs is to prevent recurrent anovulatory bleeding. They suppress ovarian hormones and adrenal androgen production. They also, indirectly, increase sex hormone–binding globulin (SHBG). This, in turn, binds and reduces circulating androgen. For women with high androgen levels and related signs (e.g., hirsutism), low-dose OCs (less than or equal to 35 mcg ethinyl estradiol) are the treatment of choice.[11] In theory, one may consider the use of an OC with a progesterone that has a larger impact on increasing SHBG. To date, there is no best OC choice for these women (e.g., those with PCOS).[15]

Specifically, for women with PCOS, the use of depot and intermittent oral medroxyprogesterone acetate suppresses pituitary gonadotropins and circulating androgens.[15] Further, the use of cyclic progesterone may benefit women over age 40 and in whom anovulatory bleeding occurs.[11]

The use of metformin and the thiazolidinediones pioglitazone and rosiglitazone results in improved insulin sensitivity. In patients with PCOS, this is associated with reducing circulating androgen concentrations, increasing ovulation rates, and improving glucose tolerance.[15] These improvements can be attributed to the increase in SHBG that occurs via increased insulin sensitivity. ❼ *These agents are of benefit not only for anovulatory bleeding and fertility but also because they improve glucose tolerance and decrease overall cardiovascular risk.*[15] If pregnancy is a desired outcome, it is important to note that metformin is a pregnancy category B agent, whereas pioglitazone and rosiglitazone are category C.

Although the use of insulin-sensitizing agents may improve fertility, if the goal of treatment is to improve fertility via inducing ovulation, then the treatment of choice is clomiphene citrate. Treatment with 50 mg/day for 5 days can be initiated between days 3 and 5 of the menstrual cycle. This often may occur following the induction of withdrawal bleeding with a progesterone such as medroxyprogesterone acetate at 10 mg/day by mouth for 10 days.

Anovulatory Bleeding in Adolescents

Anovulatory cycles are not unusual in the perimenarchal reproductive years. Ovulation typically is established a year or

more following menarche. When anovulatory bleeding occurs in this population, it may be excessive. If the bleeding is excessive, the patient should be evaluated for blood dyscrasias. The prevalence of blood dyscrasias, including von Willebrand's disease and prothrombin deficiency, and the prevalence of idiopathic thrombocytopenia purpura in this population ranges from 5% to 20%.[11]

In the adolescent population, specific blood dyscrasias should be treated. In addition, acute, severe bleeding may be managed with high-dose estrogen. Low-dose OCs (less than or equal to 35 mcg ethinyl estradiol) are the treatment of choice in adolescents with chronic anovulation.[11]

TREATMENT: DYSMENORRHEA

Desired Outcomes

The medical management of dysmenorrhea should relieve the related pelvic pain. Effective management of dysmenorrhea also results in a reduction in lost school and work days. Table 46–2 identifies the agents used in the management of dysmenorrhea, their recommended doses, and their common side effects. Figure 46–5 is a treatment algorithm for the management of dysmenorrhea.

Nonpharmacologic Therapy

Several nonpharmacologic interventions exist for the management of dysmenorrhea. Among these, topical heat therapy, exercise, and following a low-fat vegetarian diet all have been shown to reduce the intensity of the dysmenorrhea.[17,28] Dietary changes also may shorten the duration of dysmenorrhea. These interventions require little time and minimal cost and are associated with little risk. Other nonpharmacologic options that may be considered before or, in most cases, after a trial of pharmacologic interventions include the use of transcutaneous electric nerve stimulation (TENS), acupressure, and acupuncture.[17]

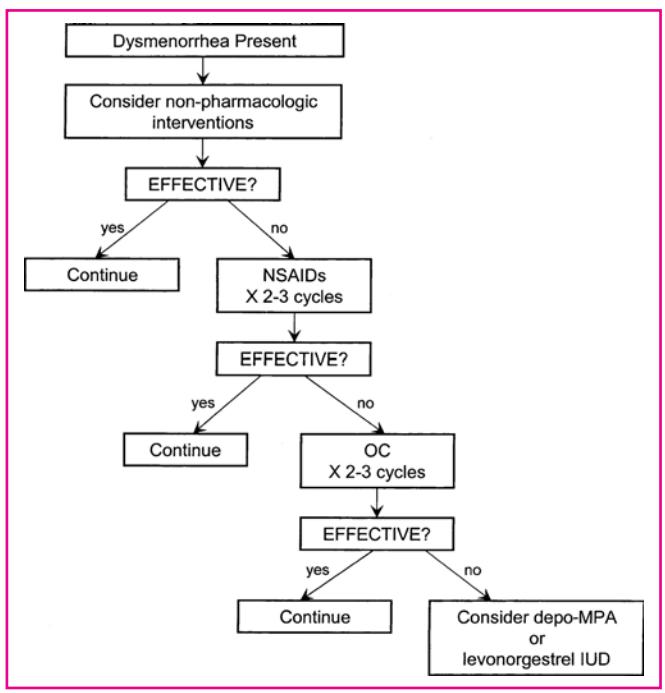


FIGURE 46–5. Treatment algorithm for dysmenorrhea.

Pharmacologic Therapy

Given the role of prostaglandins in the pathophysiology of dysmenorrhea, NSAIDs are the treatment of choice. There does not appear to be a difference between agents in efficacy. Choice of one agent over another may be based on cost, convenience, and patient preference.[17] The most commonly used agents are naproxen and ibuprofen.

It has been suggested that a loading dose (twice the usual single dose) of the NSAID be taken, followed by the usually recommended dose until symptoms resolve.[28] An alternate recommendation is to begin the NSAID at the onset of menses or perhaps even the day prior and to continue treatment around the clock instead of waiting until the onset of symptoms. For patients in whom NSAID use is contraindicated, the agents discussed below should be considered. The use of acetaminophen has been proven inferior to the use of NSAIDs for the treatment of this disorder.[17]

OCs help to improve dysmenorrhea by inhibiting the proliferation of endometrial tissue. This reduction in tissue translates into a reduction in endometrial-derived prostaglandins that are thought to contribute to the pelvic pain experienced.[28] A trial of 2 to 3 months of OC dosing is required to establish whether the patient is a responder or a non-responder.[36] Significant improvements in mild, moderate, and severe dysmenorrhea have been noted with the use of OCs. These agents have other benefits, such as the prevention of pregnancy, improving acne, and reducing ovarian cancer risk. While monophasic formulations may be more efficacious for this indication, the supporting evidence for this is limited.[17]

The benefit of depo-medroxyprogesterone acetate in dysmenorrhea is related to its ability to render most patients amenorrheic within 1 year of use.[17] This is an expected side effect. Since the pelvic pain of dysmenorrhea is related to the prostaglandins released during menses, in the setting of amenorrhea, the underlying cause of dysmenorrhea is removed.

Observational data illustrate a reduction in dysmenorrhea from 60% to 29% with the levonorgestrel-releasing IUD after 3 years.[17] As observed with depo-medroxyprogesterone acetate, this reduction is likely secondary to the increasing incidence of amenorrhea in users of this contraceptive device.

Dysmenorrhea in Adolescents

Dysmenorrhea is very common in adolescent females. Any of the treatment measures discussed earlier for other patients

would be appropriate in the adolescent population. While NSAIDs and OCs are among the top choices, use of the levonorgestrel IUD is also an option.[30] It had been thought previously that nulliparous females should avoid the use of IUDs secondary to an increased risk of pelvic inflammatory disease (PID) and a subsequent increased risk of infertility. ❽ *Recent guidelines from the American College of Obstetricians and Gynecologists (ACOG) state that any woman (regardless of parity) at low risk of sexually transmitted diseases and thus pelvic inflammatory disease is a good candidate for IUD use.*[30]

TREATMENT: PREMENSTRUAL SYNDROME AND PREMENSTRUAL DYSPHORIC DISORDER

Desired Outcomes

Interventions for managing PMS and PMDD focus on alleviation of the presenting symptoms and subsequent improvement in quality of life. See Table 46–2 for a listing of the various agents used in the management of this disorder, their recommended dosing, and common side effects.

Nonpharmacologic Therapy

It is recommended that lifestyle interventions be started and followed for 2 months while the patient charts her symptoms. While these interventions lack significant supporting clinical trial data, anecdotal reports do exist. Some lifestyle changes for women suffering from mild to moderate premenstrual symptoms include minimizing caffeine, refined sugar, and sodium intake and increasing exercise.[26] Vitamin and mineral supplements such as vitamin B_6 (50–100 mg/day) and calcium carbonate (1200 mg/day) have been observed anecdotally to help reduce the physical symptoms associated with PMS.[26] A review of clinical trials, however, supports that none of the following options should be recommended because of a lack of evidence for safety and efficacy: herbal medicines, homeopathic remedies, dietary supplements, relaxation, massage therapy, reflexology, chiropractic treatments, and biofeedback.[37]

Pharmacologic Therapy

If symptoms continue after 2 months of symptom charting and attempting lifestyle modifications, pharmacologic therapy may be considered for the management of diagnosed PMDD.

❾ *The first-line therapeutic options for PMDD include the selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, fluvoxamine, sertraline, paroxetine, and citalopram.* These agents can be given either continuously or only during the luteal phase of the menstrual cycle, i.e., initiated at the time of ovulation and discontinued on the first day of menses.

SSRIs are efficacious in more than half of treated patients compared with only 20% of patients receiving placebo.[26] This improvement was noted to be a 50% or greater reduction in symptoms compared with baseline. Further, the improvement was noted to occur during the first cycle of use.[26]

The tricyclic antidepressant clomipramine also has been studied for PMDD. In placebo-controlled trials, both continuous daily dosing and luteal phase administration proved effective.[17] Compared with the SSRIs, however, clomipramine has a less desirable side-effect profile with low tolerability.

If treatment with an SSRI or another antidepressant such as clomipramine is not successful, hormonal treatment with a GnRH agonist, such as leuprolide, may be considered. The use of leuprolide improves premenstrual emotional symptoms as well as some physical symptoms such as bloating and breast tenderness. Cost, the need for intramuscular administration, and the side effects of hypoestrogenism (e.g., vaginal dryness and hot flashes) limit its use.

A randomized, double-blind, placebo-controlled trial evaluating the use of a monophasic OC containing 30 mcg ethinyl estradiol and 3 mg drospirenone, a progesterone with antiandrogenic effects, showed improvement in the treatment arm compared with placebo.[31] In particular, appetite, food cravings, and acne improved. However, active treatment was not associated with a statistically significant improvement in the overall outcome measure, the Calendar of Premenstrual Experiences (COPE) scale, perhaps because of the small sample size ($n = 82$).

OUTCOME EVALUATION

Measure the treatment success for the various menstruation-related disorders by the degree to which the care plan (1) relieves or reverses symptoms of the disorder, (2) prevents or reverses the complications of the disorder (e.g., osteoporosis, anemia, and infertility), and (3) minimizes side effects. The return of a regular menstrual cycle with minimal premenstrual symptoms or symptoms of dysmenorrhea should occur. Depending on the desire for conception and subsequent therapy, this cycle may be ovulatory or anovulatory.

Assess the effectiveness of therapy in resuming normal menstrual cycles with minimal related pain after an appropriate treatment interval (1–2 months). Assess improvement in quality-of-life measures such as physical, psychological, and social functioning and well-being. Evaluate the patient for adverse drug reactions, drug allergies, and drug interactions. Table 46–2 illustrates the common side effects that may occur for which monitoring is required. Table 46–3 illustrates the specific expected outcome measures for each of the menstruation-related disorders discussed in this chapter.

TABLE 46–3. Expected Outcome Measures for Select Menstrual Bleeding Disorders[8,10,11,15,18,20,22,33,36]

Menstrual Disorder	Expected Outcome Measures
Amenorrhea	***Efficacy:*** Normal breast development (especially primary amenorrhea in adolescents) preservation/improvement of BMD; return of menses. ***Time to relief/effect:*** Menses should occur within 1–2 months of therapy.
Menorrhagia	***Efficacy:*** Decline in the amount of blood lost with menses (monitor a decline in the number of times feminine hygiene products such as pads and tampons require changing during menses); monitor for an increase in hemoglobin/hematocrit if anemia was present as a result of menorrhagia. ***Time to relief/effect:*** A decline in menstrual blood loss should be realized within 1–2 cycles of therapy being initiated.
Anovulatory bleeding	***Efficacy:*** Alleviation of acute bleeding when present; ovulation and subsequent pregnancy in women desiring this; reduced risk of developing the long-term complications of, for example, PCOS (e.g., diabetes and cardiovascular disease); improved quality of life. ***Time to relief/effect:*** The acute treatment of heavy bleeding should result in a decline in bleeding within 10 days of therapy onset; the return of ovulation may require several months of therapy; when OCs are used, control of abnormal bleeding can be expected within 1–2 cycles of therapy.
Dysmenorrhea	***Efficacy:*** Reduction in/absence of pelvic pain related to menses; reduction in time lost from work/school; improved quality of life. ***Time to relief/effect:*** Improvement in pain may be observed within hours of NSAID therapy; improvement with other options such as OCs may be observed after a full 1–3 cycles of their use.
PMDD	***Efficacy:*** Reduction in/absence of initial symptoms; improved quality of life. ***Time to relief/effect:*** Improvements may be observed within 1–3 cycles of therapy.

BMD, bone mineral density; NSAID, non-steroidal anti-inflammatory drug; OCs, oral contraceptives; PCOS, polycystic ovary syndrome; PMDD, premenstrual dysphoric disorder.



Patient Care and Monitoring

1. Assess symptoms to determine if patient-directed therapy is appropriate (e.g., NSAIDs for dysmenorrhea) or whether the patient should be evaluated by a physician (e.g., amenorrhea, menorrhagia, anovulatory bleeding, or PMDD). Does the patient have any related complications, such as symptoms of anemia in patients presenting with menorrhagia or complaints of difficulty conceiving in women with amenorrhea or anovulatory bleeding.
2. Review any available diagnostic data, as appropriate, to determine hormonal, reproductive, and pregnancy status.
3. Obtain a thorough history of prescription, nonprescription, and natural drug product use. Determine which treatments have been helpful to the patient in the past.
4. Educate the patient on lifestyle modifications that will improve symptoms and prevent complications.
5. Is the patient taking the appropriate dose of the prescribed medication? If not, why not?
6. Develop a plan to assess effectiveness of the prescribed medication after 1 to 2 months of therapy.
7. Determine if long-term maintenance treatment is necessary.
8. Assess improvement in quality-of-life measures such as physical, psychological, social functioning and well-being.
9. Evaluate for adverse drug reactions, drug allergies, and drug interactions.
10. Stress the importance of adherence with the therapeutic regimen, including lifestyle modifications. Recommend a therapeutic regimen that is easy for the patient to adhere to.
11. Provide patient education regarding disease state, lifestyle modifications, and drug therapy by noting the following:
    - What causes the menstruation-related disorder?
    - What are the possible complications of the menstruation-related disorder?
    - What lifestyle modifications may help to reduce the risk associated with these complications?
    - When and how should patients take their medications?
    - What potential adverse effects may occur?
    - Which drugs may interact with their therapy?

ABBREVIATIONS

CBC:	complete blood count
CEE:	Conjugated equine estrogen
CNS:	central nervous system
COPE:	calendar of premenstrual experiences
FSH:	follicle-stimulating hormone
GABA:	γ-aminobutyric acid
GnRH:	gonadotropin-releasing hormone
HCG:	human chorionic gonadotropin
HPA:	hypothalamic-pituitary-adrenal
HPO:	hypothalamic-pituitary-ovarian
IUD:	intrauterine device
LH:	luteinizing hormone
MDD:	major depressive disorder
MPA:	medroxyprogesterone acetate
NSAID:	non-steroidal anti-inflammatory drug
OC:	oral contraceptive
PCOS:	polycystic ovarian syndrome
PID:	pelvic inflammatory disease
PMDD:	premenstrual dysphoric disorder
PMS:	premenstrual syndrome
SHBG:	sex hormone–binding globulin
SSRI:	selective serotonin reuptake inhibitor
TENS:	transcutaneous electrical nerve stimulation

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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47 Hormone-Replacement Therapy in Menopause

Nicole S. Culhane and Melissa A. Somma



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Explain the pathophysiologic changes associated with menopause.
2. Identify the signs and symptoms associated with menopause.
3. Determine the desired therapeutic outcomes for a patient taking hormone-replacement therapy.
4. Explain how to evaluate a patient for the appropriate use of hormone-replacement therapy.
5. Recommend nonpharmacologic therapy for menopausal symptoms.
6. List the adverse effects of and contraindications to hormone-replacement therapy.
7. Differentiate between topical and systemic forms of hormone-replacement therapy.
8. Explain the risks and benefits associated with hormone-replacement therapy.
9. Educate a patient regarding the proper use and potential adverse effects of hormone-replacement therapy.
10. Monitor a patient taking hormone-replacement therapy for efficacy and toxicity.
11. Recognize that alternative, non-hormonal therapies for menopausal symptoms exist and should be considered in some circumstances for women unable to take hormone-replacement therapy.

Key Concepts

❶ Common symptoms of menopause include hot flashes, night sweats, vulvovaginal atrophy, and vaginal dryness. Women less commonly may experience mood swings, depression, insomnia, arthralgia, myalgia, and urinary frequency.

❷ Hormone-replacement therapy remains the most effective treatment for vasomotor symptoms and vulvovaginal atrophy and should be considered for women experiencing these symptoms.

❸ Women should receive a thorough history and physical examination, including assessing coronary heart disease (CHD) and breast cancer risk factors, before hormone-replacement therapy is considered. Patients should be informed of the risks and the benefits of hormone-replacement therapy and should be encouraged to be involved in the decision-making process. If a woman does not have any contraindications to hormone-replacement therapy, including CHD or significant CHD risk factors, and also does not have a personal history of breast cancer, hormone-replacement therapy would be an appropriate therapy option.

❹ Oral or transdermal estrogen products should be prescribed at the lowest effective dose for the relief of vasomotor symptoms. Topical products in the form of creams, tablets, or rings should be prescribed for women exclusively experiencing vulvovaginal atrophy.

❺ Women who have an intact uterus should be prescribed a progestin in addition to estrogen in order to decrease the risk of endometrial hyperplasia and endometrial cancer.

❻ Hormone-replacement therapy is also indicated for the prevention of osteoporosis but is not recommended for long-term use. Alternatives such as bisphosphonates or raloxifene should be considered as first-line therapy for the prevention of osteoporosis, in addition to appropriate doses of calcium and vitamin D.

❼ Combined estrogen plus progestin should not be used in the prevention of chronic diseases because it increases the risk of CHD, stroke, breast cancer, and venous thromboembolism.

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However, colorectal cancer and rates of fracture were reduced with combined hormonal treatment.

8. Hormone-replacement therapy improves overall well-being and mood in women with vasomotor symptoms but has not demonstrated an improvement in quality of life in women without vasomotor symptoms.
9. In appropriate women, hormone-replacement therapy should be recommended at the lowest dose for the shortest duration and should be tapered before discontinuation in order to prevent the recurrence of hot flashes.
10. Since the publication of the Women's Health Initiative study, there has been an increase in the use of non-hormonal therapies for the management of menopausal symptoms. Particularly for women with CHD and breast cancer risk factors, non-hormonal therapies may offer an alternative to assist with symptom management. A wide range of therapies, both prescription and herbal, have been studied with varying degrees of success. In choosing a particular therapy, it is important to match patient symptoms with a therapy that is not only effective but also safe.



Patient Encounter, Part 1

BW, a 50-year-old woman with a history of osteoarthritis and hypothyroidism, presents to the clinic complaining of hot flashes, vaginal dryness, and insomnia. She states that she experiences approximately two hot flashes per day and is awakened from sleep at least three to four times a week in a "pool of sweat" requiring her to change her clothes and bed linens. Her symptoms began about 3 months ago, and over that time, they have worsened to the point where they have become very bothersome. On questioning, she states her last menstrual period was 1 year ago.

- Which of the patient's symptoms and past medical history are consistent with menopause?
- What laboratory value(s) will help to confirm the diagnosis of menopause?
- What additional information do you need to know in order to make an appropriate therapeutic plan for this patient?

Menopause is the permanent cessation of menses owing to a loss of ovarian follicular function. The diagnosis of menopause is primarily a clinical one and is made after a women experiences amenorrhea for 12 consecutive months. The loss of ovarian follicular activity leads to an increase in follicle-stimulating hormone (FSH), which, on laboratory examination, may help to confirm the diagnosis.

Many women seek medical treatment for the relief of menopausal symptoms, primarily hot flashes; however, the role of hormone-replacement therapy (HRT) has changed dramatically over the years. HRT has long been prescribed for relief of menopausal symptoms and, until recent years, has been purported to protect women from CHD. The original reason behind recommending HRT in postmenopausal women revolved around a simple theory: If the hormones lost during menopause were replaced through drug therapy, women would be protected from both menopausal symptoms and chronic diseases that often follow after a woman experiences menopause. Recent studies have disproved this theory.

As of 1995, almost 38% of all women 50 to 75 years of age were using HRT.[1] It was in 1996 that the United States Preventive Services Task Force (USPSTF) first published its recommendations that not all postmenopausal women should be prescribed HRT, but rather, therapy should be individualized based on risk factors. This recommendation was further supported with publication of the Heart and Estrogen/Progestin Replacement Study (HERS) in 1998, which demonstrated that women who had established CHD were at an increased risk of experiencing a myocardial infarction within the first year of HRT use compared with a similar group of women without CHD risk factors. As a result, the authors concluded that HRT is not recommended for the secondary prevention of CHD.[2] Then, in 2002, the Women's Health Initiative (WHI) report was published. This trial demonstrated that HRT was not protective against CHD but rather could increase the risk in women with underlying CHD risk factors. The risk of breast cancer also was increased after a woman was on therapy for approximately 3 years. As a result of this study, the Food and Drug Administration (FDA) issued a statement that combined HRT should not be initiated or continued for the primary prevention of CHD.[3]

This series of trials, and many more, has led to the dramatic change in how HRT is currently prescribed and greater understanding of the associated risks. HRT, once thought of as a cure-all for menopausal symptoms, is now a therapy that should be used only to reduce the frequency and severity of **vasomotor symptoms** associated with menopause in women without risk factors for CHD or breast cancer. The changes that have occurred over the years in the use of HRT further support the importance of evidence-based practice and judicious medication use.

EPIDEMIOLOGY AND ETIOLOGY

Menopause is a period of time in a woman's life marked by the cessation of menses. It occurs in all women either naturally or surgically and usually occurs between the ages of 40 and 58 years. The median age for a woman to experience menopause is 52 years. However, women who have undergone a total abdominal hysterectomy (surgical menopause) generally experience menopause earlier compared with women who experience natural menopause. Some other factors that may be associated with early menopause include low body weight, increased menstrual cycle length, **nulliparity,** and smoking. Smokers generally experience menopause approximately 2 years earlier than non-smokers.[4]

The usual transitional period prior to menopause, known as **perimenopause** or the *climacteric,* is a period

when hormonal and biologic changes begin to occur. These changes may begin 2 to 8 years prior to menopause and eventually lead to irregular menstrual cycles, an increase in cycle interval, and a decrease in cycle length. During this time, women also may experience physical symptoms similar to menopausal symptoms, primarily vasomotor symptoms, and they may require treatment depending on symptom severity.[4,5]

Because the perimenopausal and postmenopausal periods are marked by many biologic and endocrinologic changes, women should inform their health care provider when they experience any signs and symptoms in order to discuss the most appropriate therapeutic approach.

PATHOPHYSIOLOGY

Reproductive physiology is regulated primarily by the hypothalamic-pituitary-ovarian axis. The hypothalamus secretes gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary to secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH regulate ovarian function and stimulate the ovary to produce sex steroids. These hormones are influenced by a negative-feedback system and will increase or decrease based on the levels of estradiol and progesterone.

The pathophysiologic changes that occur during the perimenopausal and menopausal periods are caused by the decrease and eventual loss of ovarian follicular activity. As women age, the number of ovarian follicles decreases, and the remaining follicles require higher levels of FSH for maturation and ovulation. During perimenopause, FSH concentrations



Clinical Presentation and Diagnosis

❶ Menopausal Symptoms
- Vasomotor symptoms (**hot flashes**, night sweats)
- Irregular menses
- Episodic amenorrhea
- Sleep disturbances
- Mood swings
- Vaginal dryness
- Depression

Less Common Symptoms
- Fatigue
- Irritability
- Migraine
- Arthralgia
- Myalgia

Diagnosis
- Amenorrhea for 1 year
- FSH greater than 40 mIU/mL
- Five-fold increase in LH



Patient Encounter, Part 2: Medical History, Physical Examination, and Diagnostic Tests

BW's work-up reveals the following additional information:

PMH
- Osteoarthritis of the lower back for 5 years controlled on acetaminophen 500 mg two tablets PO 3 to 4 times daily
- Hypothyroidism since age 25, currently controlled

FH
- Father: Alive with HTN and CHD (MI at age 60)
- Mother: Alive with hypothyroidism and GERD
- Siblings: Two sisters alive and well

SH
- Occupation: nurse
- Non-smoker
- Drinks one to two glasses of red wine with dinner on the weekends
- Denies illicit drug use

Meds
- Acetaminophen 500 mg two tablets PO 3 to 4 times daily
- Synthroid 0.075 mg PO once daily
- Multivitamin PO once daily

ROS
(+) hot flashes, night sweats, vaginal dryness and itching; (–) insomnia, myalgias, bowel changes, weight gain, constipation

PE
- **VS:** BP 128/82, P 78, RR 16, T 37.0°C (98.6°F), weight 164 lb (74.5 kg)
- **HEENT:** WNL
- **Neck:** Supple; no bruits, no adenopathy, no thyromegaly
- **Breasts:** Supple; no masses
- **CV:** RRR, normal S_1 and S_2; no murmurs, rubs, or gallops
- **Abd:** Soft, non-tender, non-distended; (+) BS, no masses
- **Genitourinary:** Pelvic examination normal except (+) mucosal atrophy

Labs
- FSH 76 mIU/mL
- TSH 2.5 mIU/L
- Chem-7: Na 135 mEq/L (135 mmol/L), K 4.5 mEq/L (4.5 mmol/L), Cl 109 mEq/L (109 mmol/L), CO_2 25 mEq/L (25 mmol/L), BUN 9 mg/dL (3.21 mmol/L), SCr 0.9 mg/dL (80 mmol/μmol per liter), Glucose 98 mg/dL (5.44 mmol/L)
- CBC: Hgb 13 g/dL (130 g/L or 8.06 mmol/L), Hct 39% (0.39 volume fraction), WBC $5.5 \times 10^3/mm^3$ ($5.5 \times 10^3/\mu L$ or $5.5 \times 10^9/L$), platelets $234 \times 10^3/mm^3$ ($234 \times 10^3/\mu L$ or $234 \times 10^9/L$)
- Fasting lipid levels: TC 232 mg/dL (6 mmol/L), LDL 145 mg/dL (3.76 mmol/L), HDL 45 mg/dL (1.17 mmol/L), TG 200 mg/dL (2.26 mmol/L)

- Assess the patient's condition based on this additional information.
- What are the goals of treatment for this patient?
- Assess the patient's risk factors for heart disease and breast cancer.
- Recommend nonpharmacologic and pharmacologic treatment for this patient. Justify your recommendations.

rise during some menstrual cycles but can fall again during subsequent menstrual cycles, leading to irregular and unpredictable menses. During menopause, FSH concentrations increase 10- to 15-fold, LH concentrations increase 5-fold, and levels of circulating estradiol decrease by over 90%.[6]

Vasomotor symptoms, as well as other menopausal symptoms, occur in over 50% of perimenopausal women and over 80% of menopausal women.[5] Menopausal symptoms tend to be more severe in women who undergo surgical menopause compared with natural menopause because of the more rapid decline in estrogen concentrations. Women who seek medical treatment should undergo laboratory evaluation to rule out other conditions that may present with similar symptoms, such as abnormal thyroid function or pituitary adenoma. Once other conditions have been excluded, HRT should be considered.

TREATMENT

Desired Outcomes

❷ *Hormone-replacement therapy remains the most effective treatment for vasomotor symptoms and vulvovaginal atrophy and should be considered for women experiencing these symptoms.* The goals of treatment are to alleviate or reduce menopausal symptoms and to improve the patient's quality of life while minimizing adverse effects of therapy. The appropriate route of administration should be chosen based on individual patient symptoms and should be continued at the lowest dose for the shortest duration consistent with treatment goals for each patient.

General Approach to Treatment

Women suffering from vasomotor symptoms should attempt lifestyle or behavioral modifications before seeking medical treatment. Women who seek medical treatment usually suffer from symptoms that start to disrupt their quality of life, such as multiple hot flashes per day or week, sleep disturbances, vaginal dryness, or mood swings. HRT should be considered for these women but is not the most appropriate choice for all women. ❸ *Women should receive a thorough history and physical examination, including assessing CHD and breast cancer risk factors, before HRT is considered. Patients should be informed of the risks and the benefits of HRT and encouraged to be involved in the decision-making process. If a woman does not have any contraindications to HRT, including CHD or significant CHD risk factors, and also does not have a personal history of breast cancer, HRT would be an appropriate therapy option.* Women who have undergone a hysterectomy need only be prescribed estrogen. A progestin should be prescribed only for women with an intact uterus. Alternative, non-hormonal treatment options are available for women who are not candidates for HRT, but they are less efficacious than hormonal therapies. Alternative treatments should be chosen based on the efficacy and safety profile of the treatment and the patient's past medical history and current medications.

Nonpharmacologic Therapy

Nonpharmacologic therapies for menopause-related symptoms have not been studied in large randomized trials, and evidence of benefit is not well documented. Owing to minimal adverse effects with these types of interventions, it may be prudent for patients to try lifestyle or behavioral modifications before and in addition to pharmacologic therapy. The most common nonpharmacologic interventions for vasomotor symptoms include[4,7,8]

- Smoking cessation
- Limit alcohol and caffeine
- Limit hot beverages (e.g., coffee/tea, soups)
- Limit spicy foods
- Keep cool, and dress in layers
- Stress reduction (e.g., meditation, relaxation exercises)
- Increase exercise
- Paced respiration

Exercise demonstrated an improvement in quality of life but did not improve vasomotor symptoms. Paced respiration, a form of deep, slow breathing, improved vasomotor symptoms in a small group of patients.

Dyspareunia may result from vaginal dryness. Water-based lubricants may provide relief for several hours after application. Moisturizers may provide relief for a longer period of time and potentially can prevent infections by maintaining the acidic environment in the vagina. Both these treatments require frequent application.

A decline in estrogen concentrations also may be associated with urinary stress incontinence. **Kegel exercises** are recommended as a first-line intervention, although pharmacologic therapy also may be necessary. Kegel exercises strengthen the pelvic floor muscles and help to keep the urethra from opening at inappropriate times, such as when lifting heavy objects, coughing, or sneezing. These exercises have no adverse effects, take little time, may be done inconspicuously, and when done correctly, may help to restore normal urine flow.

Pharmacologic Therapy

Estrogens

Estrogen currently is indicated for the treatment of moderate to severe vasomotor symptoms and vulvovaginal atrophy associated with menopause. In addition, it is indicated for the prevention of postmenopausal osteoporosis in women with significant risk; however, it is recommended that non-estrogen medications receive consideration for long-term use. ❹ *Oral or transdermal estrogen products should be prescribed at the lowest*

effective dose for the relief of vasomotor symptoms. Topical products in the form of creams, tablets, or rings should be prescribed for women exclusively experiencing vulvovaginal atrophy.

Many systemically administered estrogen products are available in the United States, but conjugated equine estrogens (CEEs), prepared from the urine of pregnant mares, is the most widely prescribed. Transdermal estrogen preparations are also available and usually are prescribed for patients who experience adverse effects, elevated triglycerides, or liver function abnormalities while taking an oral product. Transdermal preparations also have a lower incidence of venous thromboembolism than oral preparations.[9]

Progestins

❺ *Women who have an intact uterus should be prescribed a progestin in addition to estrogen in order to decrease the risk of endometrial hyperplasia and endometrial cancer.*[10] Progestins should be prescribed for at least 12 to 14 days of the month and often are prescribed continuously in order to completely prevent endometrial complications. Low doses of estrogen therapy, as well as some forms of vaginal preparations, require daily or intermittent administration of a progestin in order to provide endometrial protection. Table 47–1 lists estrogen and progestin preparations and dosages.

Adverse Effects

Therapy with estrogen with or without a progestin should be initiated at the lowest dose in order to minimize adverse effects. Because the adverse effects of these preparations can be similar, it may be difficult to assess whether the estrogen or the progestin is the cause. Changing preparations, particularly with the progestin, or changing the method of administration may help to alleviate adverse effects. Table 47–2 lists the adverse effects that may be associated with estrogen and progestin preparations.

Contraindications

HRT should not be prescribed to women with a history of or active thromboembolic disease, breast cancer or estrogen-dependent neoplasm, pregnancy, liver disease, or undiagnosed vaginal bleeding. It also should not be used for the prevention or treatment of cardiovascular disease, cerebrovascular disease, or dementia.[11]

Methods of Administration

Cyclic Estrogen and Progestin

Estrogen is administered daily, and progestin is administered for 12 to 14 days of the month. The disadvantage of this method of administration is the return of monthly menses in approximately 90% of women 1 to 2 days following the last progestin dose. However, the withdrawal bleeding does not last as long or is not as heavy as a typical menstrual period. Women also may view this disadvantage as an advantage

TABLE 47–1. Estrogen and Progestin Formulations and Dosages[11,41–44]

Product	Common Dosages
Oral Estrogens	
Conjugated equine estrogens (CEE) (Premarin®)	0.3–0.625 mg/day
Synthetic conjugated estrogens (Cenestin®)	0.3–0.625 mg/day
Esterified estrogens (Estratab®)	0.3–0.625 mg/day
Estradiol (Estrace®)	0.5–1 mg/day
Estropipate (Ogen®, Ortho-Est®)	0.625 mg/day
Transdermal Estrogens	
Estradiol patch (Alora®, Climara®, Esclim®, Estraderm®, FemPatch®, Vivelle®)	0.025–0.05 mg, changed weekly (Climara®) or changed twice weekly
Menostar®[a]	0.014 once weekly
Estradiol gel (Estragel 0.06%®)	1.25g/day
Topical Estrogens	
Vaginal creams	
Conjugated equine estrogens (Premarin®)	0.5–2g/day
Estradiol (Estrace®)	1 g 1–3 times/week
Estropipate (Ortho-Est®)	2–4 g/day
Vaginal rings	
Estradiol (Estring®, Femring®)	1 ring every 3 months
Vaginal tablet	
Estradiol (Vagifem®)	1 tablet 2 times/week
Emulsions	
Estradiol (Estrasorb®)	Apply daily
Oral Progestins[b,c]	
Medroxyprogesterone acetate (Provera®)	2.5–10 mg
Micronized progesterone	100–200 mg
Transdermal Progestins[b,c]	
Levonorgestrel	0.015 mg
Norethindrone acetate	0.25–1 mg
Norgestimate	0.09 mg
Combination Products	
Oral	
CEE + MPA (Prempro®, Premphase®)	0.3–0.625/2.5–5 mg/day
Estradiol + norethindrone (Activella®)	1/0.5 mg/day
Ethynyl estradiol + norethindrone (FemHRT®)	5 mcg/1 mg/day
Estradiol + norgestimate (Ortho-Prefest®)	1/0.09 mg/day
Transdermal	
Estradiol + norethindrone (Combipatch®)	0.05/0.14 or 0.05/0.25 mg twice weekly
Estradiol + levonorgestrel (Climara Pro®)	0.45/0.015 mg once weekly

[a]Indicated for the prevention of postmenopausal osteoporosis only.
[b]May be administered cyclically or continuously.
[c]Dose varies based on daily or weekly administration.
MPA, medroxyprogesterone acetate.

TABLE 47–2. Adverse Effects of Estrogens and Progestins[11,41,44,45]

Estrogens
Common adverse effects
Nausea
Headache
Bloating
Breast tenderness
Bleeding
Serious adverse effects
Coronary heart disease
Stroke
Venous thromboembolism
Breast cancer
Gallbladder disease
Progestins
Common adverse effects
Nausea
Headache
Weight gain
Bleeding
Irritability
Depression
Serious adverse effects
Venous thromboembolism
Decreased bone mineral density

because the bleeding is scheduled and can be anticipated, thus limiting spotting or soiling of undergarments.

Continuous Combined Estrogen and Progestin

Estrogen and progestin are administered daily and result in endometrial atrophy. Therefore, women do not experience a withdrawal bleed but may experience unanticipated breakthrough bleeding or spotting during the month. Although this may sound more appealing than a withdrawal bleed, women may view the unpredictable bleeding or spotting as a disadvantage to this type of administration. Patients should be educated that the bleeding or spotting usually resolves within 6 to 12 months. If bleeding persists beyond this time period, patients should seek medical attention to rule out more serious conditions such as endometrial hypertrophy or carcinoma.

Low-Dose Hormone Therapy

Lower doses of HRT, primarily CEE, have become more popular following publication of the WHI study results. There is an increasing body of evidence proving the effectiveness of these regimens in the management of menopausal symptoms. The Women's Health, Osteoporosis, Progestin/Estrogen (HOPE) trial demonstrated that lower doses of CEE ± medroxyprogesterone acetate (MPA) (CEE 0.45 mg or 0.3 mg ± MPA 2.5 or 1.5 mg) decreased hot flashes comparable with standard hormone therapy, improved vulvovaginal atrophy, increased bone mineral density (BMD) at the spine and hip, and provided sufficient endometrial protection.[12–15] Currently, no data are available on the effects of lower-dose HRT on the incidence of venous thromboembolism, breast cancer, or CHD. Lower-dose HRT provides women with an alternative to standard-dose HRT for menopausal symptoms but also should be recommended only for a short duration. Although many women have switched to lower-dose HRT, only time will tell if lower doses translate into lower risks.

Benefits of Hormone-Replacement Therapy

Vasomotor Symptoms

HRT is indicated primarily for the relief of moderate to severe vasomotor symptoms. It remains the most effective treatment for vasomotor symptoms and should be considered only in women experiencing those symptoms. Women with mild vasomotor symptoms may benefit from nonpharmacologic therapy alone; however, many women will seek medical treatment for these symptoms. The benefits of HRT outweigh the risks in women who do not have CHD or CHD and breast cancer risk factors; however, careful consideration should be given to alternative therapies for the relief of menopausal symptoms in women with these risks. Women should be involved in the decision and may choose to use HRT despite having some risk factors owing to the severity of their symptoms. Regardless of the situation, HRT should be prescribed at the lowest dose that relieves or reduces menopausal symptoms and should be recommended only for short-term use. Women should be reassessed every 6 to 12 months, and discontinuation of therapy should be considered.

Vulvovaginal Atrophy

HRT is indicated for the treatment of vulvovaginal atrophy. Approximately 50% of postmenopausal women experience vulvovaginal atrophy and seek medication attention for relief. Vulvovaginal atrophy is associated with vaginal dryness and dyspareunia and also may be associated with recurrent urinary tract infections, urethritis, and urinary urgency and frequency. Topical preparations generally should be prescribed as first-line therapy unless the patient is also experiencing vasomotor symptoms. Topical estrogen has demonstrated increased efficacy over systemic estrogen and does not require supplementation with a progestin in women with an intact uterus using low doses of micronized 17β-estradiol. Women using regular or high doses of other topical estrogen products do require intermittent treatment with a progestin. Although few data are available on the appropriate progestin dose, some data indicate that 10 days every 12 weeks may be sufficient to prevent endometrial hyperplasia.[16] Estradiol in the form of a tablet or a ring is not absorbed systemically and may be used safely in a woman with contraindications to estrogen therapy and symptoms of vulvovaginal atrophy.[17,18]

Osteoporosis Prevention

Postmenopausal osteoporosis is a condition that affects millions of women and is characterized by low bone mass with microarchitectural deterioration of bone tissue that can

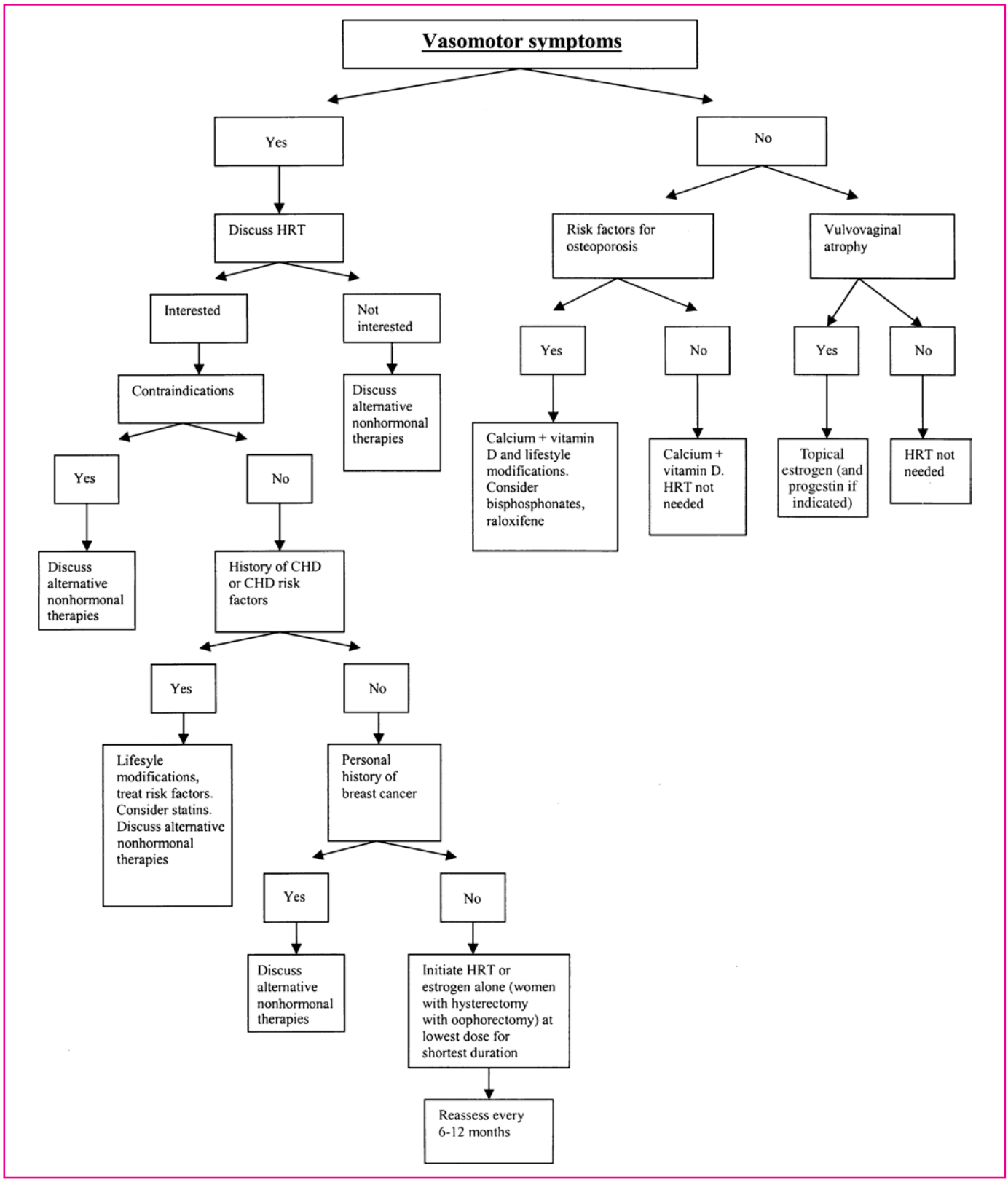


FIGURE 47–1. Treatment algorithm for postmenopausal women.[3,41,50]

lead to fractures.[19] Fractures, particularly hip fractures, are associated with a high incidence of morbidity and mortality and a decrease in quality of life (QOL). Before the WHI study, only observational data were available regarding the association of HRT and the reduction of fractures. The WHI was the first randomized controlled trial (RCT) that demonstrated a reduction in total fractures, including the hip, spine, and wrist. There were 138 fewer total fractures in women taking HRT (1.47%) compared with placebo (1.91%) [Hazard ratio (HR) 0.76, 95% confidence interval (CI) 0.69–0.85]. This translates into a number needed to treat (NNT) of 227 and 44 fewer overall fractures per year for every 10,000 women treated with HRT.[3,20] Similar benefit was found in the estrogen-alone arm.[21]

BMD will increase and the risk of fractures will decrease in women taking HRT. However, when therapy is discontinued, a decline in BMD will resume at the same rate as in women not on HRT. Therefore, therapy for osteoporosis prevention should be considered long term. ❻ *Since HRT should be maintained only for the short term, alternative therapies such as bisphosphonates or raloxifene should be considered as first-line therapy for the prevention of postmenopausal osteoporosis, in addition to appropriate doses of calcium and vitamin D.* Because of the risks associated with HRT, it should not be prescribed solely for the prevention of osteoporosis.

Colon Cancer

Retrospective observational studies suggested that HRT was associated with lower rates of colorectal cancer. The WHI was the first and largest RCT to confirm that HRT decreases the risk of colorectal cancer. In the WHI, there were 22 fewer cases of colorectal cancer in women taking HRT (0.1%) compared with placebo (0.16%) (HR 0.63, 95% CI 0.43–0.92). This translates into an NNT of 1666 and 6 fewer colorectal cancers per year for every 10,000 women treated with HRT.[3] In the WHI estrogen-alone arm, the cases of colorectal cancer were not lower in the estrogen group compared with the placebo group.[21] Unfortunately, these data are inconsistent and are not compelling enough to justify long-term use of estrogen-replacement therapy (ERT) or HRT.

Risks of Hormone-Replacement Therapy

Cardiovascular Disease

CHD is the leading cause of death among women in the United States. Retrospective data indicated that HRT was associated with a decrease in risk of CHD by 30% to 50%.[21] However, the results of recent RCTs demonstrate that HRT does not prevent or treat CHD in women and that it actually may cause an increase in CHD events. The HERS, published in 1998, was the first RCT conducted in women with established CHD. This trial demonstrated an increased incidence of CHD events within the first year of treatment with HRT and an increased risk of venous thromboembolism (VTE) and gallbladder disease. There was a trend of decreasing incidence of CHD death in years 3 to 5 that prompted a continuation of the study.[2] The HERS II was an open-label continuation of the HERS for an additional 2.7 years. No difference was found in CHD events between the HRT and placebo groups; however, there was an increased risk of VTE and biliary tract surgery in the HRT group.[22]

The WHI was the first RCT conducted in women without established CHD. Women aged 50 to 79 years with an intact uterus were assigned to receive HRT (CEE 0.625 mg + MPA 2.5 mg) daily for 8.5 years. The trial was stopped after only 5.2 years owing to an increased incidence of breast cancer in women taking HRT compared with placebo. The WHI demonstrated an increased risk of CHD within the first year of treatment of 0.37% in the HRT group compared with 0.3% in the placebo group (HR 1.29, 95% CI 1.02–1.63). This translates into a number needed to treat to harm (NNTH) of 1428. There also was an increased risk of stroke in the HRT group (0.29%) compared with placebo (0.21) (HR 1.41, 95% CI 1.07–1.85), with an NNTH of 1250. Therefore, for every 10,000 women treated per year with HRT, there would be 7 more CHD deaths and 8 more strokes.[3]

The estrogen-alone arm of the WHI, which included women aged 50 to 79 years with a history of hysterectomy, continued for another 1.6 years (average follow-up 6.8 years). This arm of the study did not demonstrate an increased risk of CHD in the ERT group compared with placebo. However, there was an increased risk of stroke in the ERT group (0.44%) compared with placebo (0.32%) (HR 1.39, 95% CI 1.10–1.77). This translates into an NNTH of 833 and 12 more strokes for every 10,000 women treated per year with ERT.[21]

The results of these trials demonstrate that ERT or HRT should not be prescribed for the prevention of CHD or in patients with preexisting CHD. For women suffering from vasomotor symptoms with a history of CHD, including CHD risk factors, alternative therapies should be considered. Additionally, lifestyle modifications should be implemented, and therapies to treat risk factors such as hypertension and hyperlipidemia should be prescribed. It is important to note that the average age of women included in the HERS and the WHI trials was 67 and 63 years, respectively. Therefore, these trials were unable to assess the true risk in younger, potentially healthier women with fewer cardiovascular risk factors.

Breast Cancer

Breast cancer is the most common cancer in women in the United States. Observational data indicated an association between HRT and breast cancer risk. The WHI was the first RCT to demonstrate an increased risk of invasive breast cancer among women taking HRT. In fact, the trial was stopped early owing to an increased incidence of breast cancer in women taking HRT (0.38%) compared with placebo (0.3%) (HR 1.26, 95% CI 1–1.59). This translates into an NNTH of 1250 and 8 more cases of invasive breast cancer for every 10,000 women treated per year with HRT. The risk of breast

cancer was evident after only 3 years of treatment and continued throughout the study duration. In this arm of the study, breast cancer was diagnosed at a more advanced stage in the HRT group compared with placebo. In addition, the percentage of women with abnormal mammograms after 1 year was significantly higher in women taking HRT than in those taking a placebo.[3,23]

Breast cancer was not increased in the ERT arm of the WHI, and in fact, the risk was non-significantly lower in the ERT group than in the placebo group.[21] These conflicting data point to a possible link of progestin with breast cancer risk; however, this theory needs to be studied further.

Because the WHI is the best evidence to date linking HRT with breast cancer, women with a personal history of breast cancer and possibly even a strong family history of breast cancer should avoid the use of HRT and consider non-hormonal alternatives for the treatment of vasomotor symptoms.

Venous Thromboembolism

The WHI demonstrated an increased risk in venous thromboembolic disease in the HRT group (0.34%) compared with placebo (0.16%) (HR 2.11, 95% CI 1.58–2.82). This translates into an NNTH of approximately 555 and 18 more cases of venous thromboembolic events for every 10,000 women treated per year with HRT.[3] The risk for deep vein thrombosis also was increased in the ERT arm of the WHI, but pulmonary embolism was not increased significantly.[21]

Observational and prospective data have consistently demonstrated an increased risk in thromboembolic events with the use of HRT.[2,3,19,20] Women taking HRT have approximately doubled the risk of those not taking HRT. Therefore, these risks need to be weighed carefully when considering the use of HRT for the treatment of vasomotor symptoms.

❼ *In summary, combined estrogen plus progestin should not be used for the prevention of chronic diseases because it increases the risk of CHD, stroke, breast cancer, and venous thromboembolism. However, colorectal cancer and rates of fracture were reduced with combined hormonal treatment.*

Other Effects of Hormone-Replacement Therapy

Quality of Life and Cognition

Although women generally consider QOL measures when deciding whether to use HRT, the effects of HRT on overall QOL have been inconsistent. HRT or ERT did not demonstrate a clinically meaningful effect on QOL; however, women taking HRT did have a small improvement in sleep disturbances, physical functioning, and bodily pain after 1 year of therapy.[24] Results from the HERS demonstrated that HRT did improve emotional measures such as depressive symptoms, but only if women suffered from flushing at trial entry. QOL scores declined significantly in women without flushing symptoms.[25] Although mood and well-being may be improved in women with vasomotor symptoms, HRT should not be prescribed for the sole purpose of improving QOL measures.

The prevalence of age-associated memory impairment is approximately 17% to 34% in the general population.[26] Observational studies have suggested a potential benefit of HRT on cognitive functioning and dementia. However, the WHI Memory Study (WHIMS), conducted in postmenopausal women aged 65 years or older, failed to demonstrate an improvement in cognitive function and demonstrated a dementia rate, including Alzheimer's disease, two times greater than with placebo (HR 2.05, 95% CI 1.21–3.48). In addition, women receiving HRT experienced a small decline in cognitive function compared with placebo.[26,27] The estrogen-alone arm of the WHIMS also demonstrated similar results.[28,29]

❽ *In summary, HRT improves overall well-being and mood in women with vasomotor symptoms, but it has not demonstrated an improvement in QOL in women without vasomotor symptoms, does not improve cognitive function, and has little effect, if any, on QOL measures.*

Discontinuation of HRT

❾ *In appropriate women, HRT should be recommended at the lowest dose for the shortest duration and should be tapered before discontinuation in order to prevent the recurrence of hot flashes.* It is not entirely clear what time interval is considered safe for HRT because some of the risks associated with HRT were found within the first year of treatment. It is also not clear how long vasomotor symptoms will last in each woman. Although vasomotor symptoms in most women will subside within 4 years, approximately 10% of women continue to experience symptoms that interfere with their QOL. Therefore, it is important to continually reassess a woman's vasomotor symptoms while taking HRT and to try to taper the therapy after 1 year. If symptoms return following a slow taper of HRT, it may be reinitiated and tried again at a later date. However, the literature suggests that one of every four women need to be reinitiated on HRT owing to persistent and bothersome symptoms.[30–32]

Discontinuing HRT can be complicated. Little evidence is available to guide health care providers regarding the most effective, safe, and least disruptive way to taper HRT. Slowly discontinuing HRT over time may be associated with less risk of symptom return. This rationale makes sense when you compare vasomotor symptoms in women who undergo surgical menopause with those in women undergoing natural menopause. It is generally thought that the rapid decline in estrogen concentrations leads to more severe vasomotor symptoms. However, the time frame for tapering HRT is unknown but can take up to 3 to 6 months or longer in some cases. Tapering HRT may be done in one of two ways: dose taper or day taper. The dose taper involves decreasing the dose of estrogen over several weeks to months and monitoring closely for a return of symptoms. If symptoms recur, the next reduction in dose should not occur until symptoms resolve or at least

stabilize on the current dose. The day taper involves decreasing the number of days of the week that a woman takes the HRT dose, e.g., decreasing a daily dose of 0.3 mg estrogen to 0.3 mg estrogen 5 days a week. Again, if symptoms recur, continue on the current dose until symptoms resolve or stabilize before trying a subsequent decrease. It is important to note that these tapering regimens have not been studied in clinical trials and may not prove to be beneficial in individual women.[32]

For women who cannot tolerate even a very slow taper, the benefits must be weighed against the risks of HRT, and often women choose to continue HRT. Alternative, non-hormonal therapies are available and may be beneficial in some women; however, the literature suggests that these therapies are less effective than HRT.

Non-hormonal Treatments

⓾ *Since publication of the WHI study, there has been an increase in the use of non-hormonal therapies for the management of menopausal symptoms. Particularly for women with CHD and breast cancer risk factors, non-hormonal therapies may offer an alterative to assist with symptom management. A wide range of therapies, both prescription and herbal, have been studied with varying degrees of success. In choosing a particular therapy, it is important to match patient symptoms with a therapy that is not only effective but also safe.*

A number of non-hormonal therapies have been studied for symptomatic management of vasomotor symptoms, including antidepressants [e.g., selective serotonin reuptake inhibitors (SSRIs) and venlafaxine], herbal products (e.g., soy, black cohosh, and dong quai), and a group of miscellaneous agents (e.g., gabapentin, clonidine, and megestrol). The choice of therapy depends on the patient's concomitant disease states, such as depression and hypertension, and the risk for potential adverse effects.

SSRIs are theorized to reduce the frequency of hot flashes by increasing serotonin in the central nervous system and by decreasing LH. Of the SSRIs, citalopram, paroxetine, and sertraline all have been studied and have demonstrated a reduction in hot flashes while treating other symptomatic complaints such as depression and anxiety.[33] Venlafaxine, which blocks the reuptake of serotonin and norepinephrine, has demonstrated a reduction in hot flashes primarily in the oncology population.[34] Overall, these antidepressant medications offer a reasonable option for women who are unwilling or cannot take hormonal therapies, particularly those who suffer from depression or anxiety. These agents should be prescribed at the lowest effective dose to treat symptoms and may be titrated based on individual response.

Herbal products used for the relief of menopausal symptoms are purported to act by a number of different mechanisms. Phytoestrogens are plant sterols that are structurally similar to human and animal estrogen. Soy protein is a common source of phytoestrogens and can be found in products such as tofu, soy milk, soy flour, and tempeh. Various studies have demonstrated conflicting results as to the efficacy of phytoestrogens in treating hot flashes.[33,35] It is also unknown as to whether phytoestrogens contribute to or protect from breast cancer. Therefore, careful consideration should be given before widely recommending soy protein to patients.

Black cohosh has been one of the most studied herbal remedies for vasomotor symptoms, and it has not demonstrated a substantial benefit over placebo. The mechanism of action, safety profile, drug-drug interactions, and adverse effects of black cohosh remain unknown. In non-placebo-controlled trials conducted for 6 months or less, black cohosh demonstrated a small reduction in vasomotor symptoms. It has not been shown to be effective for vasomotor symptoms in women with breast cancer.[33] There have been case reports of hepatotoxicity with the use of black cohosh.[36] Caution should be exercised when considering the use of this product, especially in patients with liver dysfunction.

Dong quai and several other herbal products, including evening primrose oil, passion flowers, sage, valerian root, flaxseed, and wild yam, have not demonstrated efficacy with regard to the relief of vasomotor symptoms, and the safety of these products is also questionable.[4,33,35] Therefore, these products should not be recommended for the relief of vasomotor symptoms in postmenopausal women.

There are a number of other prescription products that have been studied for the management of menopausal symptoms. Gabapentin is thought to exert its effect by affecting the thermoregulatory process of the pituitary-hypothalamic region through modulation of calcium currents that, in turn, affect adrenergic and serotonergic pathways. In an RCT, gabapentin was titrated to 300 mg three times daily for 12 weeks and demonstrated a 66% reduction in the frequency of hot flashes. Further symptom reduction was noted when the gabapentin dose was increased to 2700 mg daily and was safe for short-term therapy.[37] Clonidine is thought to work by reducing small-vessel response, both centrally and peripherally, to various stimuli. It has been studied in several small RCTs and demonstrated statistically significant reductions in hot flashes.[38,39] This agent may be considered in women with a history of hypertension, but the adverse effects of this medication may outweigh the benefits. Since the early 1970s, a combination of belladonna and phenobarbital (Bellergal S®) has been used to treat hot flashes. Bellergal S® is no longer available in the United States, but a similar product, Bellamine® and Bellamine S® [belladonna alkaloids (0.2 mg), ergotamine tartrate (0.6 mg), and phenobarbital (40 mg)] are available in the United States. Although early studies have demonstrated a reduction in hot flashes compared with placebo, the adverse events associated with these products have resulted in a greater than 30% withdrawal rate. Therefore, these products should not be recommended for hot flashes owing to the adverse-effect profile.[39] Lastly, megestrol has been used to manage hot flashes in patients with breast cancer and has demonstrated efficacy in this population. Long-term serious adverse effects limit its use, and it should not be prescribed routinely as an alternative to HRT for the relief of vasomotor symptoms.[40]

TABLE 47–3. Non-hormonal Therapies for Menopause[4,33,34,37–40,46–49]

Agent	Demonstrated Efficacy	Dosing	Adverse Effects/Precautions
Citalopram	Non-randomized trial demonstrated efficacy in hot flash reduction	20–60 mg daily	Nausea, dizziness, somnolence
Fluoxetine	RCT in breast cancer patients demonstrating 50% decrease in hot flash score	20 mg daily	Nausea, insomnia, nervousness, fatigue
Paroxetine	RCT demonstrating 37.8–62.2% reduction in hot flashes	10–20 mg daily	Headache, nausea, insomnia
Sertraline	Case series demonstrating efficacy in hot flash reduction	25–50 mg daily	Nausea, dizziness, somnolence
Venlafaxine	RCT in breast cancer patients demonstrating 55% reduction in hot flashes	12.5 mg twice daily	Nausea, dry mouth
Soy protein	Conflicting evidence; short-term (less than 6 weeks) symptomatic relief demonstrated; benefit questionable	50–80 mg isoflavones daily	GI upset; other adverse effects unknown
Black cohosh	Short-term (less than 6 months) symptomatic relief demonstrated	Varied dosing based on herbal product combination; most studied: *Reminfemin*® 20–80 mg twice daily	GI upset (take with food); potential hepatoxicity
Gabapentin	RCT demonstrating 45% reduction in hot flash frequency	300–1600 mg daily	Dizziness and somnolence
Clonidine	Demonstrated efficacy in hot flash reduction in most trials	Variety of dose regimens; most common 0.1–0.4 mg daily	Dry mouth, blood pressure lowering; monitor blood pressure
Bellamine S®	Decreased hot flashes versus placebo; withdrawal rate greater than 30% owing to adverse effects	2 tablets daily	Dry mouth, skin rash, dizziness, sleepiness
Megestrol	RCT in breast cancer patients demonstrating up to 80% reduction in hot flashes	20–40 mg daily	Vaginal bleeding, headache, weight gain, thromboembolism, edema
Dong quai	No demonstrated efficacy	Not recommended	Structurally similar to coumarins—avoid with warfarin because INR can increase
Evening primrose oil, passion flowers, sage, valerian root, and wild yam	No demonstrated efficacy	Not recommended	Caution with all plant products in women with hay fever and plant allergies

Overall, non-hormonal therapies are less effective in treating vasomotor symptoms than HRT but do offer an important option for women experiencing menopausal symptoms who cannot or are unwilling to take HRT. The antidepressants gabapentin and clonidine have the best evidence for efficacy of all the non-hormonal options and should be considered first as an alternative to HRT. The most important considerations in choosing an alternative therapy are the patient's comorbidities and the efficacy and safety of the medication.

OUTCOME EVALUATION

Evaluating the outcomes of any hormonal or non-hormonal therapy for menopausal symptoms focuses primarily on the patient's report of symptom resolution. Ask patients to report the resolution or reduction of hot flashes, night sweats, and vaginal dryness and any improvement or change in sleep patterns. Also ask women taking hormonal therapies to report any breakthrough bleeding or spotting. If abnormal or heavy bleeding occurs, refer the patient to her primary care provider. Monitor subjective parameters such as adverse effects and adherence to the therapy regimen, as well as monthly breast self-examinations. In addition, monitor objective parameters, including blood pressure, at every outpatient visit; encourage yearly clinical breast examinations, mammograms, and TSH determination, particularly for women with hypothyroidism on thyroid therapy, and conduct a BMD test every 5 years. Also perform endometrial studies, as necessary, in women with undiagnosed vaginal bleeding. Lastly, evaluate the patient's overall QOL. Because the management of menopause is largely symptomatic, it is important to document symptoms at the beginning of therapy and monitor symptom improvement and potential adverse effects at each visit. Frequent follow-up, proper monitoring, and education will help to ensure that the patient achieves optimal results from any hormonal or non-hormonal therapy chosen to treat menopausal symptoms.



Patient Encounter, Part 3: Creating a Care Plan

Based on the information presented, create a care plan for BW's hot flashes and vaginal dryness. The plan should include: (1) a statement identifying the patient problem and its severity, (2) goals of therapy, (3) a therapeutic plan based on individual patient-specific factors, (4) subjective and objective monitoring parameters, and (5) a follow-up evaluation to assess for adverse effects and adherence and to determine if the goals of therapy have been achieved.



Patient Care and Monitoring

1. Assess the patient for use of HRT by evaluating for the presence of vasomotor symptoms. If the patient is experiencing bothersome vasomotor symptoms, consider the use of HRT only after assessing for risk factors for heart disease and breast cancer. If vasomotor symptoms are tolerable and/or the patient has risk factors for heart disease and/or breast cancer, consider alternative, non-hormonal treatments for vasomotor symptoms.
2. Obtain a thorough medication history, including the use of over-the-counter and herbal products.
3. Educate the patient on lifestyle or behavioral interventions that may help to alleviate vasomotor symptoms.
4. Discuss methods of HRT administration, and have the patient decide in conjunction with the health care provider which one she feels will work best for her.
5. Recommend the appropriate dose of HRT, and use the lowest effective dose for the shortest duration possible.
6. Educate the patient regarding the proper administration, potential adverse effects, and expectations of HRT.
7. Monitor the patient for a reduction in vasomotor symptoms, vaginal dryness, and improvement in sleep. Also monitor for breakthrough bleeding and spotting, adverse effects of HRT, and improvement in QOL.
8. Monitor the following objective parameters:
   - Blood pressure at every outpatient visit
   - Yearly lipoprotein panels
   - Yearly fasting plasma glucose determinations
   - Yearly breast examinations and mammograms
   - Yearly TSH determinations, particularly for women with hypothyroidism on thyroid therapy
   - Endometrial studies in women with undiagnosed vaginal bleeding
9. Educate the patient regarding the importance of adhering to the medication regimen.
10. Educate the patient regarding the importance of obtaining a yearly mammogram and Papanicolaou (Pap) smear (if applicable), as well as performing a monthly breast self-examination.
11. Assess patient symptoms every 6 to 12 months, and consider tapering the HRT dose and discontinuing treatment after 1 year. If vasomotor symptoms return, determine if a longer tapering schedule is warranted or if long-term treatment is necessary.

ABBREVIATIONS

BMD:	bone mineral density
CEEs:	conjugated equine estrogens
CHD:	coronary heart disease
ERT:	estrogen-replacement therapy

FSH:	follicle-stimulating hormone
GnRH:	gonadotropin-releasing hormone
HDL:	high-density lipoprotein
HERS:	Heart and Estrogen/Progestin Replacement Study
HOPE:	Women's Health, Osteoporosis, Progestin/Estrogen trial
HRT:	hormone-replacement therapy
LDL:	low-density lipoprotein
LH:	leuteinizing hormone
MPA:	medroxyprogesterone acetate
NNT:	Number needed to treat
NNTH:	Number needed to treat to harm
RCT:	randomized controlled trial
QOL:	quality of life
SSRI:	selective serotonin reuptake inhibitor
TG:	triglycerides
TSH:	thyroid-stimulating hormone
USPSTF:	United States Preventive Services Task Force
VTE:	venous thromboembolism
WHI:	Women's Health Initiative
WHIMS:	Women's Health Initiative Memory Study

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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48 Erectile Dysfunction

Cara Liday and Catherine Heyneman



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Identify the structures of the male reproductive system and describe the physiology of a penile erection.
2. Differentiate between organic and psychogenic erectile dysfunction (ED) and describe the etiology and pathophysiology of each.
3. Identify the drug classes most likely to contribute to erectile dysfunction.
4. Define the essential components of history, physical examination, and laboratory data needed to evaluate the patient presenting with ED.
5. Describe current nonpharmacologic and pharmacologic options for treating ED and determine an appropriate first-line therapy for a specific patient.
6. Compare and contrast the benefits and risks for the current phosphodiesterase inhibitors.
7. Identify patients with significant cardiovascular risk and recommend an appropriate treatment approach for their ED.

Key Concepts

❶ ED can be classified as organic, psychogenic, or mixed. Many patients may initially have organic dysfunction, but develop a psychogenic component as they cope with their inability to achieve an erection.

❷ The introduction of oral medications and direct-to-consumer advertising has made patients feel more comfortable approaching practitioners for treatment advice.

❸ A thorough medical history with emphasis on cardiac disease must be taken before starting any treatment for ED to assess for ability to safely perform sexual activity and to assess for possible drug interactions.

❹ A wide range of treatment options are now available for men with ED. These include medical devices, pharmacologic treatments, lifestyle modifications, surgery, and psychotherapy.

❺ When determining the best treatment for an individual, the role of the clinician is to inform the patient and his partner of all available options while understanding his medical history, desires, and goals. The choice of treatment is primarily left up to the couple, but most often treatment is initiated with the least invasive option and then progresses to more invasive options if needed.

❻ Vacuum erection devices and intracavernosal injections are highly effective for many patients, but side effects, lack of spontaneity, and fear of needles limit their widespread use as first-line therapy.

❼ Effectiveness of the three available phosphodiesterase inhibitors is essentially comparable, but differences exist in duration of action, and to a small degree, incidence of side effects and drug interactions.

❽ Androgens are important for general sexual function and libido, but testosterone supplementation is only effective in patients with documented low serum testosterone levels.

Erectile dysfunction (ED) is defined as the inability to achieve or maintain an erection sufficient for sexual intercourse. The definition is very subjective due to differences in desired or needed rigidity in patients of different ages and in different types of relationships. Patients may refer to their dysfunction as impotence, but the National Institutes of Health Consensus Development Conference recommends that the term "erectile dysfunction" replace the term impotence due to confusion with other forms of sexual dysfunction and the negative connotation associated with the term impotence.[1] Patients may also develop **libido** or ejaculatory disorders, but these are not considered erectile dysfunction.

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Patient Encounter, Part 1

A 52-year-old man with type 2 diabetes, hypertension, and dyslipidemia returns to your clinic for follow-up on his chronic disease states. When reviewing his history, he describes problems achieving a firm erection. After further questioning, you determine that his dysfunction has progressively gotten worse over the last year. He is quite emotional and states that the problem is distressing and has caused significant marital discord. He wonders about "those ads on television" suggesting a pill.

- What other information do you need to assess for ED?
- Does he have risk factors for ED?
- Would his ED most likely be organic or psychogenic?

EPIDEMIOLOGY AND ETIOLOGY

ED becomes increasingly frequent as men age. According to data from the Massachusetts Male Aging Study the prevalence of ED of any degree is 40% among 40-year-old men and 70% among 70-year-old men.[2] The increase in incidence could be due to physiologic changes that occur with aging, the onset of chronic disease states associated with ED, increased medication use, lifestyle factors, or a combination of the above.

PATHOPHYSIOLOGY

The penis consists of three components, two dorsolateral corpora cavernosa and a ventral corpus spongiosum that surrounds the penile urethra and distally forms the glans penis. The corpora cavernosa consist of blood-filled sinusoidal or lacunar spaces, which are lined with endothelial cells, supported by trabecular smooth muscle, and surrounded by a thick fibrous sheath called the tunica albuginea. The cavernosal arteries, which are branches of the penile artery, penetrate the tunica albuginea and supply blood flow to the penis.

Sympathetic and parasympathetic nerves innervate the penis. In the flaccid state, α_2-adrenergic receptors mediate tonic contraction of the arterial and corporal smooth muscles. This maintains high penile arterial resistance and a balance exists between blood flow into and out of the corpora. With sexual stimulation, nerve impulses from the brain travel down the spinal cord to the thoracolumbar ganglia.[3] A decrease in sympathetic tone and an increase in parasympathetic activity then occurs, causing a net increase in blood flow into the erectile tissue. Erections may also occur as a result of a sacral nerve reflex arc while patients are sleeping (nocturnal erections).

Acetylcholine-mediated parasympathetic activity leads to production of the non-adrenergic–non-cholinergic transmitter nitric oxide. By enhancing the activity of guanylate cyclase, nitric oxide increases the production of cyclic guanosine monophosphate (cGMP). Vasoactive peptide and prostaglandins E_1 and E_2 stimulate increased production of cAMP. Both cyclic adenosine monophosphate (cAMP) and cGMP ultimately lead to a decrease in calcium concentration within smooth muscle cells of the penile arteries and the sinusoidal spaces, leading to smooth muscle relaxation and increased blood flow. As the sinusoidal spaces become engorged, intracavernosal pressure increases, subtunical venules are compressed, and the penis becomes rigid and elongated (Fig. 48–1).

Detumescence occurs with sympathetic discharge after ejaculation. Sympathetic activity induces smooth muscle contraction of arterioles and vascular spaces leading to a reduction in blood inflow, decompression of the sinusoidal spaces, and enhanced outflow.

Testosterone also plays a significant albeit complex role in erectile function. Testosterone is responsible for much of a man's libido. With low serum concentrations, libido declines. Additionally, testosterone helps with stabilization of intracavernosal levels of nitric oxide synthase, the enzyme responsible for triggering the nitric oxide cascade. Interestingly, some patients with low or borderline low serum concentrations of testosterone will have normal erectile function, while some with normal levels will have dysfunction.

Normal penile erections are complex events that require the full function of the vascular, neurologic, and hormonal systems. Anything that affects the function of these systems may lead to ED. ❶ *ED can be classified as organic, psychogenic, or a mixture of these.* Organic dysfunction includes abnormalities in the three systems responsible for a normal erection or may be medication-induced (Tables 48–1 and 48–2). Note that many of the risk factors for ED are the same as risk factors for cardiovascular disease. In many patients, ED is the first indication of the endothelial dysfunction associated with cardiovascular disease.[4] The presence of ED risk factors leads to the assumption that the patient has organic dysfunction. Most commonly, medical conditions that impair arterial flow into or out of the erectile tissue or affect the innervation will be strongly associated with ED. Patients with diabetes mellitus have exceptionally high rates of ED as a result of vascular disease and neuropathy.

Psychogenic dysfunction occurs if a patient does not respond to psychic arousal. It occurs in up to 30% of all cases of ED. Common causes include performance anxiety, strained relationships, lack of sexual arousability, and overt psychiatric disorders such as depression and schizophrenia.[5] It is postulated that the anxious or nervous man will have excessive stimulation of the sympathetic system, leading to smooth muscle contraction of arterioles and vascular spaces within erectile tissue.[6] ❶ *Many patients may initially have organic dysfunction, but develop a psychogenic component as they try to cope with their inability to achieve an erection.* It has been estimated that up to 80% of ED cases have an organic cause, with many having a psychogenic component as well.[1]

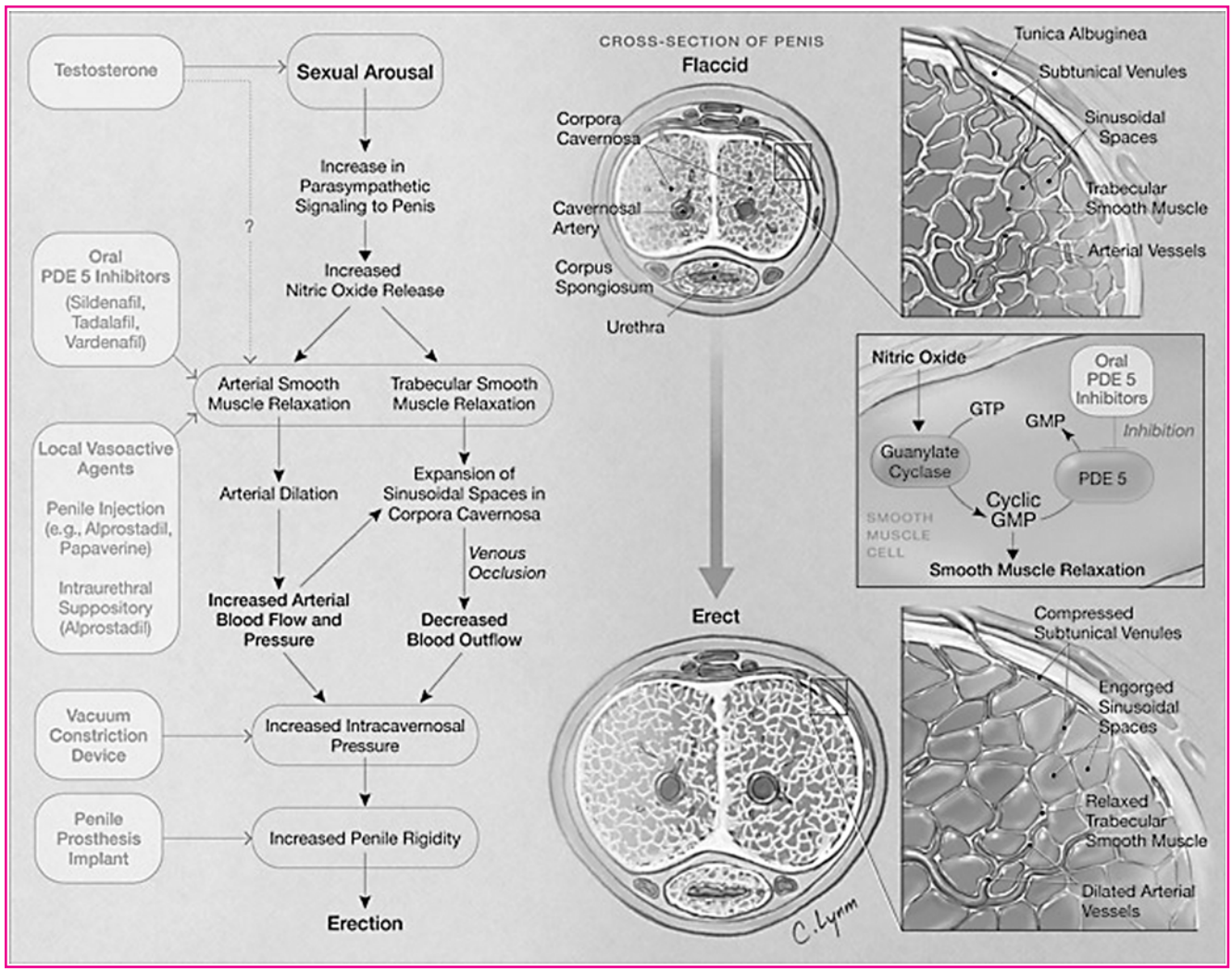


FIGURE 48–1. Mechanism of erection and sites of action of various treatment modalities for erectile dysfunction. Penile erection is achieved through relaxation of smooth muscle cells lining arterial vessels and sinusoidal spaces in the corpora cavernosa, which leads to increased arterial inflow and pressure, decreased venous outflow, and increased intracavernosal pressure. Smooth muscle relaxation is mediated by intracellular generation of cyclic guanosine monophosphate (cyclic GMP) from guanosine triphosphate (GTP) via activation of guanylate cyclase by nitric oxide. Treatment modalities for erectile dysfunction (shown in blue) include oral phosphodiesterase type 5 (PDE 5) inhibitors, which inhibit the breakdown of cyclic GMP, and local vasoactive agents. A link between testosterone and nitric oxide synthase has been demonstrated experimentally, but the significance of this observation in humans has not been established (indicated by the dashed line and question mark). Psychotherapy (not shown) may also be effective in selected individuals with erectile dysfunction. (From Morgentaler A. A 66-year-old man with sexual dysfunction. JAMA 2004;291:2996, with permission.)

CLINICAL PRESENTATION AND DIAGNOSIS

❸ *The evaluation of a patient presenting with ED should consist of a thorough medical history including sexual and psychosocial issues to determine if the dysfunction is psychogenic.* In addition, a directed physical exam and laboratory tests should be performed such as total and free serum testosterone, serum glucose, a fasting lipid panel, and a thyroid panel.[9] Identification of concomitant disease states is important for determining first line therapy. Some medical conditions and their associated medications contraindicate the use of some ED therapies or may lead to drug interactions. It is also necessary to assess the patient's ability to safely perform intercourse and to review lifestyle factors such as smoking, alcohol consumption, and regular exercise.

The International Index of Erectile Dysfunction (IIED) is the most widely used questionnaire to assess the severity of ED.[10] It consists of 15 questions with 5 domains: erectile function, libido, orgasmic function, sexual satisfaction, and overall satisfaction. The erectile function domain has a maximum score of 30 with a score of less than 26 indicating some degree of ED.

TABLE 48–1. Factors Associated with Erectile Dysfunction

Chronic Medical Conditions
Hypertension
Diabetes mellitus
Inflammatory conditions of the prostate
Coronary and peripheral vascular disease
Neurologic disorders (e.g., Parkinson's disease and multiple sclerosis)
Endocrine disorders (hypogonadism and pituitary, adrenal, and thyroid disorders)
Psychiatric disorders (depression, anxiety, and schizophrenia)
Hyperlipidemia
Renal failure
Liver disease
Penile disease (Peyronie's disease or anatomic abnormalities)
Surgical Procedures
Perineal surgery
Radical prostatectomy
Vascular surgery
Lifestyle
Age
Smoking
Excessive alcohol consumption
Obesity
Poor overall health and reduced physical activity
Trauma
Pelvic fractures
Spinal cord injuries

TABLE 48–2. Medication Classes Associated with Erectile Dysfunction[3,24,25]

Antihypertensives
β-Blockers (particularly non-selective)
Thiazide diuretics
Centrally acting agents (clonidine, methyldopa, and reserpine)
Spironolactone
α-Blockers
Lipid medications
Gemfibrozil
Antidepressants
Tricyclic antidepressants
Monoamine oxidase inhibitors
Selective serotonin reuptake inhibitors
Antipsychotics
Phenothiazines
Risperidone
Lithium
Anticonvulsants
Carbamazepine
Phenytoin
Histamine antagonists
Cimetidine
Anti-androgens and hormones
5α-Reductase inhibitors
Progesterone and estrogen
Recreational drugs
Ethanol
Cocaine
Marijuana



Clinical Presentation of ED[7,8]

❷ *The introduction of oral medications and direct-to-consumer advertising has made patients feel more comfortable approaching practitioners for treatment advice*. Despite this, some patients may only discuss their dysfunction when questioned directly by their provider or if their partner initiates the interaction. Patients may still feel that a loss in erectile function translates into a loss of masculinity.

Patients presenting with ED may show some of the following signs and symptoms:

- Embarrassment
- Anxiousness
- Anger
- Marital problems
- Low self-confidence or morale
- Full inability to achieve erections
- Ability to achieve partial erections, but not suitable for intercourse
- Erections sufficient for intercourse, but early detumescence
- The problem may have a slow or acute onset, or may wax and wane

ED may be the presenting symptom of other chronic disease states.

TREATMENT

Desired Outcomes

ED is not a life-threatening condition, but left untreated it can be associated with depression, loss of self-esteem, poor self-image, and marital discord.[11] The primary goal of therapy is achievement of erections suitable for intercourse and improvement in patient quality of life. Additionally, the ideal therapy should have minimal side effects, be convenient to administer, have a quick onset of action, and have few or no drug interactions.[7]

General Approach to Treatment

After determining if the ED is organic or psychogenic, the initial step in management is to identify associated disease states and lifestyle activities that adversely affect erectile function and treat them optimally. Medications suspected to cause or worsen ED should also be discontinued if possible.

❹ *A wide range of treatment options are now available for men with ED. These include medical devices, pharmacologic treatments, lifestyle modifications, surgery, and psychotherapy.*

❺ *When determining the best treatment for an individual, the role of the clinician is to inform the patient and his partner of all available options while understanding his medical history, desires, and goals. Most often treatment is initiated with the least invasive option and then treatment progresses to more*



Patient Encounter, Part 2: Medical History, Physical Exam, and Diagnostic Tests

PMH
Type 2 diabetes for 15 years; not controlled due to his stressful profession; he often works late, eats on the run, and has no time for exercise
Hypertension for 8 years, currently uncontrolled
Dyslipidemia for 8 years, currently controlled

FH
Father had type 2 diabetes and died of myocardial infarction at the age of 50 years; mother is alive at 75 with no major illnesses

SH
Works long hours as a business executive; drinks alcohol only occasionally, but smokes $^1/_2$ pack per day; has a 20 pack per year history

Meds
Metformin 1000 mg PO twice daily
Metoprolol XL 50 mg PO once daily
Zocor 20 mg PO once daily

ROS
(–) Morning, nocturnal, or spontaneous erections suitable for intercourse; (–) nocturia, urgency, symptoms of prostatitis; (+) significant life stressors; (+) mild pain in feet

PE
VS: Blood pressure 148/90 mm Hg, pulse 85 beats per minute, respiratory rate 18/minute, temperature 37.0°C (98.6°F)
CV: Normal exam
Genit/Rect: Normal scrotum and testicles w/o masses; penis without discharge or curvature

Labs
Complete metabolic panel, complete blood cell count, and thyroid panel within normal limits
Lipid panel: total cholesterol , low-density lipoproteins, high-density lipoproteins, triglycerides within normal limits
Hemoglobin A1c: 8.0% (0.08), testosterone: 700 ng/dL (24 nmol/L)

- Given this additional information, what is your assessment of the patient's condition? What is/are the most likely causes of his ED?
- Identify treatment goals for this patient.
- What pharmacologic and nonpharmacologic alternatives are available for this patient?
- Which of the above will be your treatments of choice based on degree of invasiveness, side effects, ease of use, and side-effect profile?
- What other information do you need before starting certain pharmacotherapeutic options?

invasive options if needed. Ultimately, the choice of therapy should be individualized, taking into account patient and partner preferences, concomitant disease states, response, administration, cost, tolerability, and safety. Common drug treatment regimens for ED are listed in Table 48–3.

Nonpharmacologic Therapy

Lifestyle Modifications

Lifestyle modifications should always be addressed in the management of ED. A healthy diet, increase in regular physical activity, and weight loss are associated with higher IIED scores and an improvement in erectile function.[12] The clinician should recommend smoking cessation, reduction in excessive alcohol intake, and discontinuation of the use of illicit drugs.

Psychotherapy

Psychotherapy is an appropriate treatment approach for patients with psychogenic or mixed dysfunction. It should address immediate causes of dysfunction, and if possible the partner should attend sessions as well. Effectiveness is not well documented for organic dysfunction unless combined with other therapies. Advantages include non-invasiveness and partner participation, while disadvantages include increased cost and time commitment.

Vacuum Erection Devices

Vacuum erection devices (VEDs) induce erections by creating a vacuum around the penis; the negative pressure draws blood into the penis by passively dilating arteries and engorging the corpora cavernosa. The erection is maintained with a constriction band placed at the base of the penis to reduce venous outflow (Fig. 48–2). They may be used as often as desired, but it is recommended that the constriction band not be in place longer than 30 minutes at a time.

❻ *VEDs are one of the most effective treatment modalities for ED. They have a success rate of greater than 90% in obtaining an erection sufficient for* ***coitus*** *and are considered a first-line non-invasive therapy.*[13] Rigidity may be improved by using a double pump technique in which the vacuum is applied for a couple of minutes, removed, then reapplied for another few minutes. Higher efficacy rates can also be achieved by combining VEDs with other therapies.

Onset of action is slow at around 30 minutes, which limits spontaneity. In addition, patients and partners may complain of a cold, lifeless, discolored penis that has a hinge-like feel. Painful ejaculation or inability to ejaculate are additional adverse effects. VEDs are contraindicated in persons with sickle cell disease and should be used with caution in patients on oral anticoagulants or who have bleeding disorders due to the increased possibility of **priapism**.

Prostheses

Penile prostheses are semi-rigid malleable or inflatable rods, which are inserted surgically into the corpus cavernosa to allow erections (Fig. 48–2). The malleable rods are rigid at all times, but may be bent into position by the patient when desired. The inflatable prostheses remain flaccid until the pump within the scrotum moves fluid from a reservoir to the cylinders within the penis. Detumescence is achieved when the fluid is then transferred back to the reservoir by activating a release button.

TABLE 48–3. Common Drug Treatment Regimens for Erectile Dysfunction

Route of Administration	Generic Name	Brand Name	Typical Dosing Range[a]	Maximum Dosing Frequency
Oral	Sildenafil	Viagra	25–100 mg 1 hour prior to intercourse	Once daily
	Tadalafil	Cialis	5–20 mg prior to intercourse	Once daily
	Vardenafil	Levitra	5–20 mg 1 hour prior to intercourse	Once daily
	Yohimbine[b]	Aphrodyne, Yocon	5.4 mg three times daily	N/A
Intracavernosal	Alprostadil	Caverject, Caverject Impulse, Edex	1.25–60 mcg 5–20 minutes prior to intercourse[c]	Three times weekly, 24 hours between injections
	Papaverine	N/A	Usually used in combination at variable doses	Three times weekly, 24 hours between injections
	Phentolamine	N/A	Usually used in combination at variable doses	Three times weekly, 24 hours between injections
Intraurethral	Alprostadil	MUSE	125–1000 mcg 5–10 minutes prior to intercourse[c]	Two times daily
Intramuscular	Testosterone cypionate	Depo-Testosterone	50–400 mg every 2–4 weeks	Once weekly
	Testosterone enanthate	Delatestryl	50–400 mg every 2–4 weeks	Once weekly
Topical	Testosterone patches	Testoderm	4–6 mg/day applied to scrotum	Once daily
		Testoderm TTS	4–6 mg/day applied to arm, back, or upper buttocks	Once daily
		Androderm	2.5–5 mg/day applied to back, abdomen, upper arms, or thighs	Once daily
	Testosterone gel	AndroGel 1%, Testim	5–10 g daily to shoulders, upper arms, or abdomen (AndroGel only)	Once daily
Buccal	Testosterone	Striant	30 mg every 12 hours to gum region above incisor; rotate to alternate sides with each dose	Twice daily

[a]Use the lowest effective dose to limit adverse effects.
[b]Not FDA approved for this indication.
[c]Initial dose must be titrated in physician's office.
MUSE, medicated urethral system for erection.

Because prostheses are the most invasive treatment available, they are only considered in patients who do not respond to medications or external devices, or those who have significant adverse effects from other therapies. Patient satisfaction rates can be as high as 80% to 90% with partner satisfaction rates just slightly lower.[9] The primary risks of insertion of prostheses are infection and device failure, although these only happen in 2% to 3% and 2% to 14% of patients, respectively. Higher infection rates have been reported in uncontrolled diabetic patients, paraplegics, and patients undergoing reimplantation or penile reconstruction.[14,15] Most prostheses can be expected to last from 7 to 10 years.[16]

Pharmacologic Therapy

Phosphodiesterase Type 5 Inhibitors

Sildenafil (Viagra®), tadalafil (Cialis®), and vardenafil (Levitra®) act by selectively inhibiting phosphodiesterase (PDE) type 5, an enzyme that breaks down cGMP. By inhibiting the breakdown of cGMP, smooth muscle relaxation is induced, leading to an erection (Fig. 48–1). However, the PDE inhibitors are only effective in the presence of sexual stimulation to drive the nitric oxide/cGMP system, making them facilitators of an erection, not initiators. Patients must be informed of the need for sexual stimulation to induce an erection, as it will not occur spontaneously.

❼ *Effectiveness of the three available phosphodiesterase inhibitors is essentially comparable, but differences exist in duration of action, and to a small degree, incidence of side effects and drug interactions* (Table 48–4). Studies directly comparing the side effects and efficacy of the drugs in this class have not been published. In addition, trials for vardenafil and tadalafil excluded subjects who did not respond to sildenafil. Review of available data for each individual agent shows a 50% to 80% response rate depending on the dose of agent used and the etiology of dysfunction. Patients with radical prostatectomy tend to have lower response rates.[6] Response rates are also lower in patients with diabetes, severe nerve damage, or severe vascular disease.[17] The PDE inhibitors are considered first-line therapies due to high efficacy rates, convenience of dosing, and minimal severe adverse effects.

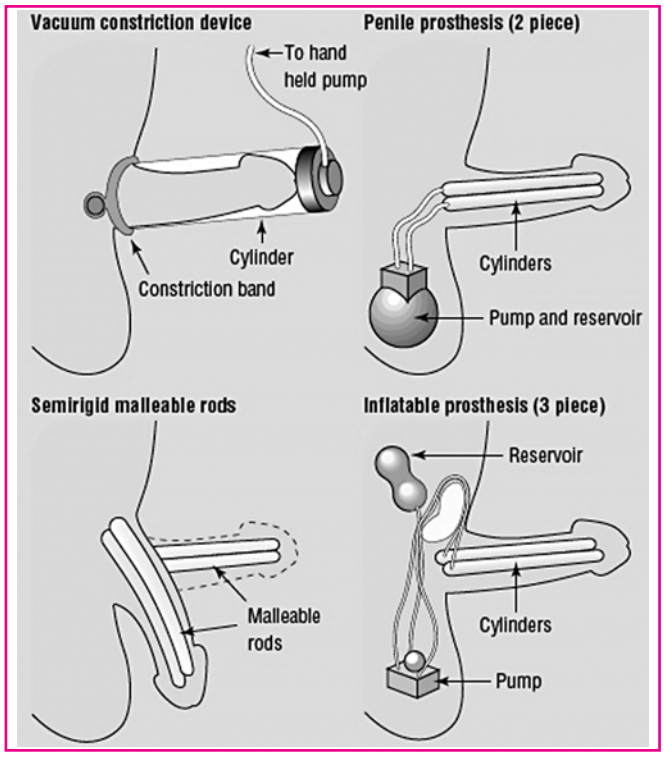


FIGURE 48–2. Available devices and prostheses used to treat erectile dysfunction. (From Wagner G, Saenz de Tejada I. Update on male erectile dysfunction. BMJ 1998;316:681, with permission.)

The most dramatic difference between the three agents is tadalafil's extended duration of action, earning it the nickname "the weekender drug." While sildenafil and vardenafil have average half-lives of 3 to 4 hours, tadalafil's half life is approximately 18 hours.[18] The extended half-life allows for more spontaneous sexual activity over a couple of days, but may increase the duration of adverse effects and liklihood of drug interactions or sildenafil.

The most common side effects experienced with PDE inhibitors include headache, facial flushing, nasal congestion, dyspepsia, and rarely priapism. Vardenafil and sildenafil may also cause difficulty in discriminating blue from green, bluish tones in vision, or difficulty seeing in dim light due to cross-reactivity with PDE 6 in the retina. There has also been a recent change in the labeling for all PDE inhibitors warning about non-arteritic ischemic optic neuropathy (NAION) in a small number of patients. This is a condition in which blood flow is blocked to the optic nerve. If patients experience sudden or decreased vision loss they should call a health care provider immediately.

Concern exists about the safety of using PDE inhibitors in patients with cardiovascular disease. Because of the numerous adverse cardiovascular events reported after the release of sildenafil, a management approach was developed to give recommendations for the use of PDE inhibitors in patients with cardiovascular disease[19] (Table 48–5). In addition to the inherent risk of renewing sexual activity, PDE inhibitors can lead to significant hypotension. Patients taking organic nitrates are

TABLE 48–4. Comparison of Phosphodiesterase Inhibitors

	Sildenafil (Viagra®)	Tadalafil (Cialis®)	Vardenafil (Levitra®)
Available strengths	25-, 50-, 100-mg tabs	5-, 10-, 20-mg tabs	2.5-, 5-, 10-, 20-mg tabs
Initial dosage in healthy adults (dosing range in mg)	50 mg every day taken 1 hour prior to sexual activity	10 mg every day taken 1 hour prior to sexual activity	10 mg every day taken 1 hour prior to sexual activity
Dosing range for healthy adults (mg)	25–100	5–20	5–20
Dosage in the elderly	25 mg every day	10 mg every day	5 mg every day
Dosage in renal impairment	50 mg every day (moderate[a]) 25 mg every day (severe[b])	5 mg every day (moderate[a] and severe[b])	5–20 mg every day
Dosage in hepatic impairment	25 mg every day	10 mg[c]	5–10 mg[d]
Time to onset	30 minutes	15 minutes	Less than 1 hour
Onset delayed by high-fat meal?	Yes	No	Yes
Duration of effect	Up to 4 hours	Up to 36 hours	Up to 4 hours
Half-life	3–4 hours	18 hours	3–4 hours
Metabolism	CYP3A4 (major) CYP2C9 (minor)	CYP3A4	CYP3A4 (major) CYP3A5 (minor) CYP2C (minor)
Drug present in semen?	18%	Less than 0.0005%	0.00018%
Clinically relevant drug interactions	Nitrates, protease inhibitors, azole antifungals	Nitrates, α_1-blockers[e], azole antifungals	Nitrates, anti-arrhythmic agents,[f] α_1-blockers

[a]Moderate renal impairment = creatinine clearance (CrCl) 31–50 mL/minute.
[b]Severe renal impairment = CrCl less than 30 mL/minute.
[c]Mild to moderate only—contraindicated in severe liver disease.
[d]Mild to moderate only—not yet evaluated in severe liver disease.
[e]Selective α_{1a}-blockers (such as 0.4 mg tamsulosin every day) are appropriate in combination with tadalafil.
[f]Vardenafil can cause QT-interval prolongation; this effect in combination with certain anti-arrhythmic agents can lead to life-threatening arrhythmias.
CYP, cytochrome P-450 isoenzyme.

TABLE 48–5. Cardiovascular Risk Assessment for Phosphodiesterase Inhibitors

Risk Category	Description of Patients' Conditions	Management Approach
Low risk	Has asymptomatic cardiovascular disease Has well-controlled hypertension Has mild, stable angina Has mild congestive heart failure (NYHA Class 1)	Patient can be started on phosphodiesterase inhibitor
Moderate risk	Has three or more risk factors for coronary artery disease Has moderate, stable angina Had a recent myocardial infarction or stroke within the past 6 weeks Has moderate congestive heart failure (NYHA Class 2)	Patient should undergo a complete cardiovascular work-up and treadmill stress testing to determine tolerance to increased myocardial energy consumption associated with increased sexual activity
High risk	Has unstable or symptomatic angina, despite treatment Has poorly controlled hypertension Has severe congestive heart failure (NYHA Class III or IV) Had a recent myocardial infarction or stroke within the past 2 weeks Has moderate or severe valvular heart disease	Phosphodiesterase inhibitor is contraindicated

NYHA, New York Heart Association.
From Lee M. Erectile dysfunction. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1524, with permission.

the most at risk, as they potentiate the drop in blood pressure. All three PDE inhibitors are absolutely contraindicated in patients taking any form of nitrate, whether scheduled or sublingual for acute situations. Caution should be used when using a PDE inhibitor in patients taking α-blockers due to an increased risk of hypotension. In addition, the labeling for vardenafil contains a precautionary statement about the possibility of QT prolongation with the use of the drug. Other drug interactions and cautions vary slightly between agents and are described in Table 48–4.

The introduction of the oral PDE inhibitors has dramatically changed the treatment of ED. Direct-to-consumer advertising has informed patients of the availability of oral drugs for treatment. However, patients must be fully informed of side effects, drug interactions, mechanism of action, and dosing before being prescribed the medication. In addition, they need to understand the need for sexual stimulation to achieve the desired result and that a single trial is not adequate. It is estimated that six to eight attempts with a medication and specific dose may be needed before successful intercourse results.[20]

Alprostadil

Alprostadil is a prostaglandin E_1 analog that induces an erection by stimulating adenyl cyclase, which leads to an increase in smooth muscle relaxation, rapid arterial inflow, and increased penile rigidity. Alprostadil is available as an intracavernosal injection (Caverject® or Edex®) or a transurethral suppository (MUSE®, medicated urethral system for erection), but the injectable form is more effective (Fig. 48–3). Both forms of alprostadil are considered more invasive than oral medications or VEDs, and are therefore second-line therapies.[8]

MUSE consists of a urethral pellet of alprostadil with an applicator. Onset of action is within 5 to 10 minutes and it is effective for 30 to 60 minutes. Initial dose titration should occur in a physician's office to ensure correct dose and prevent adverse events. Although effectiveness rates in clinical trials have been as high as 65%,[21] its success in practice has been lower. Aching in the penis, testicles, legs, and perineum, warmth or burning sensation in the urethra, minor urethral bleeding or spotting, priapism, and lightheadedness are all possible adverse effects. In addition, partners may experience vaginal burning or itching. Disadvantages include lower effectiveness, high cost, adverse effects, complicated insertion technique, and a contraindication against use with a pregnant partner unless using a condom.

Alprostadil injected into the corpus cavernosum is the more effective form and is the only Food and Drug Administration (FDA)-approved agent for injection. The onset of action is

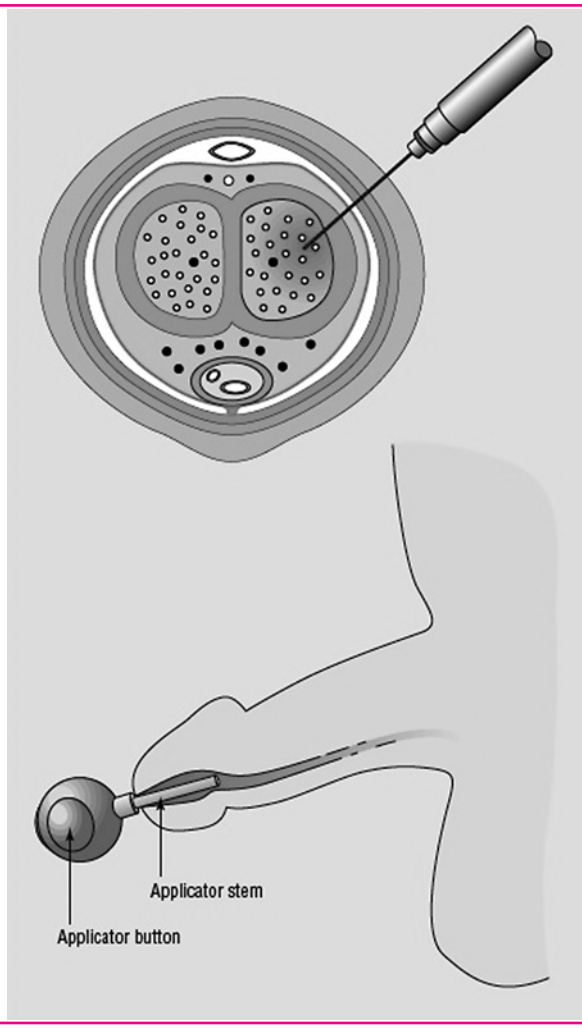


FIGURE 48–3. Intraurethral and intracavernosal administration of alprostadil. (From Wagner G, Saenz de Tejada I. Update on male erectile dysfunction. BMJ 1998;316:680, with permission.)

similar to transurethral alprostadil, but duration varies with dose and must be titrated in a physician's office to achieve an erection lasting no more than 1 hour. Injections should be done into one side of the penis directly into the corpus cavernosum, and then the penis should be massaged to distribute the drug. Because of cross-circulation, both corpora will become erect when massaging. Education is extremely important with intracavernosal injections. Patients must be adequately informed of technique, expectations, side effects, and when to seek help. ❻ *Intracavernosal injections are effective in up to 90% of patients, but side effects, lack of spontaneity, and fear of needles limit their widespread use as first-line therapy*, and therefore this therapy is most appropriate for patients in long-term stable relationships. Adverse effects include pain with injection, bleeding or bruising at the injection site, fibrosis, or priapism. Use with caution in patients with sickle cell disease, those on anticoagulants, or those who have bleeding disorders, due to an increased risk of priapism and bleeding.

Papaverine and Phentolamine

Papaverine and phentolamine are non–FDA-approved agents used for intracavernosal injection. Papaverine is a non-selective PDE inhibitor that induces an erection by relaxing smooth muscle and increasing blood flow. Phentolamine is a competitive α-adrenergic receptor antagonist that increases arterial inflow by opposing arterial constriction. Both drugs are rarely used alone, and are most often mixed in various concentrations with alprostadil for increased effectiveness and in an effort to reduce adverse effects with smaller doses of each medication. Patients typically must see a specialist for use of these medications in mixtures, as they are the most likely to compound them and adjust dosages.

Yohimbine

Yohimbine is an indole alkaloid produced in the bark of yohimbe trees. It selectively inhibits α_2-adrenergic receptors in the brain that are associated with libido and penile erection. Since there is only limited data supporting its efficacy, yohimbine is not a recommended treatment for any form of ED.[22] Adverse effects of the drug include nausea, irritability, headaches, anxiety, tachycardia, and hypertension.

Testosterone Supplementation

❽ *Androgens are important for general sexual function and libido, but testosterone supplementation is only effective in patients with documented low serum testosterone levels.* In patients with **hypogonadism**, testosterone replacement is the initial treatment of choice, as it corrects decreased libido, fatigue, muscle loss, sleep disturbances, and depressed mood. Improvements in ED may occur, but they should not be expected to occur in all patients.[23] The initial trial should be for 3 months. At that time, re-evaluation and the addition of another ED therapy is warranted. Routes of administration include oral, intramuscular, topical patches or gel, and a buccal tablet.

Injectable esters of testosterone offer the most inexpensive and effective replacement option. Testosterone cypionate and enanthate have the longest duration of action and are therefore the preferred agents. There are several drawbacks associated with parenteral testosterone including the need to administer deep intramuscular injections every 2 to 4 weeks. In addition, levels of hormone are well above physiologic values within the first few days. Concentrations then decline and eventually dip below physiologic levels just before the next dose. These extreme changes in concentration lead to mood swings and a reduced sense of well-being.[23]

Treatment with topical products is attractive to patients due to convenience, but they tend to be more expensive than

the injections. Testosterone patches and gels are administered daily and result in serum levels within the physiological range during the 24-hour dosing period.[23] Most patients prefer the non-scrotal patch or the gel since the scrotal patch requires shaving of the area, and the patch has a tendency to fall off. Care must be taken with the use of the gel to wash hands thoroughly after use and avoid baths or showers within 5 to 6 hours of application. The most common side effects of topical testosterone are dermatologic reactions caused by the absorption enhancers.

Oral testosterone products are also available for supplementation. Unfortunately, testosterone has poor oral bioavailability and undergoes extensive first-pass metabolism. Alkylated derivatives such as methyltestosterone and fluoxymesterone have been formulated to compensate for these problems, but this modification makes them considerably more hepatotoxic. This adverse effect makes oral replacement undesirable and this route of administration should not be used.

An alternative to the oral route is the buccal mucoadhesive system. The Striant® buccal system adheres to the inside of the mouth and the testosterone is absorbed through the oral mucosa and delivered to the systemic circulation. There is no first-pass effect, as the liver is bypassed by this route of administration. Patients apply a 30-mg tablet to the upper gum twice daily. The cost is similar to that of the patch or gel. Side effects unique to this dosage form include oral irritation, bitter taste, and gum edema.

General side effects of testosterone include gynecomastia, dyslipidemia, polycythemia, and acne. Weight gain, hypertension, edema, and exacerbations of congestive heart failure also occur due to sodium retention. Before initiating testosterone, the patient should undergo evaluation for benign prostatic hypertrophy and prostate cancer. Routine follow-up includes yearly prostate-specific antigen, digital rectal exam, hemoglobin, and liver function in addition to assessment of response.

OUTCOME EVALUATION

Successful therapy for ED results in an increase in erections suitable for intercourse, and most importantly in an improvement in the patient's quality of life. Ideally, the therapy chosen is free of significant adverse effects, discomfort, and inconvenience. Laboratory evaluation and a physical exam are not necessary for evaluation of effectiveness, but may be necessary to determine if adverse events are occurring.

Satisfaction and effectiveness are evaluated after a 4-week trial unless the patient initiates follow-up sooner. Some therapies such as intracavernosal injections will require multiple visits over the long term to detect adverse effects. If the initial therapy is not effective, the patient must be further evaluated to determine if the initial assessment of comorbid disease states, type of dysfunction, and patient goals were correct. After ensuring that patient goals are realistic and providing further counseling, providers will then increase the dose of drug if not at maximum, switch to another therapy, or add a therapy if indicated.



Patient Care and Monitoring

1. Assess the patient's specific symptoms to determine the type of dysfunction. Does the patient have ED or an ejaculatory or libido disorder?
2. If problems are with erectile ability, ask specific questions related to onset, frequency, and sexual relationships. Does the patient history imply psychogenic, organic, or mixed dysfunction?
3. A thorough medical history and physical exam should be performed to diagnose ED and to determine potential causes that may be treatable.
4. Perform a thorough history of prescription and non-prescription medications. Are any of the patient's medications associated with ED or are they contraindicated with possible ED therapies?
5. Generally treatment is started with the least invasive option and then progresses to more invasive options, but ultimately patient preference determines the initial therapy.
6. Discontinue medications that may cause ED if possible and optimally treat associated disease states.
7. If the patient is not satisfied, provide further counseling to ensure that they are using the therapy appropriately and that they have realistic goals.
8. Provide patient education with regard to disease state, lifestyle modifications, drug therapy, and device technique:
   - The causes of ED
   - The fact that therapy will not cure ED, but may be helpful in improving erections; it is important to have realistic expectations
   - The appropriate use of medications and devices
   - Typical adverse effects
   - Drug interactions
   - Warning signs and their management (e.g., vision changes, fibrosis, pain, priapism, or hypotension)
   - The importance of frequent follow-up with the provider

ABBREVIATIONS

cAMP:	cyclic adenosine monophosphate
cGMP:	cyclic guanosine monophosphate
ED:	erectile dysfunction
FDA:	Food and Drug Administration
GTP:	guanosine triphosphate
IIED:	International Index of Erectile Dysfunction
MUSE:	medicated urethral system for erection
NAION:	non-arteritic ischemic optic neuropathy
PDE:	phosphodiesterase
VED:	vacuum erection device

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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49 Benign Prostatic Hyperplasia

Mary Lee and Roohollah Sharifi



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Explain the pathophysiologic mechanisms underlying the symptoms and signs of benign prostatic hyperplasia.
2. Recognize the symptoms and signs of benign prostatic hyperplasia in individual patients.
3. List the desired treatment outcomes for a patient with benign prostatic hyperplasia.
4. Identify factors that guide selection of a particular α-adrenergic antagonist for an individual patient.
5. Compare and contrast α-adrenergic antagonists versus 5α-reductase inhibitors in terms of mechanism of action, treatment outcomes, adverse effects, and interactions when used for management of benign prostatic hyperplasia.
6. Describe the indications for combination drug treatment of benign prostatic hyperplasia.
7. Describe the indications for surgical intervention of benign prostatic hyperplasia.
8. Formulate a monitoring plan for a patient on a given drug treatment regimen based on patient-specific information.
9. Formulate appropriate counseling information for patients receiving drug treatment for benign prostatic hyperplasia.

Key Concepts

❶ The **lower urinary tract symptoms** and signs of benign prostatic hyperplasia are due to static, dynamic, or detrusor factors. The static factor refers to anatomic obstruction of the bladder neck caused by an enlarged **prostate** gland. The dynamic factor refers to excessive stimulation of α-adrenergic receptors in the smooth muscle of the prostate, urethra, and bladder neck. The detrusor factor refers to irritability of hypertrophied detrusor muscle as a result of long-standing bladder outlet obstruction.

❷ Drug treatment goals for benign prostatic hyperplasia include relieving obstructive and irritative voiding symptoms, preventing complications of disease, and reducing the need for surgical intervention.

❸ Single-drug treatment with an α-adrenergic antagonist is preferred for patients with moderate symptoms of benign prostatic hyperplasia. Single-drug treatment with a 5α-reductase inhibitor should be reserved for patients with significantly enlarged prostates of at least 40 g (1.4 oz).

❹ Surgical intervention should be reserved for patients with severe lower urinary tract symptoms of benign prostatic hyperplasia or those with complications of disease (such as recurrent urinary tract infections, renal failure, and bladder calculi).

❺ α-Adrenergic antagonists reduce the dynamic factor. They competitively antagonize α-adrenergic receptors, thereby causing relaxation of the bladder neck, prostatic urethra, and prostate smooth muscle. They do not shrink an enlarged prostate. The onset of action is days to weeks, depending on the need for up-titration of the daily dose to achieve a therapeutic response. Dose limiting adverse effects include hypotension and syncope. In addition, delayed or retrograde ejaculation has been reported. Combined use with antihypertensives, diuretics, or phosphodiesterase inhibitors can increase the risk of hypotensive episodes.

❻ Among the α-adrenergic antagonists, alfuzosin is considered functionally uroselective because in usual therapeutic doses, it produces relaxation of the bladder neck and prostatic smooth

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muscle with minimal peripheral vascular relaxation. Although alfuzosin appears to produce less hypotension than terazosin and doxazosin, it is not clear if it has the same cardiovascular profile as tamsulosin. Tamsulosin is unique in that it is pharmacologically uroselective and exerts greater antagonism of α_{1A}- and α_{1D}-receptors, which predominate in prostatic and bladder detrusor muscle, respectively. Tamsulosin exerts comparatively low antagonism of vascular α_{1B}-receptors. Therefore, tamsulosin can be started with a therapeutic dose, which achieves peak effects sooner than with immediate-release formulations of terazosin and doxazosin, which must be up-titrated. Tamsulosin appears to have the lowest potential to cause hypotension. In various clinical trials, tamsulosin is well tolerated in the elderly, and in patients taking diuretics and antihypertensives. It is also commercially available in a controlled-release dosage formulation. Therefore, with chronic use, tamsulosin can be taken once daily at the patient's convenience.

❼ 5α-Reductase inhibitors shrink enlarged prostates, reducing symptoms caused by the static factor. They do so by inhibiting 5α-reductase which is responsible for intraprostatic conversion of testosterone to dihydrotestosterone, the active androgen which stimulates prostate tissue growth. The onset of action is slow with peak shrinkage of the prostate taking up to 6 months. Unlike treatment with α-adrenergic antagonists, 5α-reductase inhibitors have been shown to reduce the incidence of acute urinary retention and need for prostate surgery in patients with significantly enlarged prostate glands (more than 40 g), and those with elevated serum levels of **prostate-specific antigen.** Because 5α-reductase inhibitors do not produce cardiovascular adverse effects, they are preferred for treatment of moderate to severe symptoms of benign prostatic hyperplasia when the patient is at risk of hypotension, but wants to be treated medically. Adverse effects include gynecomastia, decreased libido, erectile dysfunction, and ejaculation disorders. Drug interactions are uncommon.

❽ When monitoring efficacy of drug treatment for benign prostatic hyperplasia, subjective endpoints include relief of obstructive and irritative voiding symptoms. Objective endpoints include improvements of urinary flow rates, decreased post-void residual urinary volume, and decreased complications of disease.

The prostate is a heart-shaped, chestnut-sized organ that encircles the portion of the proximal urethra that is located at the base of the urinary bladder. The prostate produces secretions which are part of the ejaculate.

Benign prostatic hyperplasia (BPH) is the most common benign neoplasm in males who are at least 40 years of age. BPH can produce lower urinary tract voiding symptoms that are consistent with impaired bladder emptying and bladder storage. A common mode of treatment to reduce symptoms and/or delay complications of the disease is drugs. For this reason, clinicians should be knowledgeable of the medical management of this disease.

EPIDEMIOLOGY AND ETIOLOGY

BPH is present as microscopic disease in many elderly males.[1] The prevalence increases with advancing patient age. However, only about 50% and 25% of patients with microscopic BPH disease develop an enlarged prostate on palpation and clinical voiding symptoms, respectively.[2] It is estimated that 25% of males 40 years of age or more have voiding symptoms consistent with BPH,[3] and 20% to 30% of all male patients who live to the age of 80 years will require a **prostatectomy** for severe voiding symptoms of BPH.

Two etiologic factors for BPH include advanced patient age and the stimulatory effect of androgens.

- Prior to 40 years of age, the prostate in the adult male stays the same size, approximately 15 to 20 g. However, in males who have reached 40 years of age, the prostate undergoes a growth spurt, which continues as the male advances in age. Enlargement of the prostate can result in BPH.
- The testes and adrenal glands produce 90% and 10%, respectively, of circulating testosterone. Testosterone enters prostate cells, where predominantly type II 5α-reductase activates testosterone to dihydrotestosterone, which combines with a cytoplasmic receptor. The complex enters the nucleus and induces changes in protein synthesis which promote glandular tissue growth of the prostate. Thus, 5α-reductase inhibitors (e.g., finasteride and dutasteride) directly interfere with one of the major etiologic factors of BPH.
- The prostate is composed of two types of tissue: (1) glandular or epithelial tissue, which produces prostatic secretions, and (2) muscle or stromal tissue, which can contract around the urethra when stimulated. Whereas androgens stimulate glandular tissue growth, androgens have no direct effect on stromal tissue growth. It has been postulated that stromal tissue growth may be stimulated by estrogen. Since testosterone is converted to estrogen in peripheral tissues in males, testosterone may be associated indirectly with stromal hyperplasia. Stromal tissue is innervated by α_{1A}-receptors. When stimulated, prostatic stroma contracts around the urethra, narrowing the urethra and causing obstructive voiding symptoms.

PATHOPHYSIOLOGY

❶ *The symptoms and signs of benign prostatic hyperplasia are due to static, dynamic, and/or detrusor factors. The static factor refers to anatomic obstruction of the bladder neck caused by an enlarged prostate gland. As the gland grows around the urethra, the prostate occludes the urethral lumen. The dynamic factor refers to excessive stimulation of α_{1A}-adrenergic receptors in the smooth muscle of the prostate and urethra, which results in smooth muscle contraction. This reduces the caliber of the urethral lumen. The detrusor factor refers to bladder detrusor muscle*

instability, in which bladder muscle fibers have decompensated as a result of excessive, prolonged hypertrophy in response to prolonged bladder outlet obstruction. Patients with detrusor muscle instability will develop irritative voiding symptoms such as urinary urgency and frequency.[3,4] Detrusor muscle fibers are embedded with α_{1D}-receptors. Therefore, it has been proposed that some α-adrenergic$_{1D}$ antagonists may be particularly useful for controlling these symptoms.[3]

In an enlarged gland, the epithelial/stromal tissue ratio is 1:5.[3] Androgens stimulate epithelial, but not stromal tissue hyperplasia. Hence, androgen antagonism does not induce a complete reduction in prostate size to normal. This explains one of the limitations of the clinical effect of 5α-reductase inhibitors.

Stromal tissue is the primary locus of α_1-adrenergic receptors in the prostate. It is estimated that 98% of the α-adrenergic receptors in the prostate are found in prostatic stromal tissue. Of the α_1-receptors found in the prostate, 70% of them are of the α_{1A}-sub-type.[5] This explains why α-adrenergic antagonists are effective for managing symptoms of BPH.[6]

Symptoms of BPH are classified as obstructive or irritative. Obstructive symptoms result from failure of the urinary bladder to empty urine when the bladder is full. The patient will complain of a reduced force of the urinary stream, urinary hesitation, dribbling, and straining to empty the bladder. Irritative symptoms result from the failure of the urinary bladder to store urine until the bladder is full. With long-standing bladder outlet obstruction, detrusor muscle fibers undergo hypertrophy so that the bladder can generate higher pressure to overcome the bladder outlet obstruction and empty urine from the bladder. Once maximal bladder muscle hypertrophy occurs, the muscle decompensates. The detrusor becomes irritable, contracting abnormally in response to small amounts of urine in the bladder. As a result, the patient complains of urinary frequency and urgency.

The natural history of untreated BPH is unclear in patients with mild symptoms. It is estimated that up to 38% of untreated men with mild symptoms will have symptom improvement over a 2.5- to 5.0-year period.[7] It may be that such patients attribute their symptoms to aging, grow tolerant of their symptoms, or adopt behavioral changes in their lifestyle that minimize their voiding symptoms. On the other hand, a significant portion of patients with mild symptoms will likely experience disease progression. In one Veterans Affairs study, approximately one-third of men with mild BPH symptoms, who were initially randomized to watchful waiting, developed progressive symptoms and required surgical intervention within 5 years of initial diagnosis.[8] In patients with moderate to severe symptoms, the likelihood of developing complications of BPH is higher.[9] Complications of BPH include acute refractory urinary retention, renal failure, urinary tract infection, urinary incontinence, bladder stones, large bladder diverticuli, and recurrent gross hematuria. Predictors of disease progression include an enlarged prostate of at least 40 g (1.4 oz) and a prostate-specific antigen (PSA) level of at least 4 ng/mL (4 mcg/L).[10]

CLINICAL PRESENTATION AND DIAGNOSIS[11]



Clinical Presentation of BPH

General

Patients may or may not be in acute distress. In early stages of disease, the patient may complain of obstructive voiding symptoms. If untreated, in late stages of disease the patient may complain of irritative voiding symptoms, or acute urinary retention, which is painful due to maximal distention of the urinary bladder. Also, the patient may be symptomatic of disease complications, including urosepsis, pyelonephritis, cystitis, or overflow urinary incontinence.

Symptoms

Patients may complain of obstructive voiding symptoms (e.g., urinary hesitancy, decreased force of urinary stream, straining to void, incomplete bladder emptying, dribbling, and intermittency) and/or irritative voiding symptoms (e.g., urinary frequency, nocturia, dysuria, urgency, and urinary incontinence). Severity of symptoms should be assessed by the patient using a standardized instrument [e.g., the American Urological Association (AUA) Symptom Scoring Index; Table 49–1]. However, it is important to recognize that a patient's perception of the bothersomeness of their voiding symptoms may not match with the AUA Symptom Score. In this case, after thorough evaluation of the signs and complications of BPH disease, if present, the physician and patient should discuss the bothersomeness of the patient's symptoms and decide together on the most appropriate course of treatment for the patient.[9] **Lower urinary tract symptoms** (LUTS) is a term that refers to the collection of obstructive and irritative voiding symptoms characteristic of, but not specific for, BPH. That is, other urologic diseases (e.g., urinary tract infection, prostate cancer, prostatitis, or neurogenic bladder) can also cause LUTS.

Signs

- Enlarged prostate on **digital rectal exam**; check for prostate nodules or induration, which would suggest prostate cancer instead of benign prostatic hyperplasia as the cause of the patient's voiding symptoms
- Distended urinary bladder
- Rule out meatal stenosis or urethral masses which could cause voiding symptoms similar to LUTS
- Check anal sphincter tone as an indirect assessment of peripheral innervation to the **detrusor** muscle of the bladder.

Complications of Untreated BPH

Upper and lower urinary tract infection, urosepsis, urinary incontinence refractory urinary retentions chronic, renal failure, bladder diverticuli, bladder stones, or recurrent gross hematuria.

Medical History

- Check the patient's general health including previous surgery, presence of diabetes mellitus, or medications that may cause or worsen voiding symptoms.
- Have the patient provide a diary of his voiding pattern for the past week: date and time of each voiding, volume voided, and whether or not the patient had urinary leakage during the day.

(*Continued*)

Clinical Presentation of BPH (*Continued*)

Laboratory Tests

- Serum prostate specific antigen (PSA) will be increased.
- Urinalysis to rule out infection as a cause of the patient's voiding symptoms; also check urinalysis for microscopic hematuria, which typically accompanies benign prostatic hyperplasia.
- Plasma blood urea nitrogen (BUN) and serum creatinine may be increased as a result of long-standing bladder outlet obstruction.
- Urinalysis to rule out urinary tract infection as the cause of irritative voiding symptoms.

Other Diagnostic Tests (Table 49–2)

- Decreased peak and mean urinary flow rate (less than 10 to 15 mL/s) on uroflowmetry; decreased urinary flow rate is not specific for BPH; it can also be due to other urological disorders (e.g., urethral stricture, meatal stenosis, or bladder hypotonicity)
- Increased **post-void residual urine volume** (more than 50 mL)
- Digital rectal exam to check for an enlarged prostate (more than 15 to 20 g)
- Transurethral cytoscopy reveals an enlarged prostate, which decreases urethral lumen caliber; information from this procedure helps the surgeon decide on the best surgical approach
- Transrectal ultrasound of the prostate; a transrectal probe is inserted to evaluate prostate size and best surgical approach
- Transrectal prostate needle biopsy to be done if the patient has areas of nodularity or induration on digital rectal examination; tissue biopsy can document the presence of prostate cancer, which can also cause enlargement of the prostate
- **Intravenous pyelogram** (IVP) will show retention of radiocontrast in the bladder if the patient has bladder outlet obstruction due to an enlarged prostate; only indicated in patients with recurrent hematuria, recurrent urinary tract infection, renal insufficiency, and urolithiasis
- Filling cystometry provides information on bladder capacity, detrusor contractility, and the presence of uninhibited bladder contractions, which could also cause LUTS

TABLE 49–1. Questions to Determine the American Urological Association Symptom Score[5]

Directions for the patient: The patient should be asked to respond to each question based on the absence or presence of symptoms over the past month. For each question, the patient can respond using a 1 to 5 scale, where 0 = not at all or none, 1 = less than 1 time in 5, 2 = less than half of the time, 3 = about half of the time, 4 = more than half of the time, and 5 = almost always.

Directions for the clinician: After the patient completes the questionnaire, the scores for individual items should be tallied for a final score. Scores of 0–7 = mild symptoms; scores of 8–19 = moderate symptoms; scores more than 20 = severe symptoms.

Questions to Assess Obstructive Voiding Symptoms

1. How often have you had a sensation of not emptying your bladder completely after you finished urinating?
2. How often have you found you stopped and started again several times when you urinated?
3. How often have you had a weak urinary stream?
4. How often have you had to push or strain to begin urinating?

Questions to Assess Irritative Voiding Symptoms

5. How often have you found it difficult to postpone urination?
6. How often had you had to urinate again less than 2 hours after you finished urinating?
7. How many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?

TREATMENT

Desired Outcomes

- ❷[11] *Reducing or eliminating obstructive and irritative voiding symptoms. An improvement in the AUA Symptom Score should be observed. Drug treatment with an α-adrenergic antagonist or 5a-reductase inhibitor is expected to reduce the AUA Symptom Score by 30% to 50%, improve peak and mean urinary flow rate by 1 to 3 mL/second, and decrease post-void residual urine volume to normal (less than 50 mL total) when compared to pretreatment baselines. The AUA Symptom Score may not correlate with response to therapy.*
- Slowing disease progression. When compared to baseline, serum BUN and creatinine should stabilize or decrease to the normal range with treatment.
- Preventing disease complications and reducing the need for surgical intervention.
- Avoiding or minimizing adverse treatment effects.
- Providing economical therapy.
- Maintaining or improving quality of life.

General Approach to Treatment

Until recently, the principal approach to treatment focused on reducing BPH symptoms.

For patients with mild symptoms, which the patient does not consider to be bothersome, watchful waiting is a reasonable approach to treatment (Fig. 49–1). The patient is instructed to schedule return visits to the physician every 3 to 6 months. At each visit, the patient's symptoms are reassessed using the AUA Symptom Scoring Index and results are compared to baseline (Table 49–3). In addition, the patient is educated about avoiding factors that worsen obstructive and irritative voiding symptoms. The digital rectal exam is repeated annually. If the patient's symptoms are unchanged, then watchful waiting is continued. If the patient's symptoms worsen, then specific treatment is initiated.[11]

For patients with moderate to severe symptoms, the patient is usually offered drug treatment first. ❸ *α-Adrenergic antagonists are preferred over 5α-reductase inhibitors because the former have a faster onset of action (days to a few weeks) and improve symptoms independent of prostate size. 5α-reductase inhibitors have a delayed onset of action (i.e., peak effect may*

TABLE 49–2. Objective Tests Used to Assess the Size of the Prostate and Complications of Benign Prostatic Hyperplasia (BPH)

Test	How the Test Is Performed	Normal Test Result	Test Result in Patients with BPH
Digital rectal exam of the prostate (DRE)	Prostate is palpated through the rectal mucosa; the physician inserts an index finger into the patient's rectum	Prostate is soft, symmetric, mobile; size is 15–20 g	Prostate is enlarged, greater than 20 g; no areas of induration or nodularity
Peak and mean urinary flow rate	Patient drinks water until bladder is full; patient empties bladder; volume of urine output and time to empty the bladder are measured; the flow rate (mL/second) is calculated	Peak and mean urinary flow rate are at least 10 mL/second	Peak and mean urinary flow rates are less than 10 mL/second
Post-void residual urine volume (PVR)	Measurement of urine left in the bladder after the patient has tried to empty out his bladder; assessed by urethral catheterization or ultrasonography	Post-void residual urine volume should be 0 mL	Post-void residual urine volume greater than 50 mL is a significant amount of retained urine; this is associated with recurrent urinary tract infection
Urinalysis	Midstream urine is analyzed microscopically for white blood cells and bacteria	Urine should have no white cells or bacteria in it	Urine with white cells and bacteria is suggestive of inflammation and infection; if positive, urine is sent for bacteriologic culture
Prostate needle biopsy	Transrectally, a biopsy needle is inserted into the prostate. Tissue core is sent to a pathologist for analysis	A normal prostate should have no evidence of BPH or prostate cancer	The biopsy is consistent with BPH
Prostate-specific antigen (PSA)	Blood test for this chemical secreted by the prostate	Less than 4 ng/mL (4 mcg/L)	Greater than or equal to 4 ng/mL (4 mcg/L)

be delayed for up to 6 months), and are seldom effective in patients with 2 smaller size gland (less than 40 g or 1.4 oz). Any drug treatment must be continued as long as the patient responds (Table 49–4).[11]

❹ *For patients with complications of BPH disease (e.g., recurrent urinary tract infection, urosepsis, urinary incontinence, refractory urinary retention, chronic renal failure, large bladder diverticuli, recurrent gross hematuria, or bladder calculi secondary to prolonged urinary retention), surgery is indicated.* Although it is potentially curative, surgery can result in significant morbidity, including erectile dysfunction, retrograde ejaculation, urinary incontinence, bleeding, or urinary tract infection. The gold standard is a prostatectomy, which can be performed transurethrally or as an open surgical procedure. To avoid complications of prostatectomy, minimally invasive surgical procedures, such as transurethral incision of the prostate and laser prostatectomy are becoming popular options. Drug treatment is used in patients with severe disease when the patient refuses surgery or when the patient is not a surgical candidate because of concomitant diseases.[11]

In the Multiple Treatment of Prostate Symptoms Study, it was found that selected patients with moderate to severe symptoms will benefit from a combination of α-adrenergic antagonist plus 5α-reductase inhibitor drug therapy.[12] Specifically, the use of doxazosin plus finasteride is more effective than doxazosin alone or finasteride alone in relieving symptoms, reducing the need for prostatectomy, and decreasing the incidence of BPH complications in patients at highest risk of developing disease complications [i.e., those with prostate size of at least 40 g (1.4 oz) and a PSA of at least 4 ng/mL (4 mcg/L)]. Combination therapy is more expensive than monotherapy and also produces more adverse effects. Therefore, the clinician should discuss the advantages and disadvantages of combination therapy with a patient before deciding on a final treatment regimen.



Patient Encounter 1, Part 1

AA is a 65-year-old male patient with an AUA symptom score of 19, urinary hesitancy, a slow urinary stream, urinary frequency, and nocturia. He wakes up three times every night to void. A digital rectal exam reveals an enlarged prostate of approximately 40 g (1.4 oz). His PSA is 4 ng/mL (4 mcg/L).

- What stage of BPH does this patient have?

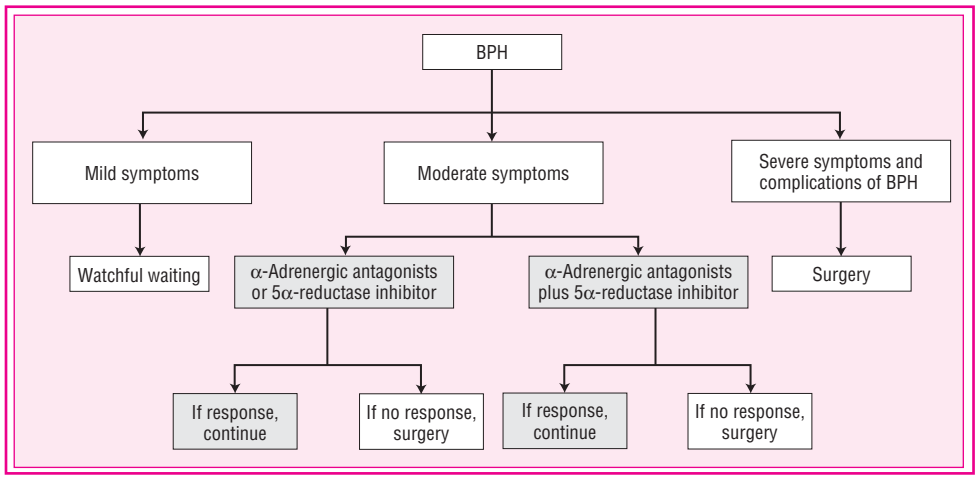


FIGURE 49–1. Algorithm for selection of treatment of BPH based on symptom severity. (From Lee M. Benign prostatic hyperplasia. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1539, with permission.)

Nonpharmacologic Therapy

To reduce nocturia, patients should be instructed to stop drinking fluids several hours before going to bed, and then voiding before going to sleep. During the day, patients should avoid excessive caffeine intake, as this may cause urinary frequency. In addition, toilet mapping (knowing the location of toilets on the way to and from various destinations) may help reassure the patient that he can still continue with many of his routine daily activities.

Below is a list of several items clinicians should tell patients to do to minimize obstructive and irritative voiding symptoms:

1. Discontinue or minimize oral fluid intake after 6 P.M.
2. Void before going to bed
3. If taking a diuretic, take the diuretic in the morning, not the evening
4. Avoid taking over-the-counter medications that can worsen obstructive voiding symptoms (e.g., antihistamines or decongestants) (Table 49–5)

TABLE 49–3. Staging the Severity of BPH Based on AUA Symptom Score and Example Signs of Disease

	AUA Symptom Score	Signs of Disease
Mild	Less than or equal to 7	Enlarged prostate on DRE, peak urinary flow rate less than or equal to 10 mL/second
Moderate	8–19	All of the above, PVR greater than 50 mL, irritative symptoms
Severe	Greater than 20	All of the above plus one or more complications of BPH

Note: The AUA Symptom Score focuses on seven items (incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia) and asks that the patient quantify the severity of his complaints on a scale of 0 to 5. Thus, the score can range from 0 to 35.
AUA, American Urological Association; BPH, benign prostatic hyperplasia; DRE, digital rectal exam; PVR, post-void residual urine volume.

Pharmacologic Therapy

Alpha-Adrenergic Antagonist Monotherapy[12]

❺ *α-Adrenergic antagonists reduce the dynamic factor causing BPH symptoms. These drugs competitively antagonize α-adrenergic receptors, thereby causing relaxation of the bladder neck, prostatic urethra, and prostate smooth muscle.* A secondary mechanism of action may be that α-adrenergic antagonists induce prostatic apoptosis,[14] which suggests that these agents may cause some shrinkage of an enlarged prostate. However, the clinical importance of this remains to be elucidated.[3]

All α-adrenergic antagonists are considered equally effective in relieving symptoms.[11] In various clinical trials, 30% to 80% of patients experience improvement in AUA Symptom Score by 30% to 45% and 20% to 40% of patients experience urinary flow rate increases of 2 to 3 mL/second.[15] The onset of action is days to weeks, depending on the need for uptitration of the dose from a subtherapeutic starting dose to a therapeutic dose. An adequate clinical trial is considered to be at least 1 to 2 weeks of continuous treatment at a full maintenance dose with any of these agents.[11] Durable responses have been demonstrated for up to 5 years of continuous use of terazosin,[16] 10 years with doxazosin,[17] and 6 years with tamsulosin.[18] However, some patients will develop disease progression despite treatment.[19] α-Adrenergic antagonists are hepatically catabolized. Therefore, in patients with significant hepatic dysfunction, these drugs should be used in the lowest possible dose. None of these drugs require dosage modification in patients with renal dysfunction. These agents can be differentiated by their adverse effect profile. Dose limiting adverse effects include hypotension and syncope, which are more common with immediate-release terazosin and doxazosin,

TABLE 49–4. Comparison of α-Adrenergic Antagonists and 5α-Reductase Inhibitors for Treatment of Benign Prostatic Hyperplasia[47]

Characteristic	α-Adrenergic Antagonists	5α-Reductase Inhibitors
Relaxes prostatic smooth muscle	Yes	No
Reduces size of enlarged prostate	No	Yes
Useful in only enlarged prostates of at least 40 g	No (works independent of the size of the prostate)	Yes
Efficacy in relieving voiding symptoms and improving flow rate	++	+±
Frequency of daily dosing	Once or twice daily, depending on the agent	Once daily
Requirement for up-titration of dose	Yes (for terazosin and doxazosin immediate-release); no (for alfuzosin; possibly for doxazosin extended-release and tamsulosin)	No
Peak onset of action	Days to 6 weeks, depending on need for dose titration	6 months
Decreases PSA	No	Yes
Cardiovascular adverse effects	Yes	No
Drug-induced sexual dysfunction	Ejaculation disorders	Decreased libido, erectile dysfunction, ejaculation disorders

PSA, prostate-specific antigen.

less frequent with extended-release doxazosin and alfuzosin, and least frequent with tamsulosin.[20–22] Delayed or retrograde ejaculation has been reported most often with tamsulosin 0.8 mg orally once a day. Combined use with antihypertensives, diuretics, or phosphodiesterase inhibitors can lead to additive blood pressure–lowering effects; however, this appears to be less of a problem with tamsulosin.[20–22]

α-Adrenergic antagonists are recommended as first-line treatment for moderate to severe BPH. The agents in this pharmacologic class can be classified by several characteristics (Table 49–6):

TABLE 49–5. Drugs That Can Cause Irritative or Obstructive Voiding Symptoms

Pharmacologic Class	Example Drugs	Mechanism of Effect
Androgens	Testosterone	Stimulate prostate enlargement
α-Adrenergic agonists	Phenylephrine, pseudoephedrine	Stimulate contraction of prostatic smooth muscle
Anticholinergic agents	Antihistamines, phenothiazines, tricyclic antidepressants, antiparkinsonian agents	Block bladder detrusor muscle contraction, thereby impairing bladder emptying
Diuretics	Thiazides diuretics, loop diuretics	Produce polyuria

- Generation of α-adrenergic antagonist. First-generation agents (e.g., phenoxybenzamine) block presynaptic and postsynaptic α-adrenergic receptors. Whereas blockade of postsynaptic α-adrenergic receptors is desirable for BPH management, blockade of presynaptic α-adrenergic receptors is undesirable, as it results in release of catecholamines and tachycardia. Thus, first-generation α-adrenergic antagonists are not used for treatment of BPH.[3] Second-generation α-adrenergic antagonists selectively block post-synaptic α-adrenergic receptors. Examples include terazosin, doxazosin, and alfuzosin. Third-generation α-adrenergic antagonists (e.g., tamsulosin) selectively block postsynaptic α_{1A}-receptors.
- Uroselectivity. Pharmacologic uroselectivity refers to preferential inhibition of α_{1A}- and α_{1D}-receptors, which predominate in the prostatic stroma and bladder detrusor muscle, respectively. Pharmacologically uroselective α_{1A}-adrenergic antagonists have the potential to produce less hypotension, as they have a lower propensity to antagonize α-adrenergic$_{1B}$ receptors in the peripheral vasculature. Tamsulosin is the only commercially available α-adrenergic antagonist with pharmacologic uroselectivity. Despite the potential of inhibiting α-adrenergic receptors in both the prostate and peripheral vasculature, functionally uroselective α-adrenergic antagonists in usually-prescribed doses, produce effective relaxation of prostatic smooth muscle with minimal vascular vasodilation. Thus, blood pressure–lowering effects are mild or absent. The only functionally uroselective α-adrenergic antagonist is alfuzosin extended-release tablets. The mechanism of functional uroselectivity is unclear. It may be related to a drug formulation which produces a higher concentration

TABLE 49–6. Comparison of Pharmacologic Properties of α-Adrenergic Antagonists

	Terazosin	Doxazosin	Alfuzosin	Tamsulosin
Brand Name	Hytrin	Cardura	Uroxatral	Flomax
Generation	Second	Second	Second	Third
Uroselective	No	No	Functionally and clinically uroselective	Pharmacologically and clinically uroselective
Need for uptitration	Yes	Yes (with immediate-release); no (with extended-release)	No	No
Daily oral dose (mg)	5–20	2–8, immediate-release; 4–8, extended-release	10	0.4–0.8; 0.8-mg/day dose has not consistently produced clinical improvement over 0.4 mg/day[20]
Best time to take doses	At bedtime	Immediate-release: anytime during the day; however, it is typically given at bedtime Extended-release: anytime during the day	After meals for best oral absorption	On an empty stomach for best oral absorption; if taken 30 minutes after a meal, as recommended by the manufacturer, peak absorption time is delayed, thereby further reducing the potential for hypotensive adverse effects[20,24]
Half-life (hours)	12	22	5	10
Formulation	Immediate-release	Immediate-release and extended-release	Extended-release	Modified-release
Cardiovascular adverse effects	++	++	+	0 to +
Ejaculation disorders	+	+	+	++
Rhinitis	+	+	+	+
Malaise	+	+	+	+

in target tissues than in non-target tissues.[23,24] Both pharmacologic and functional uroselective agents appear to be clinically uroselective, in that they improve BPH symptoms without causing cardiovascular adverse effects in humans.[13]

Pharmacologic and functional uroselectivity are dose-related phenomena. Large daily doses of tamsulosin or alfuzosin may cause loss of uroselectivity with resultant hypotension and dizziness in some patients.

- Need for up-titration of daily dose. Up-titration is required for terazosin and immediate-release doxazosin. It is minimally required for extended-release doxazosin and tamsulosin. It is not required for extended-release alfuzosin.
- Plasma half-life. α-Adrenergic receptors with short plasma half-lives (e.g., prazosin) require multiple doses during the day. This is challenging for most patients, and, thus, prazosin is not recommended for BPH.[11]
- Dosage formulation. Immediate-release formulations of terazosin and doxazosin are quickly absorbed and produce high peak plasma levels. Modified- or extended-release formulations of doxazosin, alfuzosin, and tamsulosin produce lower peak levels, but more sustained therapeutic plasma levels, than immediate-release formulations and have less potential for producing hypotensive episodes, thereby allowing initiation of treatment with a therapeutic dose and once daily dosing.[25–27]
- Adverse effects. Hypotensive adverse effects of α-adrenergic antagonists can range from asymptomatic blood pressure reductions to dizziness and syncope. This adverse effect is most commonly associated with immediate-release terazosin and doxazosin, and is less commonly associated with extended-release alfuzosin, and least commonly associated with tamsulosin.[20–22] To minimize first-dose syncope from terazosin and doxazosin immediate-release, a slow up-titration from a subtherapeutic dose of 1 mg/day to a therapeutic dose is essential. The first dose should be given at bedtime so that the patient can sleep through the peak serum concentration of the drug when the adverse effect is most likely to occur. A 3- to 7-day interval between each dosage increase should be allowed and the patient should be maintained on the lowest effective dose of α-adrenergic antagonist. If the patient is non-compliant with his regimen of terazosin or doxazosin, and he skips or interrupts treatment, the α-adrenergic antagonist should be restarted using the usual starting dose and then retitrated up.[3] He should not be instructed to simply double up on missed doses or resume treatment with his currently prescribed daily dose, as this can lead to significant hypotension.

Ejaculation disorders, including delayed and retrograde ejaculation, occur with all adrenergic antagonists and are an

extension of the pharmacologic blockade of α-adrenergic receptors at the bladder neck (i.e., the bladder neck is unable to close during ejaculation in the presence of α-adrenergic blockade). However, the incidence appears to be dose-related and highest with tamsulosin 0.8 mg daily, occurring in up to 26% of treated patients.[28] Ejaculation disorders generally do not necessitate discontinuation of treatment. Although they may decrease the patient's satisfaction with the quality of sexual intercourse, ejaculation disorders are not harmful to the patient.

Rhinitis and malaise occur with α-adrenergic antagonists and are an extension of the pharmacologic blockade of α-adrenergic receptors in the vasculature of the nasal mucosa and in the central nervous system, respectively. Tolerance often develops to these adverse effects and they rarely require discontinuation of treatment. Avoid use of topical or oral decongestants, as these may exacerbate obstructive voiding symptoms. Cautious use of antihistamines with anticholinergic adverse effects is also recommended in patients with BPH, as these drugs may cause acute urinary retention in patients with an obstructed bladder neck.

Alfuzosin has been linked to two cases of hepatitis.[29,30] The cause-effect relationship remains to be elucidated.

- Potential for drug interactions. Hypotensive adverse effects of terazosin and doxazosin can be additive with those of diuretics, antihypertensives, and phosphodiesterase inhibitors (e.g., sildenafil). In patients at greatest risk for hypotension, or in those patients who tolerate hypotension poorly, including those with poorly controlled coronary artery disease or severe orthostatic hypotension, tamsulosin appears to be the safest choice.[22,31,32] In patients who cannot tolerate tamsulosin, a 5α-reductase inhibitor or prostatectomy should be considered. When using α-adrenergic antagonists in patients taking sildenafil, tadalafil, or vardenafil, patients should be instructed to allow a 4-hour interval between each drug to minimize the likelihood of hypotensive effects.

❻ *Among the α-adrenergic antagonists, tamsulosin is unique in that it is the only commercially available third-generation α-adrenergic antagonist. It is pharmacologically uroselective and exerts greater antagonism of α_{1A}- and α_{1D}-receptors, which predominate in prostatic and bladder detrusor muscle. Tamsulosin exerts comparatively low antagonism of vascular α_{1B}-receptors. Therefore tamsulosin can be started with a therapeutic dose, which achieves peak effects sooner than with terazosin and doxazosin immediate-release, which must be up-titrated. Tamsulosin appears to have the lowest potential to cause hypotension.[20–22] In various clinical trials, tamsulosin has minimal hypotensive adverse effects and is well tolerated in the elderly, as well as in patients taking diuretics, antihypertensives, or phosphodiesterase inhibitors. It is also commercially available in a modified-release dosage formulation, which is dosed at 0.4 mg orally once a day. With chronic use, tamsulosin can be taken at any time of the day and at the patient's convenience. Although the package insert states that the dose can be increased to 0.8 mg daily, no consistent improvement in clinical efficacy has been observed in patients taking the higher dose.[21,33]*



Patient Encounter 2

BB has moderate BPH symptoms and is started on tamsulosin 0.4 mg orally once a day. After 2 to 3 weeks, BB states that his symptoms have not improved. He is not experiencing any drug-related adverse effects.

- What should be the next step in management of this patient?

In patients with BPH and hypertension, it is not recommended to use an α-adrenergic antagonist alone to treat both disorders. In the ALLHAT study, where doxazosin was compared to other agents for treatment of essential hypertension, doxazosin was associated with a higher incidence of congestive heart failure. Therefore, in patients with hypertension and BPH, it is recommended that an appropriate antihypertensive be added to an α-adrenergic antagonist.[11]

5-Alpha-Reductase Inhibitor Monotherapy

❼ *5α-Reductase inhibitors reduce the static factor, which results in shrinkage of an enlarged prostate. They do so by inhibiting 5a-reductase which is responsible for intraprostatic conversion of testosterone to dihydrotestosterone, the active androgen which stimulates prostate tissue growth.* In the prostate, there are two subtypes of 5α-reductase; the majority is the type II isoenzyme type and the minority is the type I isoenzyme type. In addition, 5α-reductase inhibitors induce apoptosis of prostatic epithelial cells.[34] The onset of action is slow with peak shrinkage of the prostate taking up to 6 months.[11] Unlike treatment with α-adrenergic antagonists, 5α-reductase inhibitors have been shown to reduce the incidence of acute urinary retention and need for prostate surgery in patients with significantly enlarged prostate glands [greater than 40 g (1.4 oz)],[11] and those with serum levels of prostate-specific antigen of at least 4 ng/mL (4 mcg/L).[10] Because 5α-reductase inhibitors do not produce cardiovascular adverse effects, they are preferred for treatment of moderate to severe BPH when the patient has an enlarged prostate of at least 40 g (1.4 oz), is at risk of hypotension, and wants to be treated medically. When compared to α-adrenergic antagonists, 5α-reductase inhibitors relieve BPH symptoms in 30% to 70% of patients and increase urinary flow rate by 1 to 2 mL/second, which is less improvement than that seen with α-adrenergic antagonists.[11] A minimum of 6 months is required to evaluate the effectiveness of treatment. This is a disadvantage in patients with moderate to severe symptoms, as it will take that long to determine if the

drug is or is not effective. Durable responses have been demonstrated in responding patients treated up to 6 years with finasteride and 4 years with dutasteride.[35–38] These agents are hepatically metabolized. No specific recommendations for dosage modification are currently available in patients with significant hepatic dysfunction; however, due to drug specificity for its enzyme target, it is unlikely that any dosage adjustment will be required. No dosage adjustment is needed in patients with renal impairment. Adverse effects include decreased libido, erectile dysfunction, and ejaculation disorders, which generally decrease in frequency with continued use, and gynecomastia and breast tenderness.[34] Serum testosterone levels increase by 10% to 20% in treated patients; however, the clinical significance of this is not clear at this time.[11] Drug interactions are uncommon. These drugs do produce a mean 50% decrease in serum levels of PSA. Therefore, to preserve the usefulness of this laboratory test as a diagnostic and monitoring tool, it is recommended that prescribers obtain a baseline PSA prior to the start of treatment and repeat it at least annually during treatment. A significantly elevated PSA in treated patients is an indicator for further diagnostic work-up.[36] Exposure to 5α-reductase inhibitors is contraindicated in pregnant females, as the drugs may cause feminization of a male fetus. Pregnant females should not handle these drugs unless they are wearing gloves.

5α-Reductase inhibitors include finasteride and dutasteride. Finasteride is a selective type II 5α-reductase inhibitor, whereas dutasteride is a non-selective type I and II 5α-reductase inhibitor. When compared to finasteride, dutasteride produces a faster and more complete inhibition of 5α-reductase in prostate cells. However, no difference in clinical efficacy or adverse effects has been demonstrated between these two agents. Thus, finasteride and dutasteride are considered therapeutically interchangeable (Table 49–7).[39]

By reducing serum levels of dihydrotestosterone, which is linked to the development of prostate cancer, it has been hypothesized that 5α-reductase inhibitors may prevent the development of prostate cancer. The Predict Trial reported that finasteride reduced the detection of prostate cancer with prostatic needle biopsy by 25%; however, higher-grade tumors were more common in treated patients.[40] The ongoing Reduce Trial, which will follow dutasteride-treated patients for 4 years, may provide more clarification on this issue.[41]

TABLE 49–7. Comparison of Pharmacologic Properties of 5α-Reductase Inhibitors[36,48]

	Finasteride	Dutasteride
Brand name	Proscar	Avodart
Sub-type inhibition of the 5α-reductase enzyme	Type II	Types I and II
Percent of inhibition of serum dihydrotestosterone level	70–76	90–95
Percent of patients with reduction in serum dihyrotestosterone	49	Greater than 85
Time to peak onset of reduction in serum dihydrotestosterone level	6 months	1 month
Percent inhibition of intraprostatic dihydrotestosterone	85–90	Greater than 95
Half-life	6.2 hours	3–5 hours
Daily dosage (mg)	5	0.5



Patient Encounter 1, Part 2

AA is started on finasteride 5 mg orally once a day. Four weeks later the patient returns for a follow-up visit and complains that he is not experiencing any symptom improvement.

- What should be the next step in management of this patient?

Combination Therapy

A combination of an α-adrenergic antagonist and 5α-reductase inhibitor may be considered in patients at high risk of BPH complications, which are defined as those with an enlarged prostate of at least 40 g (1.4 oz) and a PSA of at least 4 ng/mL (4 mcg/L). In such patients, combination therapy may relieve voiding symptoms, and also reduce the risk of developing BPH-related complications and reduce the need for prostatectomy by 67%.[12] Since combination therapy is more expensive and associated with the array of adverse effects associated with each drug in the combination, clinicians should discuss the advantages and disadvantages of each treatment regimen with the patient before a final decision is made.[11]

To streamline and reduce the cost of treatment regimens, it has been suggested that the α-adrenergic antagonist may be discontinued after the first 6 to 12 months of combination therapy. However, long-term treatment is required to determine if such a regimen is as effective as continuous combination therapy.[42,43]

Another enhancement to BPH symptom management is the addition of an anticholinergic agent to an α-adrenergic antagonist. The rationale for the anticholinergic agent is that irritative symptoms are thought to be due to hyper-reactive bladder detrusor muscle contraction, which can be ameliorated by blockade of acetylcholine receptors.[4] A recent study documenting the addition of tolterodine to tamsulosin showed significant irritative symptom improvement, more than what was observed with tamsulosin alone. No cases of urinary retention were reported.[45] In another study, the addition of tolterodine to doxazosin improved overactive bladder symptoms in patients with BPH; however, acute urinary retention developed in 3.3% of patients treated with the combination. This adverse effect responded to discontinuation of tolterodine and insertion of an indwelling urethral catheter.[46]

OUTCOME EVALUATION

❽ *Once the peak effects of drug treatment are expected to occur, monitor the drug for effectiveness. Assess symptom improvement using the AUA Symptom Scoring Index. A reduction in symptom score is anticipated with symptom improvement. However, it should be noted that the AUA Symptom Score may not match the patient's perception of the bothersomeness of his voiding symptoms. If the patient perceives his symptoms as bothersome, independent of the AUA Symptom Score, consideration should be given to modifying the patient's treatment regimen. Similarly, a patient may regard his symptoms as not bothersome even though the AUA symptom score is high. In this case, the physician should objectively assess symptoms at baseline and during treatment by performing a repeat uroflowmetry, which can detect an improvement in peak and mean urinary flow rate. If the patient shows a response to treatment, instruct the patient to continue the drug regimen and have the patient return at 6-month intervals for monitoring. If the patient shows an inadequate response to treatment, the dose of α-adrenergic antagonist can be increased (except for extended-release alfuzosin) until the patient's symptoms improve or until the patient experiences adverse drug effects.*

For the α-adrenergic antagonists, the severity of hypotensive-related adverse effects, which may manifest as dizziness or syncope, may require a dosage reduction or a slower up-titration of immediate-release terazosin or doxazosin, or halting the up-titration of extended-release doxazosin or tamsulosin. Extended-release alfuzosin is only available as a single 10 mg tablet. If the patient develops adverse effects at this dose, the drug should be discontinued. Other adverse effects of α-adrenergic antagonists are nasal congestion, malaise, headache, and ejaculation disorders. None of these generally require discontinuation of treatment and these often improve as treatment continues. For the 5α-reductase inhibitors, the most bothersome adverse effects are decreased libido, erectile dysfunction, and ejaculation disorders. In sexually active males, erectile dysfunction may be improved with erectogenic drugs; however, this adverse effect may necessitate discontinuation of treatment.

During continuing treatment of BPH, the patient should undergo an annual repeat PSA and DRE. A rising PSA level suggests that the patient has worsening BPH, new-onset prostate cancer, or that the patient is non-compliant with his regimen of 5α-reductase inhibitor. An abnormal DRE suggestive of prostate cancer would reveal a nodule or area of induration on the prostate, or a gland which is fixed in place. In such a case, a prostate biopsy is required to rule out prostate cancer.

Drug treatment failures may result from a variety of factors. Initial failure to respond to α-adrenergic antagonists occurs in 20% to 70% of treated patients. It is likely in these patients that the static factor may predominate as the cause of symptoms in these patients. Initial failure to respond to 5α-reductase inhibitors occurs in 30% to 70% of treated patients. It is likely that the dynamic factor may predominate as the cause of symptoms in these patients. In contrast, drug treatment failures after an initial good response to drug therapy will likely be an indication of progressive BPH disease. In such patients, surgical intervention may be indicated.

Table 49–8 summarizes the adverse effects of the agents used to treat BPH and has management suggestions for these situations.

TABLE 49–8. Summary of Adverse Effects of α-Adrenergic Antagonists and 5α-Reductase Inhibitors and Management Suggestions

Drug Class	Adverse Reaction	Management Suggestion
α-Adrenergic antagonist	Hypotension	Start with lowest effective dose, give doses at bedtime, and slowly up-titrate at 0.5- to 1-week intervals to a full therapeutic dose, if using terazosin or doxazosin immediate-release Use tamsulosin, extended-release doxazosin, or alfuzosin, as alternatives to immediate-release products, particularly in patients taking other antihypertensives
	Malaise	Educate the patient that this is a common adverse effect; tolerance may develop to malaise; usually it is not so severe that it requires discontinuation of treatment
	Rhinitis	Educate the patent that this is a common adverse effect; tolerance may develop to rhinitis; usually it is not so severe that it requires discontinuation of treatment
	Retrograde ejaculation	Educate the patient that this is a common adverse effect and it is not harmful
5α-Reductase inhibitor	Gynecomastia	Educate the patient that this may be bothersome, but not harmful
	Decreased libido	If the patient is sexually active, sexual counseling may be helpful
	Erectile dysfunction	The addition of sildenafil or an other erectogenic drug may be helpful
	Ejaculation disorders	Educate the patient that this may occur but it is not harmful



Patient Care and Monitoring

- Monitor the patient for the drug's effectiveness in relieving symptoms by using the AUA Symptom Scoring Index. Monitor ensure that the score improves and that the patient subjectively feels that symptoms have improved. If the patient has no improvement after several weeks of a therapeutic dose of α-adrenergic antagonist or after 6 months of a 5α-reductase inhibitor, consider surgical intervention.
- If the patient is started on an α-adrenergic antagonist, monitor the patient for hypotension, dizziness, or syncope. If present, assess the severity of each symptom. Reduce the drug dose or discontinue the drug, as necessary. If the patient has malaise or rhinitis, reassure the patient that these are usual, but bothersome, adverse effect, that often improve with continued therapy.
- If the patient is started on a 5α-reductase inhibitor, monitor the patient for drug-induced decreased libido, erectile dysfunction, or ejaculation disorders. If severe, discontinue the drug.

ABBREVIATIONS

AUA: American Urological Association
BPH: benign prostatic hyperplasia
BUN: blood urea nitrogen
DRE: digital rectal exam
IVP: intravenous pyelogram
LUTS: lower urinary tract (voiding) symptoms
PSA: prostate-specific antigen
PVR: post-void residual urine volume

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

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KEY REFERENCES AND READINGS

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50 Urinary Incontinence and Pediatric Enuresis

David R.P. Guay



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Explain the pathophysiology of the major types of urinary incontinence (urge, stress, overflow, and functional) and pediatric enuresis.
2. Recognize the signs and symptoms of the major types of urinary incontinence and pediatric enuresis in individual patients.
3. List the treatment goals for a patient with urinary incontinence or pediatric enuresis.
4. Compare and contrast anticholinergics/antispasmodics, α-adrenoceptor agonists, dual serotonin-norepinephrine reuptake inhibitors, vaginal estrogens, cholinomimetics, tricyclic antidepressants, and vasopressin analogues in terms of mechanism of action, treatment outcomes, adverse effects, and drug-drug interaction potential when used to manage urinary incontinence or pediatric enuresis.
5. Identify factors that guide drug selection for an individual patient.
6. Formulate a monitoring plan for a patient on a given treatment regimen based on patient-specific information.
7. Describe indicators for combination drug therapy of urinary incontinence or pediatric enuresis.
8. Describe nonpharmacologic treatment approaches (including surgery) for urinary incontinence or pediatric enuresis.
9. Formulate appropriate patient counseling information for patients undergoing drug therapy for urinary incontinence or pediatric enuresis.

Key Concepts

❶ Accurate diagnosis and classification of urinary incontinence type is critical to the selection of appropriate drug therapy.

❷ Patient-specific treatment goals should be identified. This frequently requires reaching a compromise between efficacy and tolerability of drug therapy. These goals are not static and may change with time.

❸ Patient characteristics (e.g., age, comorbidities, concurrent drug therapies, and ability to adhere to the prescribed regimen) can also influence drug therapy selection.

❹ Careful dose titration is necessary to maximize efficacy and tolerability.

❺ If therapeutic goals are not achieved, a switch to an alternative agent should be made.

❻ Many medications can influence the lower urinary tract, including those not used for managing genitourinary disorders, and can precipitate new onset or aggravate existing voiding dysfunction and urinary incontinence.

❼ Nonpharmacologic treatment can allow the use of lower drug doses. The combination of both therapies may have at least an additive effect on urinary incontinence signs and symptoms.

❽ The anticholinergic/antispasmodic drugs are the pharmacologic first-line treatments for urge urinary incontinence. They are the most effective agents in suppressing premature detrusor contractions, enhancing bladder storage, and relieving symptoms.

❾ Vaginally-administered estrogen plays only a modest role in managing stress urinary incontinence (urethral underactivity), unless it is accompanied by local signs of estrogen deficiency (e.g., atrophic urethritis or vaginitis).

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⑩ The major impediment to using the α-adrenoceptor agonist class is the extensive list of contraindications.

⑪ The use of duloxetine in stress urinary incontinence is complicated by (1) the potential for multiple clinically relevant drug-drug interactions with cytochrome P-450 2D6 and 1A2 inhibitors, (2) withdrawal reactions if abruptly discontinued, (3) high rates of nausea and other side effects, (4) the hepatotoxicity that contraindicates its use in patients with any degree of hepatic impairment, and (5) its mild hypertensive effect.

⑫ In overflow urinary incontinence due to atonic bladder, a trial of bethanecol may be reasonable if contraindications do not exist.

⑬ In overflow urinary incontinence due to obstruction, the goal of treatment is to relieve the obstruction.

⑭ Considering that pharmacotherapy is inferior to select nonpharmacologic treatment modalities in pediatric enuresis, pharmacotherapy will be most valuable in patients who are not candidates for nonpharmacologic therapy due to nonadherence or who do not achieve the desired outcomes on nonpharmacologic therapy alone.

⑮ Desmopressin is the first-line drug choice in pediatric enuresis.

URINARY INCONTINENCE

Urinary incontinence (UI) is defined as the complaint of involuntary leakage of urine.[1] It is often associated with other bothersome lower urinary tract symptoms such as **urgency**, increased daytime **frequency**, and **nocturia**. Despite its prevalence across the lifespan and in both sexes, it remains an underdetected and underreported health problem that can have significant negative consequences for the individual's quality of life. Patients with UI may be depressed due to a perceived loss of self-control, loss of independence, and lack of self-esteem, and often curtail or substantially modify their activities for fear of an "accident." Serious medical and economic consequences may also occur in untreated or undertreated patients, including perineal dermatitis and infections, worsening or lack of healing of pressure ulcers, urinary tract infections (UTIs), falls, and the need for long-term institutionalization in extended care facilities [including skilled nursing facilities (SNFs), or nursing homes].



Patient Encounter, Part 1

A 50-year old woman with hypertension and diabetes comes into your clinic seeking advice about which incontinence pads work best. After questioning her, you determine that she has multiple issues of low volume urine loss daily, which is a significant change (increase) from 1 year ago. All episodes occur at times of physical activity. She's a single mother of three grown children, all delivered vaginally. Her last menstrual period was 11 months ago.

- What information suggests that she has UI?
- Does she have risk factors for UI?
- What additional information do you need to know before creating a treatment plan for this patient?

EPIDEMIOLOGY AND ETIOLOGY

The true prevalence of UI has been difficult to determine because of methodologic issues such as varying definitions of UI and reporting bias.[2] Although the condition occurs across the lifespan, the peak prevalence, at least in women, is around the age of menopause (~50 years) which is followed by a slight decrease in the 55- to 60-year-old age group, and then a steadily increasing prevalence after age 65. In general, the median prevalences of UI are as follows[3]:

- 20% to 30% in young females
- 30% to 40% in middle-aged females
- 30% to 50% in elderly females (50% to 75% in female SNF residents)
- 10% in adult males (in excess of 50% in elderly male SNF residents)

Urinary incontinence can result from abnormalities within (intrinsic to) and outside of (extrinsic to) the urinary tract. Within the urinary tract, abnormalities may occur in the urethra (including the bladder outlet and urinary sphincters), the bladder, or a combination of both structures. Focusing on abnormalities in these two structures, a simple classification scheme emerges for all but the rarest intrinsic causes of UI. ❶ *Accurate diagnosis and classification of UI type is critical to the selection of appropriate drug therapy.*

Stress Urinary Incontinence (SUI) (Urethral Underactivity)[4]

In SUI, the urethra and/or urethral sphincters cannot generate enough resistance to impede urine flow from the bladder when intra-abdominal pressures (that are transmitted to the bladder, which is an intra-abdominal organ) are elevated. Intra-abdominal pressures are elevated by exertional activities like exercise, running, lifting, coughing, and sneezing. The amount of urine lost is generally small with each episode. Nocturia and **enuresis** are rarely seen. The factors responsible for urethral underactivity are incompletely understood, although the loss of the **trophic** effects of estrogen on the uroepithelium at menopause is thought to be important. The peak of SUI prevalence in the perimenopausal years supports

this hypothesis. Clearly established risk factors for SUI include[5]:

- Pregnancy
- Childbirth (vaginal delivery)
- Menopause
- Cognitive impairment
- Obesity
- Increasing age

Unless the sphincter mechanism is compromised by surgery or trauma, SUI is exceedingly rare in males. The most common surgeries predisposing to SUI in males are radical prostatectomy for prostate cancer and transurethral resection of the prostate for benign prostatic hyperplasia.

Urge Urinary Incontinence (UUI) (Bladder Overactivity)[4]

In UUI, the detrusor (bladder) muscle is overactive and contracts inappropriately during the filling phase. The amount of urine lost per episode can be as large as the entire contents of the bladder may empty. Sleep may be disrupted by nocturia and enuresis.

In most patients, the cause of bladder overactivity is unknown (idiopathic). Clearly-established risk factors for UUI include:

- Increasing age
- Neurologic disorders (e.g., stroke, Parkinson's disease, multiple sclerosis, and spinal cord injury)
- Bladder outlet obstruction (e.g., benign or malignant prostatic enlargement or hyperplasia)

Overactivity may be myogenic or neurogenic in origin or a combination of both. These etiologies appear to be interconnected and complementary.

Overflow Urinary Incontinence (OUI) (Urethral Overactivity and/or Bladder Underactivity)[4]

In OUI, an important but uncommon form of UI in both sexes, the bladder is filled to capacity at all times but cannot empty, causing urine to leak out episodically. If caused by bladder underactivity, the detrusor muscle has weakened, in some cases enough to lose the ability to voluntarily contract. In this case, the bladder cannot be emptied completely and large volumes of residual urine remain after **micturition**. Clinically, this is most commonly seen in the setting of long-term chronic bladder outlet obstruction due to benign or malignant prostatic enlargement. However, this may also be a manifestation of neurogenic bladder, frequently a consequence of neuropathy in patients with diabetes. If due to urethral overactivity, the resistance of the urethra and/or sphincters cannot be overcome by detrusor contractility. This functional or anatomic obstruction results in incomplete bladder emptying. Clinically, in males this most frequently occurs in the context of long-term chronic bladder outlet obstruction as outlined previously. In females, urethral overactivity is rare but may result from **cystocele** formation or surgical overcorrection during anti-SUI surgery. In both sexes, systemic neurologic diseases such as multiple sclerosis or spinal cord injury may be the etiology.

Functional Urinary Incontinence[4]

Functional urinary incontinence is not generally caused by intrinsic urinary tract pathology. It is usually caused by factors extrinsic to the urinary tract. Examples of factors predisposing to functional incontinence include:

- Immobility (due to pain, traction, or use of non-portable medical devices)
- Lack of or slowed access to toileting facilities
- Cognitive impairment (difficulty with recognition of the urinary urge and proper response to it)
- UTIs
- Postmenopausal atrophic urethritis and/or vaginitis
- Diabetes mellitus (glucosuria leading to polyuria)
- Diabetes insipidus (polyuria due to decreased antidiuretic hormone)
- Pelvic malignancy (extrinsic pressure on urinary tract structures causing obstruction)
- Constipation or fecal impaction (see section on pelvic malignancy)
- Congenital malformations
- Central nervous system disorder resulting in a decreased level of consciousness (see section on cognitive impairment)
- Depression (apathy leading to recognition and response difficulties)

Mixed and Drug-Induced Urinary Incontinence[4]

Frequently, two or more types of UI may co-exist in a given patient, combinations termed mixed UI. This can lead to diagnostic and therapeutic difficulties due to the confusing array of presenting symptoms and the opposing effects that a given treatment can have in different types of UI (i.e., a given drug may reduce symptoms of one type of UI but worsen those of other types). Another interesting type of mixed UI is co-existing bladder overactivity (UUI) and impaired bladder contractility (OUI). Most common in the elderly, this combination is called *detrusor hyperactivity with impaired contractility* (DHIC).

❻ *Many medications can influence the lower urinary tract, including those not used for managing genitourinary disorders, and can precipitate new onset or aggravate existing voiding dysfunction and UI (Table 50–1).*

CLINICAL PRESENTATION AND DIAGNOSIS



Clinical Presentation of Urinary Incontinence Related to Urethral Underactivity[4]

General
The patient usually notes UI during activities like exercise, running, lifting, coughing, or sneezing. This type of UI is much more common in females (seen only in males with lower urinary tract surgery or injury compromising the sphincter).

Symptoms
Urine leakage with physical activity (volume is proportional to activity level). No UI with physical inactivity, especially when supine (no nocturia). May develop urgency and frequency as a compensatory mechanism (or as a separate component of bladder overactivity).

Diagnostic Tests
Observation of urethral meatus (opening) while patient coughs or strains.



Clinical Presentation of Urinary Incontinence Related to Bladder Overactivity[4]

General
Can have bladder overactivity and UI without urgency, if sensory input from the lower urinary tract is absent.

Symptoms
Urinary frequency (greater than 8 micturitions/day), urgency with or without urge incontinence; nocturia (greater than or equal to 2 micturitions/night) and enuresis may be present as well.

Diagnostic Tests
Urodynamic studies are the gold standard for diagnosis. Also urinalysis and urine culture should be negative (rule out urinary tract infection as cause of frequency).



Clinical Presentation of Urinary Incontinence Related to Urethral Overactivity and/or Bladder Underactivity[4]

General
Important but rare type of UI in both sexes. Urethral overactivity usually due to prostatic enlargement (males) or cystocele formation or surgical overcorrection following antiurethral underactivity (SUI) surgery (females).

Symptoms
Lower abdominal fullness, hesitancy, straining to void, decreased force of stream, interrupted stream, sense of incomplete bladder emptying. May have urinary frequency and urgency, too. Abdominal pain if acute urinary retention is also present.

Signs
Increased postvoid residual urine volume.

TABLE 50–1. Medications Influencing Lower Urinary Tract Function

Medication	Effect
Diuretics	Polyuria, frequency, urgency
α-Adrenoceptor antagonists	Urethral relaxation; may relieve obstruction in males, induces/worsens SUI in females
α-Adrenoceptor agonists	Urethral constriction; aggravates obstruction in males (may cause urinary retention), potential SUI treatment in females
Calcium channel blockers (dihydropyridines)	Urethral constriction (may cause urinary retention), especially in males
Opioid analgesics	Impaired bladder contractility (may cause urinary retention)
Sedative-hypnotics	Functional UI due to immobility, delirium, sedation
Psychotherapeutics with anticholinergic properties Anticholinergics	Urinary retention due to impaired bladder contractility or potential UUI treatment
TCAs	Combination of anticholinergic and α-adrenoceptor blocking activities can lead to unpredictable effects on UI
Ethanol	Polyuria and frequency (via effects on ADH), functional UI (delirium, sedation), urgency
ACEIs	Cough leading to SUI (ARBs do not induce cough)
Cyclophosphamide	Hemorrhagic cystitis due to acrolein metabolite (prevent with MESNA)

ACE-I, angiotensin-converting enzyme inhibitor; ADH, antidiuretic hormone (or vasopressin); ARB, angiotensin II receptor blocker, MESNA, sodium 2-mercaptoethanesulfonate; TCA, tricyclic antidepressant; UI, urinary incontinence; SUI, stress urinary incontinence; UUI, urge urinary incontinence.

The clinical presentation of UI depends on the underlying pathophysiology. The literature evaluating the prevalences of different UI types by age and sex has produced widely varying results due to a number of factors. The clinician should thus consider a given patient as having virtually any type of UI until ruled out during diagnostic evaluation.

A complete medical history and targeted physical examination are essential to correctly classify the type(s) of UI present. It is important to assess the degree of annoyance due to symptoms of the patient during the assessment. The degree of annoyance to the patient may not correlate well with the results of quantitative tests such as symptom frequency/severity, use of

absorbent products, frequency/severity of neurologic signs, and postvoid residual urine volume. This is especially the case in "hypersensitive" and "stoic" individuals. Items to address during the evaluation are illustrated in Table 50–2. Components of the physical examination include[4]:

- Abdominal examination (look for distended bladder)
- Neurologic evaluation of perineum and lower extremities (includes digital rectal exam to check rectal tone, reflexes, ability to perform a voluntary pelvic muscle contraction in females and size and surface quality of prostate in males)
- Pelvic exam (females) (look for evidence of **prolapse** of bladder, small bowel, rectum, or uterus, or estrogen deficiency)
- Genital/prostate exam (men)
- Direct observation of urethral meatus (opening) when patient coughs/strains (urine spurt consistent with SUI)
- Perineum exam (looking for skin maceration, redness, breakdown, ulceration and evidence of fungal skin infection)

TABLE 50–2. Items Which Should Be Addressed During Diagnostic Evaluation of Urinary Incontinence (UI)

Item	Comments
Urine leakage	
Use of absorbent products	Yes/no, type(s), quantity, times of day worn Quantity may relate more to personal preference and hygiene than to UI type and severity (e.g., use of large number of pads by a fastidiously hygienic patient with low volume loss)
Quantity lost per episode	Dribbling versus small volumes intermittently versus large volumes Consistent or varied quantities
Precipitants	Yes/no, physical activity, excessive fluid intake, drug(s)
Times of day	Daytime/nighttime/both
Symptoms	
Urgency	Yes/no, how often, how severe, duration from urge onset to micturition
Frequency	Yes/no, daytime/nighttime/both, how often
Nocturia	Yes/no, how often, proportion with UI
Obstructive symptoms	Yes/no, type(s) (**hesitancy**, strain to void, decreased force of stream, start and stop stream, sense of incomplete emptying), severity
Lower abdominal fullness	Yes/no, how often, how severe
Comorbidities	
Current medication use	See Table 50–1 Remember **CAMs**, OTCs
Evidence of preexisting or new-onset	
Diabetes mellitus	
Metastatic or genitourinary malignancy	
Multiple sclerosis or other neurologic disease	
CNS disease above the pons	Usually UUI
Spinal cord injury	UUI or OUI, depending on level and degree of completeness of injury
Recent non-genitourinary surgery	Functional UI
Previous local surgery/radiation	Prostate surgery, lower abdominal cavity surgery (direct injury vs. **denervation**), radiation (direct injury)
Gynecologic history	Childbirth (vaginal vs. cesarean section), prior gynecologic surgery, hormonal status (pre- vs. postmenopausal)
Pelvic floor disease	Constipation, diarrhea, fecal incontinence, **dyspareunia**, sexual dysfunction, pelvic pain
UTI	**Dysuria**, CVA tenderness, frequency
Gross hematuria	Possible bladder or other genitourinary cancer

CAM, complementary and alternative medications; CNS, central nervous system; CVA, costovertebral angle; OTC, over-the-counter; OUI, overflow urinary incontinence; SUI, stress urinary incontinence; UTI, urinary tract infection; UUI, urge urinary incontinence.



Patient Encounter, Part 2: The Medical History, Physical Examination, and Diagnostic Tests

PMH
Insulin-dependent diabetes mellitus since age 7; it is "reasonably well-controlled" per patient
Hypertension for 2 years, currently "controlled" per patient

FH
Mother had diabetes and died of a myocardial infarction at 62 years of age; father smoked 1 to 3 packs of cigarettes per day and developed fatal lung cancer at age 57

SH
Works two jobs as a waitress; denies alcohol use or smoking

Meds
NPH insulin 20 units before breakfast and 5 units before supper
Enalapril 10 mg twice daily
Aspirin 325 mg once daily

ROS
(+) Recurrent coughing, urinary incontinence, dyspareunia, vaginal itching, multiple UTIs; (–) nocturia, enuresis, urgency, dysuria, frequency, lower abdominal fullness, decreased force of stream

PE
VS: Blood pressure 124/70 mm Hg, pulse 80 beats per minute, respiratory rate 16/minute, temperature 37.0°C (98.6°F)
CV: RRR; normal S_1, S_2; no murmurs, rubs, gallops
Abd: Soft, non-tender, non-distended; (+) bowel sounds; bladder not palpable
Neuro: Within normal limits (gross sensory, motor, reflexes)
GU: Valsalva caused urine spurt; friable, bleeding vaginal lining on pelvic exam

Labs
Hemoglobin A1c 8.2% (0.082); rest within normal limits

- Given this additional information, what is your assessment of the patient's condition?
- Identify your treatment goals for the patient.
- What nonpharmacologic and pharmacologic alternatives are available to the patient?

TREATMENT

❷ *Patient-specific treatment goals should be identified. This frequently requires reaching a compromise between efficacy and tolerability of drug therapy. These goals are not static and may change with time.*

Desired Outcomes

- Restoration of continence
- Reduction of the number of UI episodes (daytime and nighttime) and frequency of nocturia
- Prevention of disease complications (e.g., dermatologic infections and skin breakdown, delay institutionalization)
- Avoidance or minimization of adverse consequences of treatment
- Minimization of treatment costs
- Improvement in patient's quality of life

Nonpharmacologic Treatment

At the primary care level, nonpharmacologic treatment of UI constitutes the chief approach to UI management. In patients in whom pharmacologic or surgical management is inappropriate or undesirable or refused, non-surgical nonpharmacologic treatment is the only option. Examples of patients fitting this scenario include:

- Those not medically fit for surgery
- Those who plan future pregnancies (as pregnancy/childbirth can compromise the long-term results of certain types of continence surgery)
- Those with OUI whose condition is not amenable to surgical or drug treatment
- Those with comorbidities which place them at high risk for significant side effects to drug therapy
- Those who wish to delay or avoid surgery
- Those with mild to moderate symptoms who do not wish to undergo surgery or take medication

Nonpharmacologic approaches include lifestyle modifications, scheduled voiding regimens, pelvic floor muscle rehabilitation, anti-incontinence devices, and supportive interventions.[4,6] Many of these are best utilized through attendance at multidisciplinary UI clinics staffed by specialist nurses and/or physical therapists in addition to physicians. Behavioral interventions are among the first-line treatment approaches for SUI, UUI, and mixed UI. However, these lifestyle modifications, scheduling regimens, and pelvic floor muscle rehabilitation methods require a motivated patient and/or caregiver who can play an active role in developing the treatment plan. Anything that interferes with active participation (including cognitive dysfunction) will render these approaches suboptimal. Patients/caregivers also must attend regular follow-up visits to monitor outcomes. Even if the results of nonpharmacologic treatment have not fully achieved the desired outcomes, if it has provided at least some improvement in UI signs and symptoms, it should be continued during pharmacologic treatment. ❼ *Nonpharmacologic treatment can allow the use of lower drug doses. The combination of both therapies may have at least an additive effect on UI signs and symptoms.*

Surgery is rarely a first-line treatment for UI. Surgery is generally considered only when the degree of bother or lifestyle compromise is sufficient and other non-operative therapies are either undesired or have been ineffective. Surgery can be used to manage urethral overactivity due to benign prostatic enlargement and

bladder outlet obstruction (via endoscopic incision using a cystoscope). Bladder underactivity cannot be managed surgically and rarely is surgery considered for UUI. Surgery is most effective in the management of SUI. Surgery for SUI is directed toward stabilizing the urethra and bladder neck and/or augmenting urethral resistance using periurethral collagen and other injectables. In males, SUI is best treated by implanting an artificial urinary sphincter.[4]

Pharmacologic Treatment

❽ *The anticholinergic/antispasmodic drugs are the first-line pharmacologic treatment for urge urinary incontinence. They are the most effective agents in suppressing premature detrusor contractions, enhancing bladder storage, and relieving symptoms.* It must be emphasized that the improvements in clinical and urodynamic parameters are modest at best, although still considered by experts in the field to be positive.[13] In a recent systematic review/meta-analysis of 56 clinical trials in UUI, only four statistically-significant differences in efficacy between drugs were found. Solifenacin produced greater reductions in the frequency of urgency episodes and frequency of micturition than did tolterodine immediate-release (IR). Oxybutynin extended-release (ER) produced a greater reduction in the frequency of incontinence episodes and a greater proportion of patients returned to continence compared to tolterodine long-acting (LA).[13]

The major problem with existing agents is their lack of selectivity to bladder muscarinic receptors, thus leading to dose-limiting side effects outside of the urinary tract. These include dry mouth, constipation, blurred vision, confusion, cognitive dysfunction, and tachycardia. With oxybutynin, orthostasis due to α-receptor blockade and sedation and weight gain due to histamine-receptor blockade may also occur. Dry mouth is the most problematic of the anticholinergic side effects and is frequently dose-limiting. In the systematic review and meta-analysis cited previously, there were multiple significant differences between agents. From the perspective of all-cause premature discontinuation from therapy, tolterodine LA followed by darifenacin and solifenacin were the best tolerated, while oxybutynin IR was the least tolerated. From the perspective of adverse-event profiles, oxybutynin IR 5 to 7.5 mg/day and tolterodine (IR and LA) were the best tolerated, while darifenacin, oxybutynin IR at greater than 7.5 mg/day, oxybutynin transdermal (TD), solifenacin (5 and 10 mg/day), and trospium chloride (40 mg/day) were the least tolerated. Oxybutynin IR at greater than 7.5 mg/day was the least tolerated compared to all other anticholinergics in 13/20 (65%) rate comparisons, and was the only drug to be significantly associated with urinary retention.[13]

Details regarding the pharmacokinetics, contraindications/precautions, and dosing of the five recommended agents (oxybutynin, tolterodine, trospium chloride, solifenacin, and darifenacin) are illustrated in Table 50–3.[7–12,14–16] A current clinical controversy is which of these agents should be considered first-line in UUI, and in the case of oxybutynin and tolterodine, which formulations should be recommended. There are few head-to-head clinical trials to assist in decision making and those few that exist have demonstrated either broad equivalence or clinically-unimportant differences in efficacy. ❸ *Patient characteristics (e.g., age, comorbidities, concurrent drug therapies, and ability to adhere to the prescribed regimen) can also influence drug therapy selection.* Drug selection frequently will be based on differences in tolerability (wherein the extended-release oral or transdermal formulations are better tolerated than the immediate-release formulations) and cost. ❹ *Careful dose titration is necessary to maximize efficacy and tolerability.* The selected agent should be titrated to the maximum tolerated dose and maintained there for at least 4 weeks in order to assure an adequate therapeutic trial. ❺ *If therapeutic goals are not achieved, a switch to an alternative agent should be made.* There is no rationale for use of two or more anticholinergics concurrently at low doses.

Other drugs, such as propantheline, flavoxate, tricyclic antidepressants (especially imipramine), dicyclomine, and scopolamine, are less effective, no safer, and/or have not been adequately studied; therefore, their use is not recommended.[6]

Women with mixed UI (UUI plus SUI) or UUI plus atrophic vaginitis and/or urethritis may also benefit from the addition of a locally-administered (per vagina) estrogen to anticholinergic therapy.

Stress Urinary Incontinence

The goal of pharmacologic therapy of urethral underactivity is to improve the urethral closure mechanism by one or more of the following:

- Stimulating α adrenoceptors in the smooth muscle of the proximal urethra and bladder neck
- Enhancing the supportive structures underlying the urethral mucosa
- Enhancing the positive effects of serotonin and norepinephrine in the afferent and efferent pathways of the micturition reflex

There is no role for pharmacologic therapy in SUI in males resulting from surgery or trauma.[17] It should be kept in mind that SUI (in contrast to UUI) is frequently curable by surgery, thus obviating years of drug therapy that may be incompletely effective in symptom relief.

Estrogens[4]

❾ *Vaginally-administered estrogen plays only a modest role in managing stress urinary incontinence (urethral underactivity), unless it is accompanied by local signs of estrogen deficiency (e.g., atrophic urethritis or vaginitis).*

Although not supported by rigorous clinical trial evidence, local (per vagina) and systemic estrogens have been considered mainstays of pharmacologic management since the 1940s. They are believed to work by a trophic effect on uroepithelial cells and underlying collagenous subcutaneous tissue,

TABLE 50–3. Anticholinergic/Antispasmodic Drugs Recommended For Urge Urinary Incontinence

Parameter	Oxybutynin	Tolterodine	Trospium chloride	Solifenacin	Darifenacin
Dosage forms	IR tablets, solution SR-XL tablets, SR-TD patch	IR tablets SR-LA capsules	IR tablets	IR tablets	ER tablets
Dosing	IR: 2.5–5 mg two to four times daily SR (oral): 5–30 mg once daily SR (TD): 3.9 mg/day patch applied twice weekly	IR: 1 or 2 mg twice daily SR: 2 or 4 mg once daily	20 mg twice daily	5–10 mg once daily	7.5–15 mg once daily
Kinetics	Active metabolite (N-desethyl) Not altered in renal or hepatic disease or advanced age	Active metabolite (5-hydroxymethyl) **Polymorphic** metabolism (CYP4502D6) Not altered in advanced age. Sign. altered in hepatic disease (decreased CL in cirrhosis) and renal disease (decreased CL)	Food decreased BA 70–80% Sign. altered in renal disease (decreased CL) but not hepatic disease or advanced age	Metabolized via CYP4503A4 but only one active metabolite (4-hydroxy) Sign. altered in severe renal impairment, moderate hepatic impairment (Child-Pugh B), and advanced age (decreased CL in all)	Complex metabolism (polymorphic CYP4502D6, CYP4503A4) Not altered in advanced age, renal impairment, mild hepatic impairment (Child Pugh A) Sign. altered in moderate hepatic impairment (Child-Pugh B) (decreased CL)
Contraindications and precautions	Use caution if CYP4503A4 inhibitors are also being taken (decreased oxybutynin CL)	Reduce dose 50% in those taking CYP4503A4 inhibitor(s) or with hepatic cirrhosis or with CrCl less than 30 mL/minute Antacid-SR (oral) prep. interaction (dose-dumping) (not seen with PPI)	Give on empty stomach Decrease dose 50% when CrCl less than 30 mL/minute	Do not exceed 5 mg/day if CrCl less than 30 mL/minute, patient has moderate hepatic impairment, or patient is taking CYP4503A4 inhibitor(s) If severe hepatic impairment, do not use	Do not exceed 7.5 mg/day if patient is taking potent CYP4503A4 inhibitor(s) Use caution if patient is taking moderate CYP4503A4 inhibitor(s) or CYP4503A4 or 2D6 substrate(s) Do not chew, divide, or crush the extended-release tablets

BA, bioavailability; CL, total body clearance; CrCl, creatinine clearance; CYP450, cytochrome P-450; ER, extended-release; IR, immediate-release; LA, long-acting; PPI, proton pump inhibitor; Sign., significantly; SR, sustained-release; TD, transdermal.

enhancement of local microcirculation, and enhancement of the number and/or sensitivity of α adrenoceptors. Open trials have supported the use of estrogens administered by the parenteral, oral, transdermal, and local routes of administration. However, randomized controlled trials have found no significant clinical or urodynamic effects of oral estrogen compared to placebo in SUI. Systemic estrogen therapy also carries numerous short- and long-term side effect risks (mastodynia, uterine bleeding, nausea, thromboembolism, cardiac and cerebrovascular ischemic events, and enhanced breast and endometrial cancer risks). If estrogens are to be used in SUI management, only locally-administered products should be used (Table 50–4).

TABLE 50–4. Drugs Used for Stress Urinary Incontinence

Parameter	Estrogens	Pseudoephedrine	Duloxetine
Dosage forms	Avoid systemic (parenteral, oral, TD); vaginal: tablet, cream, intravaginal ring	Tablets, solution	DR capsules
Dosing	Estradiol 25 mcg vaginal tablets (insert one PV daily × 14 days, then one PV twice weekly) CEE vaginal cream (1/2–2 g daily PV; consider 3 weeks on, 1week off; may be able to decrease frequency of use over time) Estradiol 2 mg vaginal ring (1 ring PV every 3 months)	15–60 mg three times daily	40–80 mg/day (1 or 2 doses)
Kinetics	Use local route to minimize systemic BA and side effects	Less than 1% of dose is metabolized (inactive metabolite) Primarily renal elimination of unchanged drug Would not expect hepatic impairment to have an effect (no data) Expect sign. effect of renal impairment and no effect of advanced age (beyond decreased CrCl with age) (no data)	Extensive metabolism via CYP4502D6 and 1A2 (inactive metabolites) Not altered in advanced age, mild to moderate renal impairment, mild hepatic impairment (Child-Pugh A). Sign. altered in severe renal disease and moderate hepatic impairment (Child-Pugh B) Systemic exposure to duloxetine decreased by 1/3 in smokers (dose change not recommended)
Contraindications/ Precautions	Contraindications include known or suspected breast or endometrial cancer Abnormal genitourinary bleeding of unknown etiology Active thromboembolism (or history of TE assoc. with previous estrogen use)	Contraindications include hypertension, tachyarrhythmias, coronary artery disease, MI, cor pulmonale, hyperthyroidism, renal failure, narrow-angle glaucoma	Multiple drug-drug interactions possible with CYP4502D6 and 1A2 substrates/ inhibitors Avoid if CrCl less than 30 mL/minute and in all patients with hepatic disease Can raise BP Do not discontinue abruptly (withdrawal syndrome) Suicide risk even in patients without psychiatric disease Avoid in uncontrolled narrow-angle glaucoma (causes mydriasis) Hepatotoxic; avoid in alcoholics even if signs/symptoms of hepatic disease are absent.

BA, bioavailability; BP, blood pressure; CEE, conjugated equine estrogens; CrCl, creatinine clearance; CYP450, cytochrome P-450; DR, delayed-release; MI, myocardial infarction; PV, per vagina; Sign., significantly; TD, transdermal; TE, thromboembolism.

Alpha-Adrenoceptor Agonists[4]

Open and randomized controlled trials utilizing clinical and urodynamic endpoints have supported the use of a variety of α-adrenoceptor agonists, including phenylpropanolamine, ephedrine, and pseudoephedrine, in the therapy of mild and moderate SUI. In addition, several studies have demonstrated clinical and urodynamic benefits for combination estrogen–α-adrenoceptor agonist use over those of the individual agents. Phenylpropanolamine was removed from the United States market in late 2000 due to the risk of ischemic stroke in women taking this drug.[18] However, this drug is still available via the Internet, so clinicians need to monitor and discourage its use. Although still available by prescription, ephedrine is considerably more toxic than other α-adrenoceptor agonists and its use is not recommended. Although phenylephrine is now available in oral formulations, the lack of data regarding its use in SUI and the reported lack of efficacy in maximum recommended doses for rhinitis suggest that this agent should be avoided at present.

This leaves the clinician with only one practical agent to use: pseudoephedrine (Table 50–4). Side effects include hypertension, headache, dry mouth, nausea, insomnia, and restlessness.[19] ⑩ *The major impediment to using the α-adrenoceptor agonist class is the extensive list of contraindications (Table 50–4).* In the past, α-adrenoceptor agonist therapy was generally added to estrogen therapy in those insufficiently improved with estrogen alone and in whom its use was not contraindicated. With the recent availability of duloxetine, treatment is now available for estrogen non- or hypo-responders who cannot take α-adrenoceptor agonists.

Duloxetine[20]

Duloxetine is a selective serotonin-norepinephrine reuptake inhibitor similar pharmacologically to venlafaxine. Approved for the treatment of major depression and painful diabetic peripheral neuropathy, its use in SUI is off-label. Duloxetine enhances central serotonergic and adrenergic tone which is involved in ascending and descending control of urethral smooth muscle and the internal urinary sphincter. Urethral and urinary sphincter smooth muscle tone during the filling phase are thus enhanced.[21,22] The pharmacokinetics, contraindications/precautions, and dosing of duloxetine are illustrated in Table 50–4.[20,23] Clearly, duloxetine has demonstrated modest efficacy in SUI and a major question is its role in SUI compared to estrogen and α-adrenoceptor agonists. In the absence of head-to-head clinical trial data, this is a difficult question to answer, at least for the comparison of duloxetine to α-adrenoceptor agonists. ⑪ *The use of duloxetine in stress UI is complicated by (1) the potential for multiple clinically-relevant drug-drug interactions with cytochrome P450 (CYP450)2D6 and CYP4501A2 inhibitors, (2) withdrawal reactions if abruptly discontinued, (3) high rates of nausea and other side effects, (4) hepatotoxicity contraindicating its use in patients with any degree of hepatic impairment, and (5) its mild hypertensive effect.*



Patient Encounter, Part 3: Creating a Care Plan

Based on the information presented, create a care plan for this patient's UI. Your plan should include: (1) a statement of the drug-related needs and/or problems, (2) the goals of therapy, (3) a patient-specific detailed therapeutic plan, and (4) a plan for follow-up to determine whether or not the goals have been achieved and adverse events avoided.

Overflow Incontinence Due to Bladder Underactivity[4]

⑫ *In overflow UI due to atonic bladder, a trial of bethanecol may be reasonable if contraindications do not exist.* There is no established effective pharmacologic therapy for OUI due to poor bladder contractility (atonic bladder). The efficacy of the cholinomimetic bethanecol (25 to 50 mg three or four times daily) is uncertain and in well done clinical trials it has had mixed results. In addition, its cholinomimetic effect is not urospecific and its side effects are bothersome, including muscle and abdominal cramping, hypersalivation, diarrhea, and potentially life-threatening bradycardia and bronchospasm. α-Adrenoceptor blockers such as prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin may benefit this condition by relaxing the bladder outflow tract and hence reducing outflow resistance. If pharmacologic therapy fails, intermittent urethral catheterization by the patient or caregiver three or four times per day is recommended. Less satisfactory alternatives include indwelling urethral or suprapubic catheters or urinary diversion.

Overflow Incontienence Due to Obstruction

⑬ *In overflow UI due to obstruction, the goal of treatment is to relieve the obstruction.*

OUTCOME EVALUATION

- Monitor the patient for symptom relief. Have the desired outcomes jointly developed by the health care team and the patient/caregiver been achieved and to what degree? Inspect the daily diary completed by the patient/caregiver since the last clinic visit and quantitate the clinical response (e.g., number of micturitions, number of incontinence episodes, and pad use). If a diary has not been used, ask the patient how many incontinence pads have been used and how they have been doing in terms of "accidents" since the last visit. If appropriate, administer a short-form instrument used to measure symptom impact and condition-specific quality of life and compare previous result(s).
- Elicit adverse effects of drug therapy using a non-leading approach and ask the patient/caregiver to judge their severity and what measures, if any, the patient used to ameliorate them. Assess adherence (ask patient about missed doses or do a pill count if the prescription container was brought to the visit).

- The balance of clinical response and tolerability will dictate the approach to adjusting drug dosage. Potential approaches include dosage increase, maintenance, or decrease. If adverse effects are quite bothersome to the patient and patient safety and/or adherence are compromised, stop, or taper, the offender and initiate another drug option.



Patient Care and Monitoring

1. Assess the patient's symptoms to determine if patient-directed therapy is appropriate or whether the patient should be evaluated by a physician. Assessment includes the types and severities of symptoms and the presence or absence of exacerbating factors. Does the patient have any UI-related complications?
2. Review any available diagnostic data to determine disease status.
3. Obtain a thorough medication history, including use of prescription, non-prescription, and complementary and alternative drug products. Determine which, if any, treatments in the past had been helpful as judged by the patient. Could any of the patient's current medications be contributing to UI?
4. Educate the patient on lifestyle modifications that may improve symptoms, including but not limited to, smoking cessation (for patients with cough-induced stress UI), weight reduction for those patients with stress and urge UI, prevention of constipation in patients at risk, caffeine reduction, and modification of diet and fluid intake (e.g., timing and quantity of fluid intake and avoidance of foods or beverages that worsen UI).
5. Is the patient taking the appropriate drug(s) for his or her type(s) of UI? Are the dose(s) appropriate? If not (to either question), why?
6. Develop a plan to assess efficacy after a minimum of 4 weeks.
7. Assess changes in quality of life (physical, psychological, social functioning, and well-being).
8. Evaluate the patient for drug-related adverse events, allergies, and interactions (drug-drug and drug-disease).
9. Stress the importance of adherence with the prescribed regimen, including lifestyle modifications. Recommend the most "patient-friendly" treatment regimen possible.
10. Provide patient education regarding the disease state, lifestyle modifications, and drug therapy:
    - Causes of UI and what things to avoid (see #3 and #4, above)
    - Possible UI complications
    - Timing of medication intake
    - Potential adverse events (limit to most frequent and/or clinically-relevant)
    - Potential drug-drug interactions

PEDIATRIC ENURESIS

Pediatric enuresis is not a disease but a symptom, which can present alone or at the same time as other disorders, in children and adolescents. It is defined as the repeated voiding of urine into bed or clothes at least twice a week for at least three consecutive months in a child at least 5 years old (per the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision).[24,25] Enuresis can still be present even if the above frequency and duration parameters are not met, provided that associated distress or functional impairment exists. The terms "nocturnal" and "diurnal" refer to periods during sleep and while awake, respectively. Primary enuresis refers to a process wherein the patient has never been consistently dry throughout the night. Secondary enuresis refers to a process wherein the patient has resumed wetting after a period of dryness of at least 6 months in duration. Lastly, monosymptomatic and polysymptomatic enuresis should be differentiated. Monosymptomatic enuresis refers to wetting at nightttract symptoms and no daytime symptoms. Polysymptomatic enuresis refers to wetting at nighttime associated with other urinary tract symptoms (e.g., urge or freqime without any other urinary uency) and daytime symptoms as well.

Enuresis is not a benign disorder that children will just "grow out of." Emotional and/or physical abuse of the child by adult caregivers lead to secondary problems such as chronic anxiety, low self-esteem, and delayed developmental milestones such as attending camp or going on "sleepovers" at the homes of friends. The emotional and developmental damage produced by enuresis may be more significant to the child than the enuresis itself.

The American Academy of Child and Adolescent Psychiatrists and the International Children's Continence Society (ICCS) have published practice guidelines for the assessment and treatment of pediatric enuresis.[24,25]

EPIDEMIOLOGY AND ETIOLOGY

Five to seven million children and adolescents in the United States suffer from nocturnal enuresis. Primary enuresis is twice as common as secondary enuresis. Enuresis is twice as common in boys as compared to girls. The incidence of enuresis varies as a function of age[24,25]:

- 40% in 3-years-old
- 12% to 25% in 4-years-old
- 15% to 20% in 5-years-old
- 10% in 6-years-old
- 6% to 10% in 7- and 8-years-old
- 5% in 10-years-old
- 2% to 3% in 12-years-old
- 1% to 3% in adolescents
- 0.5% in adults

Five to ten percent of children with enuresis will suffer the condition as adults. It may also predispose to UUI in adults. In the enuretic population, 80% to 85% are monosymptomatic, 5% to 10% are polysymptomatic, and under 5% have an organic cause. The spontaneous annual cure rate (i.e., restoration of continence) ranges from 14% to 16% (exception: at about 4 or 5 years of age, it may be as high as 30%).

The etiology of enuresis is poorly understood, but there is a clear genetic link. The incidence in children from families in whom there are no members with enuresis, where one parent had enuresis as a child, and where both parents had enuresis as children are 14%, 44%, and 77%, respectively. Loci for enuresis have been located on chromosomes 12, 13, and 22. Sleep disorders are not considered major contributors with the exception of sleep apnea. Enuresis occurs in all sleep stages in proportion to the time spent in each stage. However, a small proportion of individuals are not aroused from sleep by bladder distention and have uninhibited bladder contractions preceding enuresis.

PATHOPHYSIOLOGY

The vast majority of children with enuresis have normal urodynamics, including nocturnal bladder capacity. Functional bladder capacity can be estimated using this formula: age in years + 2 = ounces of capacity. In some children, there appears to be a relationship between developmental immaturity (motor and language milestones) and enuresis, but the mechanism is unknown. Drugs like lithium, clozapine, risperidone, valproic acid, and theophylline can rarely cause and aggravate enuresis. Psychological factors are clearly contributory in only a minority of individuals. The most frequent example of this is secondary enuresis precipitated by a stressor such as divorce, school trauma, sexual abuse, or hospitalization. In rare cases, the family may be so dysfunctional that the child has never been properly toilet-trained.



Clinical Presentation and Diagnosis

Proper assessment of the child or adolescent with enuresis should explore every aspect of urinary incontinence, especially the genitourinary and nervous systems. The minimum assessment should include[24,25]:

- Interview of child and parent(s), being sensitive to the emotional consequences of the enuresis
- Direct physical examination, looking for enlarged adenoids/tonsils, bladder distention, fecal impaction, abnormal genitalia, spinal cord anomalies, and abnormal neurologic signs (look for an organic cause amenable to surgery or drugs; Table 50–5)
- Obtain a urinalysis (consider a urine culture at the same time)

A 2-week diary of wet and dry nights prior to intervention is useful in that it can be used to monitor the response to treatment. A first-morning urine specific gravity may help to predict response to desmopressin therapy. Polysymptomatic presentation may require a more elaborate work-up, including voiding cystourethrogram, renal and/or bladder ultrasound, urodynamics, and sleep studies.

TABLE 50–5. Major Potentially Treatable Organic Causes of Enuresis

Potentially Treatable by Surgery
• Ectopic ureter
• Lower UTI (correct congenital anomalies)
• Neurogenic bladder
• Bladder calculus (stone) or foreign body
• Obstructive sleep apnea
Potentially Treatable by Drugs
• UTI
• Diabetes mellitus
• Diabetes insipidus
• Fecal impaction
• Constipation

UTI, urinary tract infection.

TREATMENT

Desired Outcomes

- Restoration of continence, which may not be an initially realistic outcome
- Reduction in the number of enuresis episodes
- Prevention or amelioration of disease complications including adverse psychological effects on the patient and caregivers or delay in developmental milestones
- Avoidance or prevention of adverse treatment effects
- Minimization of treatment costs
- Improvement in the patient's and caregivers' quality of life

General Approach to Treatment

Treatment is guided by the findings of the patient assessment. Daytime wetting, abnormal voiding such as unusual posturing, discomfort, straining, or poor stream, history of recurrent UTIs, and abnormalities of the genitalia suggest the need for referral to a urologist. In the rare circumstance of a true psychological cause, individual and/or family psychotherapy and crisis intervention are recommended.

In the absence of an identified cause and comorbidities, monosymptomatic nocturnal enuresis is present which can be amenable to nonpharmacologic and pharmacologic therapies. Nonpharmacologic therapy should be utilized initially, provided that the patient and family are sufficiently motivated. Use of one nonpharmacologic method at a time is reasonable, provided that each is given an adequate trial period. If response is suboptimal after 6 months, a different method should be substituted or added. There is some evidence to

justify combination therapy. There is no consensus as to when pharmacologic therapy should be added to or substituted for nonpharmacologic therapy. ⓮ *Considering that pharmacotherapy is inferior to select nonpharmacologic treatment modalities in pediatric enuresis, pharmacotherapy will be most valuable in patients who are not candidates for nonpharmacologic therapy due to non-adherence or who do not achieve the desired outcomes on nonpharmacologic therapy alone.*

Nonpharmacologic Treatment[26]

The standard first-line therapy is supportive in nature. This involves education about the condition, demystification, and assurance that the parents do not punish the child for enuresis. Journal keeping, fluid restriction, and nighttime awakenings of the child to preempt "accidents" make for a high level of caregiver involvement. The behavioral treatments of enuresis are explained in Table 50–6. Alarms, overlearning, and dry-bed training are the most complex and effective nonpharmacologic treatments available and compare favorably to pharmacologic therapy. A 3- to 6-month trial is recommended. Once dryness is achieved, relapse rates are low.

Measures that *do not* help include:

- Bladder stretching exercises (done by delaying voiding despite the urge to do so)
- Hypnotherapy
- Dietary changes
- Desensitization to allergens
- Acupuncture[27]
- Chiropractic

Pharmacologic Treatment

The two primary agents used to treat enuresis are desmopressin and imipramine (Table 50–7). ⓯ *Desmopressin is the drug of choice in pediatric enuresis.* Anticholinergics have a limited role (Table 50–7). Other agents have been studied with inconclusive results.[28]

Desmopressin (DDAVP) [29,30]

A synthetic analogue of antidiuretic hormone (ADH), desmopressin (DDAVP) was first studied in enuresis in the 1970s. It was approved by the Food and Drug Administration (FDA) in 1990 for the treatment of nocturnal enuresis in children at least 6 years of age. It decreases the number of wet nights per week by a mean of 1.34. The between-study variability in response to DDAVP is quite large, with a frequency of wetting ranging from 10% to 91% of patients, but only 25% become completely dry on the drug. Response is dose-independent for the nasal formulation (20 = 40 = 60 mcg); however, 20 mcg is the minimum dose resulting in therapeutic benefit. Response is dose-dependent for the oral formulation (for example, the number of wet nights fell 27%, 30%, and 40% with 0.2-, 0.4-, and 0.6-mg doses, compared to 10% with placebo in one study). Benefit exists only as long as

TABLE 50–6. Behavioral Treatments For Enuresis

Lifting	Procedure wherein the caregiver takes the child to the toilet at regular intervals during the night to urinate without fully awakening him or her
Night awakening	Procedure wherein the caregiver fully awakens the child to void shortly before he or she would usually have wet the bed; once the child is consistently dry, the frequency of awakening drops or (for single awakenings) the time of awakening is gradually moved to earlier in the night (i.e., closer to bedtime) until the child is dry when awakened 1 hour after going to bed
Alarm	An alarm device and a moisture-sensitive sensor are used in combination, with the sensor being placed under the sheets, or more commonly, attached to the child's pajamas or underwear near the urethra
Overlearning	This is commenced at a minimum of 2 weeks after the alarm has rendered the child dry; the child drinks 500 mL during the hour before going to bed; alarm use is continued until he or she is dry for 14 consecutive nights with the extra fluid intake; is used to reduce relapse rates seen with alarm use alone
Dry-bed training	This begins with an intensive first night of training which involves increased fluid consumption, hourly awakenings, praise when the bed is dry at hourly awakenings, and, when the alarm goes off, a mild reprimand and cleanliness training (child changes wet clothes and bed linens, remakes the bed, resets the alarm); before going to bed and after each wetting, the child engages in 20 practice trials of appropriate toileting (i.e., positive practice): for each practice trial, the child lies in bed, counts to 50, arises and attempts to urinate in the toilet, then returns to bed; on subsequent nights, child is woken only once, usually about 3 hours after the child has gone to bed; after a dry night, the night awakening moves up 30 minutes earlier; it is discontinued when it is scheduled to occur 1 hour after bedtime; after 7 consecutive dry nights, the alarm is discontinued, but is reinstituted if two episodes of wetting occur in a 1-week period

TABLE 50–7. Dosing of Pharmacologic Treatments of Enuresis

Desmopressin	Nasal: Start with 10 mcg 1 hour before bedtime and titrate upward in 10 mcg increments every week to a maximum of 40 mcg per day Oral: Start with 0.2 mg 1 hour before bedtime and titrate upward in 0.1 mg increments every week to a maximum of 0.6 mg per day
Imipramine	Start with 1 mg/kg per day (approx. 25 mg in 5- to 8-years-old and 50 mg in older children and adolescents) and titrate in 0.5 mg/kg-per-day increments every 2 weeks to a maximum of 2.5 mg/kg per day
Oxybutynin	Start with 0.1 mg/kg per day and titrate upward; available in oral solution to facilitate pediatric dosing.

the patient takes DDAVP, with relapse rates of up to 94% after discontinuation. Insufficient data are available to judge the relative efficacies of the two formulations. DDAVP appears to work better with monosymptomatic versus polysymptomatic enuresis. The oral route is generally preferred since nasal congestion and sinusitis can reduce the bioavailability of the nasal formulation. DDAVP is an ideal agent for rapid-onset, short-term use such as attendance at camp or going on a "sleepover." If the desire is for long-term therapy and if it is sufficiently effective short-term, a 3- to 6-month trial is reasonable. At the end of this period, the drug should be tapered off by 0.1 mg (oral) or 10 mcg (nasal) per month. Relapse is less likely with a tapered withdrawal compared to an abrupt discontinuation. Side effects to DDAVP are minor and infrequent.[31] The most serious complication, water intoxication, is extremely uncommon when DDAVP is used to treat enuresis, with only 50 reported cases.[31] However, electrolyte monitoring is recommended if intercurrent illness complicates the situation. Children should also not drink more than 8 ounces of fluid at dinnertime, 8 ounces in the evening, and none in the 2 hours prior to bed in order to reduce the risk of water intoxication.

Imipramine[32]

The tricyclic antidepressant (TCA) imipramine was first used in the treatment of enuresis in the 1960s. Although trials involving other TCAs have been performed over the years, there is insufficient evidence to assess the relative performance of these agents versus imipramine and the latter is considered the gold standard TCA in enuresis management. Its mechanism of action is unclear, although it is an anticholinergic and antispasmodic and may increase plasma ADH concentrations. Up to 80% of treated patients may respond, although the long-term continence rate is only about 25%. A patient can expect approximately one fewer wet night per week with imipramine use. As with DDAVP, benefit only occurs as long as the drug is being taken, with relapse rates after discontinuation of therapy of up to 50%. There is no significant correlation of drug concentration with response. If sufficiently effective short-term, a 4- to 6-month trial is reasonable, followed by a weaning-off period of 3 to 4 weeks. There is a high frequency of neurologic side effects in children, including lethargy, dizziness, and headache in 5%; irritability in 11%; anxiety in 10%; and sleep disturbances in 16%.[31] Gastrointestinal symptoms occur in about 25% of pediatric patients.[31]

Anticholinergics

Oxybutynin has no significant effect in monosymptomatic nocturnal enuresis. Oxybutynin and related agents (see adult UI section of this chapter) should be used only if the patient has concurrent daytime urgency or frequency.

Comparison of Therapies

Most of the comparisons between treatments have been made by means of meta-analyses conducted by the Cochrane Enuresis Collaborative.[28,30,32–34] Unfortunately, most enuresis treatment studies have been so poorly designed they compromise the

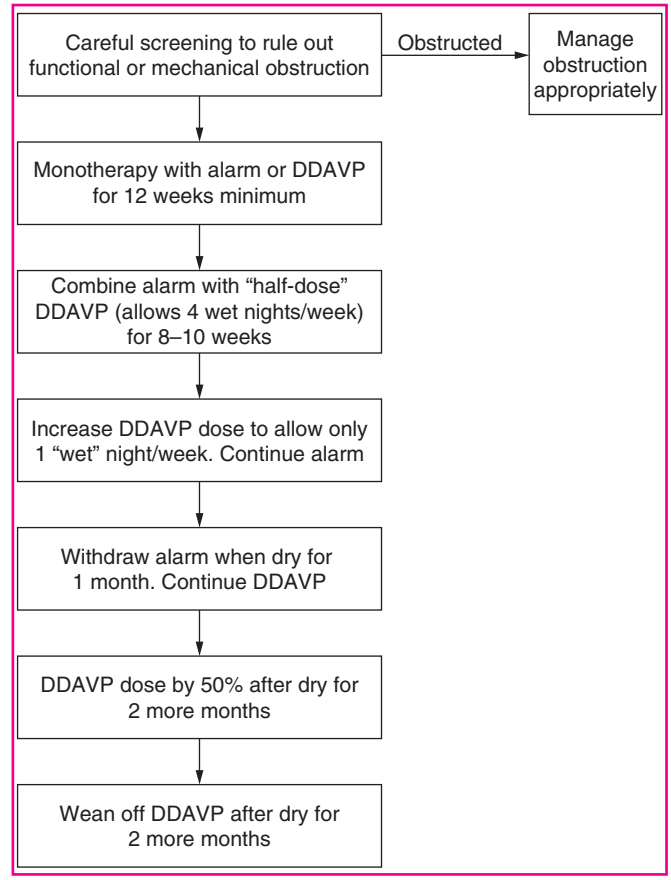


FIGURE 50–1. Preliminary (unvalidated) enuresis protocol proposed by the International Children's Continence Society (2004). DDAVP, desmopressin.

ability to pool studies for meta-analysis. With this in mind, the comparative efficacies of monotherapy and combination therapies using the best data available follow.

The most effective nonpharmacologic method is the use of bed alarms. Defining success as less than 1 wet night per month, the initial success rate for alarms is 66%, with long-term success after discontinuation occurring in 45% (versus 1% with no treatment). However, this method requires highly motivated families and the development of improvement is slow (over 4 to 12 or more weeks). Data are inadequate to compare the various commercial brands of alarms available to consumers or to compare alarms to other behavioral interventions. Supplementing this method with either overlearning or dry-bed training significantly reduces the already low relapse rates seen with alarms. Alarm therapy is also significantly more effective than DDAVP, evaluated at both the end of therapy and long-term. Similar findings are noted for the alarm-versus-imipramine comparison. There are conflicting data regarding the value of supplementing the alarm method with DDAVP. A preliminary algorithm utilizing a combination of alarm therapy and DDAVP for the treatment of pediatric enuresis has been formulated by the ICCS (Fig. 50–1).[25]

OUTCOME EVALUATION

- Monitor the patient for symptom relief. Have the desired outcomes jointly developed by the health care team, the patient, and his or her parents/guardians been achieved and to what degree? Evaluate the daily diary completed by the patient or parents/guardians since the last clinic visit and quantitate the clinical response (the number of dry nights versus the total number of nights, and the frequency of nights with greater than or equal to 2 enuresis episodes). If a diary has not been used, elicit the clinical response, in general terms, since the last visit.
- Elicit adverse events of therapy in a non-leading manner and ask the patient to judge their severity. Ask the patient or parents/guardians what measures if any were used to ameliorate them. Assess adherence (ask patient or parents/guardians about missed doses; do pill counts if the prescription vial is available).
- The balance of clinical response, tolerability, and burden on the family will dictate the approach to management. As most nonpharmacologic approaches are "all or none" and drug dosages after an initial titration period are fixed, the major decision process involves either changing therapy if clinical results are inadequate, or beginning or continuing tapering-off and discontinuation of therapy after success. There is no consensus on which approach to withdraw first, although the ICCS recommends the nonpharmacologic (alarm) therapy first, then pharmacologic (DDAVP) therapy.



Patient Care and Monitoring

1. Assess the patient's symptoms to determine if patient-directed therapy is appropriate or whether the patient should be evaluated by a physician. Assessment includes the types and severities of symptoms and the presence or absence of exacerbating factors. Does the patient have any enuresis-related complications?
2. Review any available diagnostic data to determine disease status.
3. Obtain a thorough medication history, including use of prescription, non-prescription, and complementary and alternative drug products. Determine which, if any, treatments in the past had been helpful as judged by the patient and/or caregiver(s). Could any of the patient's current medications be contributing to enuresis?
4. Educate the patient and/or caregiver(s) on lifestyle modifications that may improve symptoms or assist the clinician in monitoring the responses to therapy, including but not limited to, fluid restriction and journal keeping. The patient and/or caregiver(s) should be referred to local enuresis clinics (if available) for training in nonpharmacologic treatments such as use of bed alarms, overlearning, and dry-bed training.
5. Assess if the patient is taking the appropriate drug(s) for his or her enuresis? Are the doses appropriate?
6. Develop a plan to assess efficacy after a minimum of 3 months.
7. Assess changes in quality of life (physical, psychological, and social functioning and well-being).
8. Evaluate the patient for drug-related adverse events, allergies, and interactions (drug-drug and drug-disease).
9. Stress the importance of adherence with the prescribed regimen, including lifestyle modifications and nonpharmacologic treatment. Recommend the most "patient-friendly" treatment regimen possible.
10. Provide the patient and/or caregiver(s) with education regarding the disease state, lifestyle modifications, and drug therapy:
    - The causes of enuresis and what things the patient and/or caregiver(s) can do to reduce its frequency
    - Possible enuresis complications
    - Timing of medication intake
    - Potential adverse events (limit to most frequent and/or clinically relevant)
    - Potential drug-drug interactions.

ABBREVIATIONS

ADH:	antidiuretic hormone
BA:	bioavailability
CAM:	complementary and alternative medicine

CL:	total body clearance
CNS:	central nervous system
CrCl:	creatinine clearance
CVA:	costovertebral angle
CYP450:	cytochrome P-450
DDAVP:	desmopressin
DHIC:	detrusor hyperactivity with impaired contractility
ER:	extended-release
FDA:	Food and Drug Administration
ICCS:	International Children's Continence Society
IR:	immediate-release
LA:	long-acting
MESNA:	sodium 2-mercaptoethanesulfonate
OTC:	over-the-counter
OUI:	overflow urinary incontinence
PV:	per vagina
SNF:	skilled nursing facility
SR:	sustained-release
SUI:	stress urinary incontinence
TCA:	tricyclic antidepressant
TD:	transdermal
UI:	urinary incontinence
UTI:	urinary tract infection
UUI:	urge urinary incontinence

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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51 Allergic and Pseudoallergic Drug Reactions

J. Russell May and Philip H. Smith



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Describe the potential incidence of allergic and pseudoallergic drug reactions and why it is difficult to obtain accurate numbers.
2. Describe the Gell and Coombs categories of reactions.
3. Identify the classes of drugs associated most commonly with allergic and pseudoallergic reactions.
4. Recommend specific treatment for a patient experiencing anaphylaxis.
5. Recommend an approach to drug selection in patients with multiple drug allergies.
6. Describe drug desensitization procedures for selected drugs.

Key Concepts

❶ Allergic and pseudoallergic reactions represent 23.8% of reported adverse drug reactions, cause considerable morbidity and mortality, and are costly.

❷ Drug allergy is an adverse immune response to a stimulus; such responses traditionally are placed in the Gell and Coombs categories: type I (immediate hypersensitivity), type II (complement-mediated antibody reactions), type III (immune complex reactions), and type IV (cellular or delayed-type hypersensitivity). However, drug exposures may stimulate several or all of these types of reactions. To complicate the picture further, drug reactions do not always fit the categories.

❸ Reactions that resemble allergic reactions clinically but lack an immune basis have been referred to as pseudoallergic. They include almost the entire range of immediate hypersensitivity clinical patterns and range in significance from the alarming but trivial anxiety or vasovagal reactions caused by local dental anesthetics to the potentially fatal reactions to ionic radiocontrast media.

❹ Penicillins and cephalosporins both have a β-lactam ring joined to an S-containing ring structure (penicillins: a thiazolidine ring; cephalosporins: a dihydrothiazine ring). Because of their structural likeness, allerginicity between penicillins and cephalosporins occurs. However, because of their structural differences, the extent of cross-allergenicity between penicillins and cephalosporins appears to be relatively low. Cross-allergenicity is less likely with newer-generation cephalosporins than with the first-generation agents.

❺ Reactions to sulfonamide antibiotics, ranging from mild (most common) to life-threatening (rare), occur in 2% to 4% of healthy patients, with rates as high as 60% in patients with acquired immune deficiency syndrome (AIDS).

❻ IgE-mediated urticarial/angioedema reactions and anaphylaxis are associated with aspirin and non-steroidal anti-inflammatory drugs. Urticaria is the most common form of IgE-mediated reaction. This class is second only to β-lactams in causing anaphylaxis.

❼ Radiocontrast media may cause serious immediate pseudoallergic reactions such as urticaria/angioedema, bronchospasm, shock, and death. These reactions have been reduced with the introduction of non-ionic, lower-osmolality products.

❽ Opiates (e.g., morphine, meperidine, codeine, hydrocodone, and others) stimulate mast cell release directly, resulting in pruritus and urticaria with occasional mild wheezing. Although these reactions are not allergic, many patients state that they are "allergic" to one or more of the opiates. Pretreatment with an antihistamine may reduce these reactions. These pseudoallergic reactions are rarely life-threatening.

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❾ Drug desensitization is a potentially life-threatening procedure that requires continuous monitoring in a hospital setting with suitable access to emergency treatment and intubation. It should be undertaken only under the direction of a physician with suitable training and experience. In such hands, desensitization presents less risk than treatment failure with a less effective alternative medication.

Allergic and pseudoallergic drug reactions are reported together. They are rarely confirmed by testing, making statistical reporting imprecise, with both overreporting and underreporting. But there is no doubt that they are costly and cause considerable morbidity and mortality. ❶ *Allergic and pseudoallergic reactions may represent as many as 23.8% of reported adverse drug reactions.*[1] Between 10% and 15% of hospitalized patients incur drug reactions, with about a third possibly due to hypersensitivity; however, most allergic drug reactions are not reported.[1,3,4] Patients experiencing an allergic drug reaction require longer hospitalizations (close to 2 days) at a cost of more than $2,000 per day.[2] A potential financial burden can occur owing to the increased indirect cost of: (1) lost time and labor, (2) the use of costlier alternative medications, and (3) treatment failures. Outpatient rates are not well studied and are much more formidable to collect. Relying on a patient's history without an attempt to clarify the relationships between drugs taken and symptoms experienced results in a confusing scenario. Often, health care professionals and patients use the term "drug allergy" in such a general way that it is not useful medically and, further, perpetuates a level of fear and concern in the public and in medical practice that is inappropriate and costly. This same confusion often seems to lead medical personnel to ignore or forget "drug allergy" with sometimes catastrophic results. Clearly, an understanding of how allergic and pseudoallergic reactions occur and how they might be managed or prevented is important to health care professionals and their patients.

PATHOPHYSIOLOGY

Drug allergies are immune responses resulting from different methods of recognition and activation, and reactions are affected by multiple physiologic mechanisms. This produces a confusing spectrum of clinical pictures and complex pathophysiologic mechanisms. ❷ *Drug allergy is an adverse immune response to a stimulus; such responses traditionally are placed in the Gell and Coombs categories: type I (immediate hypersensitivity), type II (complement-mediated antibody reactions), type III (immune complex reactions), and type IV (cellular or delayed-type hypersensitivity). Drug exposures may stimulate several or all of these types of reactions, and drug reactions do not always fit neatly into the categories.*

The immune system uses many tools such as blood vessel dilation or constriction, causing fluid to flood an infected area, or designing special cells to kill bacteria or the infected cells in which they harbor. The pattern of these responses is either immediate and inborn (the innate immune response) or learned from previous infections and injuries (the adaptive immune response). Most drug reactions involve the adaptive response and certainly, in the sense that they cause more harm than good, are "mistakes."

T cells control these learned responses and decide which tools to use in the reaction. Sometimes they choose several different tools at once, and multiple reactions ensue, such as when a person becomes sensitized to penicillin and has not only **anaphylaxis** but hemolytic anemia and **serum sickness**. There are different types of T cells, and they communicate either directly with other cells or by chemical messages called **cytokines**. The pattern of cytokines released is one way T cells have of determining which kind of response will occur. They are broadly called Th1 and Th2 responses, with Th1 mostly responding to infections and Th2 often producing allergy or asthma.

Drug reactions generally represent T cell activation. The type of T cell activated determines the type of reaction to the drug. Th1 cytokines (largely interferon-γ) produce many more chronic (and at times serious) skin reactions and destruction of cells (as in hemolytic anemia or thrombocytopenia); sometimes these responses can damage tissues, such as the kidney (e.g., interstitial nephritis). Th2 cytokines tend to cause any antibodies produced to be switched to the immune globulin E (IgE) or allergic antibody class, which can result in hives or anaphylaxis. Other classes of antibodies are made frequently, and these can produce serum sickness or indirect destruction of cells (e.g., thrombocytopenia). T-cell receptors respond to one peptide only, which makes each activation response exclusive to the original stimulus (drug) or to chemical structures with very close resemblance.

Antigens

Antigen-presenting cells recognize complex three-dimensional protein molecules of at least 1000 daltons (Da) in size. Most drugs are much smaller than this and cannot be recognized on their own. Only proteins such as insulin or exogenous sera are identified and their peptides presented directly to T cells.

Drugs that are reactive chemicals may bond covalently to body proteins, altering them and forming large enough molecules for antigen-presenting cells to recognize. This process is called **haptenation**, and the smaller reactive molecule is called a hapten. Other drugs are inert until they are partially metabolized (prohaptens), and their breakdown products bind native proteins to serve as antigens. Metabolic variations in some patients may produce more active haptens or prevent these fragments from being detoxified, causing them to accumulate and make binding proteins more likely.

Gell and Coombs

Type I reactions occur when the drug or its bound hapten incites an IgE antibody response. IgE binds to high-affinity receptors on mast cells and basophils. When the original antigen cross-links the cell-bound IgE, the effector cell releases enormous amounts of preformed mediators, producing the

well-known symptoms of immediate hypersensitivity: **urticaria,** rhinitis, bronchoconstriction, and anaphylaxis.

Type II reactions are produced by IgG (or IgM) antibody. The drug or hapten that elicited the antibody response binds to target cells. When antibody binds the drug, complement activation destroys the cell. **Blood dyscrasias** such as thrombocytopenia and hemolytic anemia are the most common examples of type II reactions.

Type III or immune complex reactions also involve IgG antibody production. In this case, when the concentration of the sensitizing drug or hapten is in slight excess to the antibody, the two combine in the serum, producing lattices of antigen-antibody complexes. These are deposited, particularly in vessel walls. They activate complement, causing vasculitis. The classic forms of type III reactions are serum sickness (usually including arthralgias, fever, malaise, and urticaria that develop 7 to 14 days after exposure to the causative antigen) and the localized **Arthus reaction,** a local inflammatory response owing to the deposition of immune complexes in tissues.

Type IV reactions are mediated by T cells themselves. Delayed-type hypersensitivity reactions from positive tuberculin tests to contact dermatitis are typical type IV reactions, but understanding T-cell function allows us to further define this category, as shown in Table 51–1.

Pseudoallergic Drug Reactions

❸ *Reactions that resemble allergic reactions clinically but lack an immune basis have been referred to as pseudoallergic. They include almost the entire range of immediate hypersensitivity clinical patterns. Pseudoallergic reactions range in significance from the alarming but trivial anxiety or vasovagal reactions caused by local dental anesthetics to sometimes fatal reactions to ionic radiocontrast media.* Cytotoxic reactions, serum sickness, and severe dermatologic reactions (e.g., Stevens-Johnson syndrome and **toxic epidermal necrolysis**) are immunologic processes that are not likely to be mimicked by non-immune processes seen with pseudoallergic reactions.

Pseudoallergic reactions are important in patient counseling and management considerations. The reactions represent common biologic functions [e.g., direct histamine (H) release by vancomycin and opiates], whereas immunologic (allergic) reactions are based on the structure of the drug. Even a mild drug allergy carries significant potential for anaphylaxis on readministration. In contrast, pseudoallergic reactions tend to remain constant whether mild or severe.

Pseudoallergic reactions, then, are reactions where the tools of the immune system are used in exactly the same way as true allergic reactions but without the "learning" response by T cells and generally without the much greater danger that true immunologic sensitization implies. Pseudoallergic reactions may be thought of as a sub-type of idiopathic reactions rather than an activation of the patient's immune system with all its potential for change and variety of adverse responses. The pathophysiology of pseudoallergic reactions generally is unknown, but indicators of immune activation are not seen when they occur.



Clinical Presentation and Diagnosis

The clinical presentation of a patient experiencing an allergic reaction varies greatly. The primary reactions are as follows:

Anaphylaxis
Anaphylaxis is an acute life-threatening allergic reaction. Signs and symptoms involve the skin (e.g., pruritus and urticaria), respiratory tract (e.g., dyspnea and wheezing), gastrointestinal tract (e.g., nausea and cramping), and cardiovascular system (e.g., hypotension and tachycardia). Onset is usually within 30 minutes but can be as long as 2 hours. Treatment for anaphylaxis must begin immediately. Anaphylaxis may recur 6 to 8 hours after exposure, so patients experiencing anaphylaxis should be observed for at least 12 hours.

Cytotoxic Reactions
These reactions usually take the form of hemolytic anemia, thrombocytopenia, granulocytopenia, or agranulocytosis.

Immune Complex Reactions
These reactions involve a serum sickness like syndrome (e.g., arthralgias, fever, malaise, and urticaria) that usually develops 7 to 14 days after exposure to the causative antigen.

Dermatologic Reactions
Rashes may range from mild to life-threatening.

- *Urticaria*—itchy, raised, swollen areas on the skin, also known as *hives*.
- *Maculopapular rash*—a rash that contains both macules and papules. A macule is a flat discolored area of the skin, and a papule is a small raised bump. A maculopapular rash is usually a large area that is red and has small, confluent bumps.
- ***Erythema multiforme***—a rash characterized by papular (small raised bump) or vesicular lesions (blisters) and reddening or discoloration of the skin often in concentric zones about the lesion.
- ***Stevens-Johnson syndrome***—a severe expression of erythema multiforme (also known as *erythema multiforme major*). It typically involves the skin and the mucous membranes with the potential for severe morbidity and even death.
- *Toxic epidermal necrolysis*—a life-threatening skin disorder characterized by blistering and peeling of the top layer of skin.

PROBLEMATIC DRUG CLASSES AND TREATMENT OPTIONS

The first priority when caring for patients with an allergic reaction is to avoid doing serious harm by administering a drug that the patient cannot tolerate. We can establish the likelihood of a relationship between the suspected drug and

TABLE 51–1. Reaction Classification, Clinical Symptoms, and Potential Causative Drugs[5,6]

Gell and Coombs Classification	Immune Response	Clinical Symptoms	Potential Causative Drugs[a]
Type I	IgE	Anaphylaxis, urticaria	β-Lactam antibiotics: penicillins (primarily), cephalosporins, carbapenems Non-β-lactam antibiotics: sulfonamides, vancomycin Others: insulin, heparin
Type II	IgG	Hemolytic anemia, thrombocytopenia	Quinidine, methyldopa, penicillins, heparin
Type III	IgG and IgM	Vasculitis, serum sickness, lupus	Penicillins, sulfonamides, radiocontrast agents, phenytoin
Type IV			β-Lactam antibiotics, sulfonamides, and phenytoin
IVa	Th1 cytokines	Tuberculin reaction, eczema	
IVb[b]	Th2 cytokines	Maculopapular and bullous exanthema	
IVc[b]	Cytotoxic T cells (CD4 and CD8)	Same as IVb, also eczema, pustular exanthema	
IVd	T cells (IL-8)	Pustular exanthema	

[a]These drugs represent a list of likely causative agents. Many drugs can cause these reactions.
[b]IVb and IVc reactions may combine to produce erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

the observed reaction and also whether it is likely to be an immune or idiopathic reaction by examining the time course and specific signs and symptoms as precisely and objectively as possible. Re-evaluating the patient's physical examination and laboratory values (taking into account preexisting diseases) allows further clarification of the need to change treatments and to add therapy for the reaction itself.

Reviewing the original indications for the treatment that caused the reaction is important. For example, in many respiratory illnesses, a prescribed antibiotic may be unnecessary. If the disease persists and indications for some treatment are established, alternatives must be sought either by adjusting dose or administration rate, finding effective and unrelated alternative medication, or desensitizating the patient to the original drug.

When drug reactions occur, the health care provider should carefully describe the nature of the reaction and the potential for it to reoccur. Many patients have frightening associations of the term "allergy" with severe and unpredictable anaphylaxis. It is difficult to undo the fears and behaviors created by injudicious labeling of someone as allergic in the medical record. Labeling a person as allergic may hamper future medical care because patients who are labeled allergic to a certain medication simply may refuse treatment or fail to adhere to regimens containing the offending medication. If documentation clearly describes the original reaction, health care providers can appropriately counsel patients about any true dangers.

Managing patients experiencing an allergic reaction begins with stopping the offending agent. Anaphylaxis is a true medical emergency and must be treated promptly. Understanding the allergic reaction and potential for **cross-allergenicity** between similar drugs will assist in selecting an alternative medication. Desensitization is a management option if the patient truly needs the medication and alternative drugs are not acceptable. While any drug can cause an allergic or pseudoallergic reaction, several drugs and drug classes are strongly associated with such reactions. These drugs and drugs classes include β-lactam antibiotics, sulfonamide antibiotics, aspirin and non-steroidal anti-inflammatory drugs (NSAIDS), radiocontrast media, opiates, cancer chemotherapeutics agents, insulin, and anticonvulsants.

β-Lactam Antibiotics

Hypersensitivity reactions with β-lactam antibiotics, especially penicillin, may encompass any of the type I through IV Gell-Coombs classifications. The most common reactions are **maculopapular** and urticarial eruptions.[7] While rare (less than 0.05%), anaphylaxis to penicillins causes the greatest concern because they are responsible for the majority of drug-induced anaphylaxis deaths in patients, accounting for 75% of all anaphylaxis cases in the United States.[5,8] The treatment of anaphylaxis is given in Table 51–2.[9]

The health care professional is faced with a difficult task when approaching a patient who claims a history of penicillin allergy. While as many as 12% of hospitalized patients state that



Patient Encounter 1

JB, a 44-year-old man, is admitted to the hospital for treatment of a cellulitis. He states that he has no known allergies. JB is prescribed intravenous nafcillin for his infection. During the first infusion, he notices that his ears are itching, and he calls for a health care practitioner. On the practitioner's arrival, JB appears nervous and is having difficulty breathing.

- What type of allergic reaction is JB most likely having?
- What is the first action that this practitioner should take?
- Outline the medical treatment for JB's reaction and when the medical treatment should start.

TABLE 51–2. Pharmacologic Management of Anaphylactic Reactions[9]

Immediate Intervention

Epinephrine 1:1000 (1 mg/mL)
- *Adults:* Give 0.2–0.5 mg intramuscularly (IM) or subcutaneously (SC); repeat every 5 minutes as needed
- *Children:* 0.01 mg/kg (maximum 0.3 mg) IM or SC; repeat every 5 minutes as needed

Subsequent Interventions

Normal saline infusion
- *Adults:* 1 to 2 L at a rate of 5–10 mL/kg in the first 5 minutes, followed by slow infusion
- *Children:* Up to 30 mL/kg in the first hour

Epinephrine infusion

If patient is NOT responding to epinephrine injections and volume resuscitation:
- *Adults:* Epinephrine infusion [1 mg in 250 mL dextrose 5% in water (D_5W)]: 1–4 mcg/minute, titrating based on clinical response or side effects
- *Children:* Epinephrine 1:10,000 (0.1 mg/mL): 0.01mg/kg (up to 0.3 mg) over several minutes

Other Considerations after Epinephrine and Fluids

Diphenhydramine
- *Adults:* 25–50 mg intravenously (IV) or IM
- *Children:* 1–1.25 mg/kg (maximum of 300 mg/24 hours)

Ranitidine
- *Adults:* 50 mg in D_5W 20 mL IV over 5 minutes
- *Children:* 1 mg/kg (up to 50 mg) in D_5W 20 mL IV over 5 minutes

Inhaled albuterol (bronchospasm resistant to epinephrine)

2–5 mg in 3 mL of normal saline, nebulized, repeat as needed

Dopamine (hypotension refractory to fluids and epinephrine)

2–20 mcg/kg per minute titrated to maintain systolic blood pressure greater than 90 mm Hg

Hydrocortisone (severe or prolonged anaphylaxis)
- *Adults:* 250 mg IV (prednisone 20 mg can be given orally in mild cases)
- *Children:* 2.5–10 mg/kg per 24 hours

D_5W, dextrose 5% in water; IM, intramuscular; IV, intravenous; SC, subcutaneous.

TABLE 51–3. Procedure for Performing Penicillin Skin Testing

A. Percutaneous (prick) skin testing

MATERIALS	VOLUME
Pre-Pen[a] 6×10^6 M	1 drop
Penicillin G 10,000 units/mL	1 drop
β-Lactam drug 3 mg/mL	1 drop
0.03% albumin-saline control	1 drop
Histamine control (1 mg/mL)	1 drop

1. Place a drop of each test material on the volar surface of the forearm.
2. Prick the skin with a sharp needle inserted through the drop at a 45° angle, gently tenting the skin in an upward motion.
3. Interpret skin responses after 15 minutes.
4. A wheal at least 2 × 2 mm with erythema is considered positive.
5. If the prick test is non-reactive, proceed to the intradermal test.
6. If the histamine control is non-reactive, the test is considered uninterruptible.

B. Intradermal skin testing

MATERIALS	VOLUME
Pre-Pen[a] 6×10^6 M	0.02 mL
Penicillin G 10,000 units/mL	0.02 mL
β-Lactam drug 3 mg/mL	0.02 mL
0.03% albumin-saline control	0.02 mL
Histamine control (0.1 mg/mL)	0.02 mL

1. Inject 0.02–0.03 mL of each test material intradermally (amount sufficient to produce a small bleb).
2. Interpret skin responses after 15 minutes.
3. A wheal at least 6 × 6 mm with erythema and at least 3 mm greater than the negative control is considered positive.
4. If the histamine control is non-reactive, the test is considered uninterruptible.

Antihistamines may blunt the response and cause false-negative reactions.

[a]Pre-Pen is not currently commercially available. The product is anticipated to return to the market in the near future. Until it is available, skin testing is not recommended.

they have an allergy to penicillin, about 90% will have negative skins tests.[10] Table 51–3 shows the traditional regimen for penicillin skin testing.[11] However, Pre-Pen is not commercially available at this time. The product is anticipated to return to the market in the near future. Until it is available, skin testing is not recommended. This test only determines IgE-mediated reactions. A patient with a history of other serious reactions such as erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis should not receive penicillins.

❹ *Penicillins and cephalosporins both have a β-lactam ring joined to an S-containing ring structure (penicillins: a thiazolidine ring; cephalosporins: a dihydrothiazine ring). Because of their structural likeness, allerginicity between penicillins and cephalosporins occurs. However, because of their structural difference, the extent of cross-allergenicity between penicillins and cephalosporins appears to be relatively low. Cross-allergenicity is less likely with newer-generation cephalosporins than with the first-generation agents.* Anaphylactic reactions to cephalosporins are rare, with a predicted range of 0.0001% to 0.1%. Minor skin reactions, including urticaria, **exanthem**, and pruritus, are the most common allergic reactions to cephalosporins, with severe reactions seen less often than with penicillins.[13] If a patient has a history of penicillin allergy but a penicillin skin test is negative, a cephalosporin may be given. If the test is positive, an alternative drug should be selected.

For other β-lactam agents, the recommendations are fairly straightforward.[9] Carbapenems should be considered cross-reactive with penicillins. Monobactams (e.g., aztreonam) do not cross-react with any β-lactam drugs except ceftazidime because they share an identical R-group side chain.

Sulfonamide Antibiotics

Sulfonamides are compounds that contain a sulfonamide moiety (i.e., SO_2NH_2). This group includes sulfonamide antibiotics, furosemide, thiazide diuretics, sulfonylureas, and celecoxib. The sulfonamide antibiotics contain an aromatic amine at the

N-4 position and a substituted ring at the N-1 position. Because of this different chemical structure, cross-allergenicity with the other sulfonamides may not occur. However, because this has not been well studied, if a patient has a reaction to a sulfonamide antibiotic, whether or not he or she will have a reaction to these other sulfonamides remains controversial. Predisposition to allergic reactions is a more likely reason than cross-reactivity between these differing molecules.[14] The sulfonamide antibiotics are significant because they account for the largest percentage of antibiotic-induced toxic epidermal necrolysis and Stevens-Johnson syndrome cases.[15]

❺ *Reactions to sulfonamide antibiotics, ranging from mild (most common) to life-threatening (rare), occur in 2% to 4% of healthy patients, with rates as high as 60% in patients with acquired immune deficiency syndrome (AIDS).*[7] Anaphylaxis or **anaphylactoid** reactions occur within 30 minutes, most commonly after parenteral administration. Isolated **angioedema** or urticaria can occur within minutes to days. Serum sickness occurs within 1 to 2 weeks. Fixed drug eruptions (lesions) occur within a half-hour to 8 hours. These lesions resolve within 2 to 3 weeks after drug removal. The more severe conditions of Stevens-Johnson syndrome and toxic epidermal necrolysis occur 1 to 2 weeks after initiation of therapy. Because trimethoprim-sulfamethoxazole is the drug of choice for patients infected with *Pneumocystis carinii*, desensitization may be necessary. A history of Stevens-Johnson syndrome or toxic epidermal necrolysis is an absolute contraindication to the desensitization procedure.

TABLE 51–4. Multiple Antibiotic Allergies: Obtaining Background Information[15]

For ***each*** antibiotic the patient claims to be allergic to, gather the following information:

- What type of infection was being treated?
- Have you ever received the drug without experiencing a reaction?
- How many times have you received the drug and experienced a reaction?
- What was the drug dose and route of administration with the last reaction?
- How many doses did you take before the onset of the last reaction?
- How many doses did you take after the last reaction?
- Can you describe the adverse reaction?
- What was the duration of the reaction?
- What treatment was given for the reaction?
- Was there any permanent damage?

For ***each*** antibiotic that the patient has received and does not claim to be "allergic" to, gather the following information:

- What was the last type of infection being treated?
- What was the drug dose and route of administration?
- Have you received this drug more than once without reactions?

Other information to be gathered:

- Have you had adverse reactions to any other drugs? If so, give dates and describe the reaction.
- Document any risk factors for allergic reactions such as chronic urticaria, liver or kidney disease, human immunodeficiency virus, or any other immune deficiencies.

Patients with Multiple Antibiotic Allergies

Dealing with patients who claim to have multiple antibiotic allergies can be challenging. Combining knowledge of cross-allergenicity with a careful assessment of patient history may be helpful in designing an antimicrobial regimen. Table 51–4 outlines a series of questions that can be useful in developing an effective treatment plan.[16] If available, skin testing may be useful to complete the puzzle. Often, an antibiotic of choice may be used when the patient's initial history would have suggested otherwise (i.e., patient's initial history suggests the patient has an allergy to the medication). Based on data gathered, the patient's record should reflect: antibiotics that are safe to use if needed, antibiotics to be avoided, and antibiotics that can be used only after desensitization. While this table was designed with antibiotics in mind, it can be modified for any allergy situation or multiple allergy situations.

Aspirin and Non-steroidal Anti-Inflammatory Drugs

Aspirin and NSAIDs can induce allergic and pseudoallergic reactions. Because these drugs are used so widely, with much over-the-counter use, the health care professional must have a basic understanding of the types of reactions that can occur and how to prevent them. Three types of reactions occur: bronchospasm with rhinoconjunctivitis, urticaria/angioedema, and anaphylaxis. Remember that patients with gastric discomfort or bruising from these agents may describe themselves as being allergic; however, these are not allergic or pseudoallergic reactions.

Two specific conditions, aspirin-exacerbated respiratory disease (AERD) and chronic idiopathic urticaria, are important because they are seen commonly. AERD consists of asthma, rhinitis with nasal polyps, and aspirin sensitivity.[17] On exposure to aspirin or an NSAID, patients experience rhinorrhea, nasal congestion, conjunctivitis, laryngospasm, and asthma. Chronic idiopathic urticaria is a major risk factor for aspirin- or NSAID-induced pseudoallergic reactions.[18] Patients with a history of chronic idiopathic urticaria are likely to see a flare of urticaria if aspirin or a cyclooxygenase (COX)-1-inhibiting NSAID is given. Cross-reactions between aspirin and older COX-1-inhibiting NSAIDs exist in patients with AERD and chronic idiopathic urticaria. Even though product warning labels for COX-2 inhibitors state that these agents should not be used in these two conditions, there are no reports of cross-reactivity in AERD and only rare reports in patients with chronic idiopathic urticaria.[19]

❻ *IgE-mediated urticarial/angioedema reactions and anaphylaxis are associated with aspirin and NSAIDs. Urticaria is the most common form of IgE-mediated reaction. This class is second only to β-lactams in causing anaphylaxis.* The potential for cross-reactivity between agents in IgE-mediated reactions appears small, but caution is advised. Because aspirin therapy is highly beneficial in primary and secondary prevention in

coronary artery disease (CAD), aspirin desensitization should be considered in patients who have had reactions to aspirin. Desensitization is contraindicated in patients who have experienced aspirin-induced anaphylactoid reaction, hypotension, tachypnea, or altered consciousness. Alternate agents must be used. A comprehensive approach to aspirin-sensitive patients with CAD has been described.[20]

Radiocontrast Media

❼ *Radiocontrast media may cause serious immediate pseudoallergic reactions such as urticaria/angioedema, bronchospasm, shock, and death. These reactions have been reduced with the introduction of non-ionic, lower-osmolality products.* Because a small percentage of patients who have reacted previously to radiocontrast media will react if re-exposed, several steps should be taken to prevent reactions, including:

- Determine if the study is necessary.
- Be sure that the patient understands the risks.
- Ensure adequate hydration.
- Use non-ionic, lower osmolarity agents.
- Pretreat with prednisone 50 mg orally 13, 7, and 1 hour before the procedure and diphenhydramine 50 mg orally 1 hour before the procedure.

These steps also should be followed in patients with high risk factors: asthmatic patients, patients on β-blockers, and patients with cardiovascular disease.[5]

Delayed reactions with radiocontrast media occur in 1% to 3% of patients.[21] Although reactions occasionally are severe, most are mild and manifest as maculopapular rashes, fixed eruptions, erythema multiforme, and urticarial eruptions.

Opiates

❽ *Opiates (e.g., morphine, meperidine, codeine, hydrocodone, and others) stimulate mast cell release directly, resulting in pruritus and urticaria with occasional mild wheezing. Although these reactions are not allergic, many patients state that they are "allergic" to one or more of the opiates. Pretreatment with an antihistamine may reduce these reactions. These pseudoallergic reactions are rarely life-threatening.*[5] Patients also may state they are allergic if they have experienced gastrointestinal upset, a common side effect to opiates, with previous exposures. Obtaining a thorough history from the patient will prove useful. If a more serious reaction has occurred, a non-narcotic analgesic should be selected.

Cancer Chemotherapeutic Agents

Hypersensitivity reactions have occurred with all cancer chemotherapeutic agents. Reactions are most common with the taxanes, platinum compounds, asparaginases, and epipodophyllotoxins.[7] Reactions range from mild (e.g., flushing and rashes) to severe (e.g., dyspnea, bronchospasm, urticaria, and hypotension). IgE-mediated type I reactions are the most common. To reduce the risk, patients are routinely pre-medicated with corticosteroids and H_1 and H_2 receptor antagonists. The platinum compounds have produced anemia, probably via a cytotoxic immunologic mechanism.

Insulin

Allergic reactions to insulin include erythema, pruritus, and indurations,[22] which usually are transient. For the more troublesome reactions, treatment options include dexamethasone, desensitization, or change in delivery system (i.e., insulin pump or inhaled insulin).

Anticonvulsants

A life-threatening syndrome can occur following a few weeks of therapy with anticonvulsants, such as phenytoin, phenobarbital, and carbamazepine. Symptoms include fever, a maculopapular rash, generalized lymphadenopathy, and varying degrees of internal organ dysfunction. The rash may be mild at first but can progress to **exfoliative dermatitis.** The causative agent should be withdrawn immediately. Valproic acid, gabapentin, and lamotrigine may be acceptable alternatives.[5]

Drug Desensitization

Drug desensitization may be undertaken in the absence of useful alternative medications. The risk of severe systemic reactions and anaphylaxis associated with desensitization must be compared with the risk of not treating the patient. Thorough evaluation should establish that the drug probably caused the reaction by an



Patient Encounter 2

CS, a 55-year-old woman, is admitted to the hospital with an intraabdominal infection. During the patient interview, CS states that she is allergic to aspirin, codeine, sulfa drugs, penicillin, levofloxacin, and vancomycin. The reactions are described as follows:
Aspirin: Easy bruising.
Codeine: Upset stomach and itching after one dose.
Sulfa drugs: Mild rash occurred 2 hours after taking a double-strength trimethoprim-sulfamethoxazole tablet prescribed for a urinary tract infection.
Penicillin: Rash, itching, and shortness of breath.
Levofloxacin: Upset stomach.
Vancomycin: Burning sensation when the drug was infused.

- Based on CS's descriptions, which of the reactions represents an allergic or pseudoallergic reaction?
- Which medications would you want CS to avoid based on her history?
- What further questions would be useful to ask CS before developing a care plan?
- If narcotic analgesics are required to treat CS, what medication may be helpful as a pretreatment?

allergic mechanism. Because of the dangers involved with drug desensitization, a diagnostic evaluation of the patient's indication for the drug should be conducted. Consider the possibility that the patient does not really need the drug.

❾ *Drug desensitization is a potentially life-threatening procedure that requires continuous monitoring in a hospital setting with suitable access to emergency treatment and intubation if required. It should be undertaken only under the direction of a physician with suitable training and experience. In such hands, desensitization presents less risk than treatment failure with a less effective alternative medication.* The possibility of readministering a suspected drug may be safely tested by gradual dose escalation in most cases, and there are certainly many more patients who are harmed by inappropriately withholding medications than there are those who suffer significant harm from testing and desensitization.[23]

Only type I IgE-mediated allergy may be treated by classic desensitization. Most protocols achieve desensitization within hours to a few days, unlike specific immunotherapy injections for inhalant allergy (i.e., "allergic shots," which may take months of therapy before a patient realizes any benefit). The mechanism of drug desensitization is poorly understood but produces temporary drug-specific tolerance of the offending drug. Any interruption of therapy of 24 hours or more requires full repeat desensitization, and abrupt, significant increases in dosage have been reported to break through the tolerance.

The process probably involves either: (1) cross-linking small subthreshold numbers of bound IgE molecules gradually depleting mast cells of their mediators, or (2) binding of the IgE by monomers or hapten-protein entities that cannot cross-link the antibody. The low doses used at the beginning of all protocols would provide small amounts of antigen, favoring these mechanisms. Both drug-specific IgE and IgG serum concentrations increase after successful desensitization, but skin-test positivity generally decreases.[24]

Oral and intravenous protocols are available for most drugs in this category, with the oral route producing somewhat milder reactions and the intravenous route providing more precision in dosing. Intravenous administration also can be used in unresponsive patients in whom the oral route is not feasible. Protocols generally begin at about 1% of the therapeutic dose and increase in intervals defined by the patient's reaction and the distribution and metabolism of the drug itself. Half-$\log_{10}$ dose increases (about three-fold) are often tolerated.

Penicillin desensitization is the most common drug desensitization protocol and is required for penicillin-allergic patients when penicillin is clearly the best treatment option, e.g., when syphilis is present in pregnancy. Protocols have been adapted to most antibiotics. Tables 51–5 and 51–6 describe procedures for oral and intravenous penicillin desensitization.[25]

Aspirin desensitization is useful in diseases where low-level antiplatelet action is needed and in the care of patients with aspirin sensitivity and intractable nasal polyps. Lysine aspirin availability in Europe allows desensitization by inhalation at greatly reduced risk. As with all desensitizations, constant daily administration must be maintained once the desired dose is reached. Table 51–7 summarizes several similar aspirin desensitization protocols.[26] Table 51–8 depicts a 2-day alternative protocol.[27]

All desensitization procedures are expected to produce mild symptoms in the patient at some point, and the patient

TABLE 51–5. Protocol for Oral Penicillin Desensitization[25]

	Phenoxymethyl Penicillin			
Step	Concentration (units/mL)	Volume (mL)	Dose (units)	Cumulative Dose (units)
1	1000	0.1	100	100
2	1000	0.2	200	300
3	1000	0.4	400	700
4	1000	0.8	800	1500
5	1000	1.6	1600	3100
6	1000	3.2	3200	6300
7	1000	6.4	6400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1	80,000	176,700
12	80,000	2	160,000	336,700
13	80,000	4	320,000	656,700
14	80,000	8	640,000	1,296,700
Observe for 30 minutes				
15	500,000	0.25	125,000	
16	500,000	0.5	250,000	
17	500,000	1	500,000	
18	500,000	2.25	1,125,000	

TABLE 51–6. Parenteral Penicillin Desensitization Protocol[25]

Injection No.	Benzylpenicillin Concentration (units)	Volume (mL)	(Route)
1	100	0.1	ID
2	100	0.2	SC
3	100	0.4	SC
4	100	0.8	SC
5	1000	0.1	ID
6	1000	0.3	SC
7	1000	0.6	SC
8	10,000	0.1	ID
9	10,000	0.2	SC
10	10,000	0.4	SC
11	10,000	0.8	SC
12	100,000	0.1	ID
13	100,000	0.3	SC
14	100,000	0.6	SC
15	1,000,000	0.1	ID
16	1,000,000	0.2	SC
17	1,000,000	0.2	IM
18	1,000,000	0.4	IM
19	Continuous IV infusion at 1,000,000 units/hour		

ID, intradermal; IM, intramuscular; SC, subcutaneous.

TABLE 51–7. Oral Aspirin Desensitization Protocols[26]

Dose Increments (mg)	Dose Interval	Cumulative Dose (mg)
30, 60, 100, 325, 600	2 hours	1115
1, 10, 50, 100, 300	30–40 minutes	461
1, 10, 50, 100, 500	60 minutes	661
30, 60, 120, 300, 600	2 hours	1110
10, 20, 50, 80, 150, 300	30 minutes	610
30, 60, 125, 250, 500	60 minutes	965

should be warned of this before doses are started. Mild sensitivity to the drug still remains, and large dose increases as well as missing doses should be avoided. Late complications, such as urticaria, may occur with type I desensitization, and serum sickness or hemolytic anemia also may occur with high-dose therapy in allergic, desensitized patients.

Some regimens are designed for outpatient administration over much longer time periods and have been used, for example, with allopurinol dermal reactions. Such late-onset morbiliform reactions, sometimes overlapping with erythema multiforme minor, are difficult to evaluate because it is often unclear to what extent the patients were at risk for recurrent reaction.

Severe life-threatening reactions not mediated by IgE, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, are absolute contraindications to testing, desensitization attempts, and readministration.

OUTCOME EVALUATION

To treat a patient with a drug allergy or pseudoallergy successfully, several goals must be accomplished:

- Identify and quickly manage a reaction if one occurs.
- Educate the patient about the reaction.
- Avoid true drug contraindications if at all possible.
- Ensure that patients receive the medications they need or a suitable alternative.
- A suitable alternative may be drug desensitization.
- Monitor patients for adverse drug reactions.

TABLE 51–8. Oral Aspirin Desensitization Protocol[27]

Day 1		Day2	
Doses (mg)[a]	Cumulative Dose (mg)	Doses	Cumulative Dose (mg)
30	30	150	330
60	90	325	655
90	180	650	1305

[a]Doses administered every 3 hours, patient observed for 3 hours after final dose.



Patient Encounter 3

RM, a 50-year-old man, is visiting the clinic for a routine check-up. Pertinent findings are as follows:

PMH
- Hypertension diagnosed 5 years ago, currently controlled
- Seasonal allergic rhinitis

FH
- Father died of myocardial infarction at age 59.
- Grandfather died of a stroke at age 62.

SH
- Smokes less than one pack per day.
- Drinks one glass of red wine daily.

Meds
- Hydrochlorothiazide 25 mg orally once daily
- Atenolol 50 mg once daily
- Fluticasone nasal spray, one spray in each nostril daily during allergy season
- Loratadine 10 mg daily during allergy season

Allergies: History of urticaria after taking aspirin for headaches

- Based on RM's history, is he a candidate for daily aspirin therapy?
- If so, is RM a candidate for aspirin desensitization? Why or why not?



Patient Care and Monitoring

1. Before administering any medication, take a thorough drug history to establish any past allergic or adverse reactions experienced by the patient.
2. For any reaction, use questions given in Table 51–4 to establish the nature of the reaction and the likelihood that it was caused by the suspected drug. For non-antibiotics, the first question regarding infection type is not needed.
3. Document the reaction, in detail, in the patient's medical record.
4. Recommend an alternative choice if the prescribed drug is contraindicated, and develop a plan to assess safety and effectiveness.
5. Consult with a physician trained in desensitization if the patient has a true allergy and no acceptable alternative medication is available.
6. Educate the patient about the allergy or pseudoallergy so that he or she is able to work with health care providers to avoid the reaction in the future.

ABBREVIATIONS

AERD:	aspirin-exacerbated respiratory disease
AIDS:	acquired immune deficiency syndrome
CAD:	coronary artery disease
COX:	cyclooxygenase
D_5W:	dextrose 5% in water
Da:	daltons
H (H_1, H_2):	histamine
ID:	intradermal
Ig:	immune globulin (followed by the specific type of immune globulin: E, G, or M)
IM:	intramuscular
IV:	intravenous
NSAIDs:	non-steroidal anti-inflammatory drugs
SC:	subcutaneous

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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52 Solid-Organ Transplantation

Steven Gabardi and Ali J. Olyaei



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Describe common reasons for the various solid-organ transplants.
2. Differentiate between the functions of cell-mediated and humoral immunity and how they relate to organ transplantation.
3. Describe the roles of the antigen-presenting cells in initiating the immune response.
4. Compare and contrast the types of rejection, including hyperacute, acute, chronic, and humoral.
5. Define the terms "host-graft adaptation" and "tolerance," paying close attention to their differences.
6. Discuss the desired therapeutic outcomes and appropriate pharmacotherapy used to avoid allograft rejection.
7. Compare and contrast the currently available immunosuppressive agents in terms of mechanisms of action, adverse events, and drug-drug interactions.
8. Design an appropriate therapeutic regimen for the management of immunosuppressive drug complications based on patient-specific information.
9. Develop a therapeutic drug-monitoring plan to assess both the effectiveness and the adverse events of immunosuppressive drugs.

Key Concepts

❶ T cells are the chief components initiating the immune response against the allograft. The activity of T cells is mediated largely through the synthesis and release of interleukin-2 (IL-2).

❷ An antigen-presenting cell (APC) is a cell that displays a foreign antigen complex with Major Histocompatibility Complex (MHC) on its cell surface. Its major responsibility is to present these foreign antigens to T cells. There are three main types of APCs: dendritic cells, macrophages, and activated B cells.

❸ The goal of pharmacotherapy in transplantation is to induce immunosuppression with a multidrug approach to target various parts of the immune system with resulting long-term allograft and patient survival while minimizing the complications of suppressing the immune system.

❹ The goal of induction therapy is to provide a high level of immunosuppression in the critical early posttransplant period when the risk of acute rejection is highest.

❺ The calcineurin inhibitors cyclosporine and tacrolimus block T cell activation by inhibiting the production of IL-2. They are associated with significant adverse events, such as nephrotoxicity, cardiovascular disease, posttransplant diabetes, and neurotoxicity.

❻ The antiproliferatives azathioprine and the mycophenolic acid derivatives inhibit T cell proliferation. Myelosuppression is the most significant adverse event associated with these agents.

❼ Sirolimus, a target of rapamycin inhibitor, works by decreasing the ability of T cells to respond to IL-2. The major adverse events associated with sirolimus are decreased wound healing, hyperlipidemia, and myelosuppression. This agent appears to have promising effects because it may allow calcineurin inhibitor withdrawal in some patients.

❽ Corticosteroids induce a non-specific immunosuppresion. Owing to their overwhelming incidence of adverse events, many practitioners attempt to use low-dose maintenance therapy or, in some cases, complete steroid withdrawal. Corticosteroids are also effective in reversing acute rejection.

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⑨ Obtaining excellent long-term patient and allograft survival is difficult owing to complications from drug-drug interactions with the immunosuppressive agents, infectious diseases, cardiovascular disease, new-onset diabetes after transplantation, and malignancy. The goals of treating these complications are to prevent allograft damage, improve patient quality of life, and increase survival.

The earliest recorded attempts at organ transplant date back thousands of years.[1] More than a few apocryphal descriptions exist from ancient Egypt, China, India, and Rome documenting experimentation with transplantation. For example, an Indian text from the second century BC describes a procedure for nasal reconstruction surgery with the use of **autografted** skin. Also, Roman Catholic lore has saints Damian and Cosmas replacing the gangrenous leg of a man with the leg of a recently deceased man in the third century AD.[1]

French surgeon Alexis Carrel pioneered the surgical techniques for transplantation in the early 1900s.[1] Together with Charles Guthrie, Carrel experimented in artery and vein transplantation. Using revolutionary methods in anastomosis operations and suturing techniques, Carrel laid the groundwork for modern transplant surgery. He was one of the first to identify the dilemma of rejection, an issue that remained nearly impossible to circumvent for nearly half a century.[1]

Prior to the work of Carrel, malnourishment was the prevailing theory regarding the mechanism of **allograft** rejection.[1] In 1910, however, Carrel noted that tissue damage in the transplanted organ likely was caused by multiple circulating biologic factors. It was not until the late 1940s, with the work of Peter Medawar, that we began to gain a better understanding of transplant immunology. Medawar was able to define the immunologic nature of rejection using skin allografts. In addition, George Snell observed fewer rejections with grafts shared between inbred animals and greater rejections in transplants between non-inbred animals.[1]

The seminal work by early transplant researchers eventually led to the concept of histocompatibility.[1,2] Histocompatibility describes the process where polymorphic genes encode cell membrane antigens that serve as targets for immune response, even within a species. Further research in transplant immunobiology has led to an accurate understanding of the immune response after transplantation.[1,2]

Joseph Murray performed the first successful organ transplant in 1954, a kidney transplant between identical twins.[1] This was a success in large part because no immunosuppression was necessary since the donor and recipient were genetically identical. Murray's success led to attempts with other organs over the next 20 years (Table 52–1).

TABLE 52–1. Solid-Organ Transplantation History

Event	Year
First successful deceased donor kidney transplant	1963
First successful pancreas transplant	1966
First successful liver transplant	1967
First successful heart transplant	1967
First successful heart-lung transplant	1981
First successful single-lung transplant	1983
First successful double-lung transplant	1987
First successful intestine transplant	1987
First successful living-donor liver transplant	1989
First successful living-donor lung transplant	1990
First successful live-donor partial pancreas transplant	1998

EPIDEMIOLOGY AND ETIOLOGY

Heart

Functions of the Heart

The heart is located underneath the sternum and between the lungs. In most adults, it weighs between 250 and 350 grams (0.55–0.77 lb). Its major role is to provide oxygen-rich blood to all organs and areas of the body. As a secondary function, the heart secretes atrial natriuretic factor (ANF), a hormone that regulates blood pressure and volume status. The inability of the heart to pump enough blood to maintain normal body requirements is known as heart failure. Refer to Chapter 3 for more information on heart failure.

Cardiac transplantation is one option for patients with severe heart failure. Candidates for cardiac transplantation generally present with New York Heart Association (NYHA) class III or IV symptoms and have an ejection fraction of less than 25%.[1,3] The general indications for cardiac transplantation include rapidly declining cardiac function and a projected 1-year mortality rate of greater than 75%. Mechanical support with an implantable left ventricular assist device may be appropriate while patients await the availability of a viable organ.[1,3] Some additional reasons for heart transplant include:

- Cardiomyopathy (e.g., dilated myopathy, hypertrophic cardiomyopathy, restrictive myopathy)
- Congenital heart disease
- Coronary artery disease
- Retransplantation after a previous graft failure
- Valvular heart disease

Most heart transplants are **orthotopic;** however, in certain situations, heterotopic (placing a transplanted organ into an abnormal anatomic location) cardiac transplants have been performed. There have been a handful of cardiac transplants that involved living donation. Although this seems strange, this occurs when one patient receives a simultaneous heart-lung transplant but his or her native heart (native is a term meaning "belonging to"; in this case, it refers to the original heart of the

individual, not the transplanted heart) is well functioning and may be transplanted subsequently into another recipient. In other words, when a patient receives a new heart in a heart-lung transplant, that patient's native heart, which is still in good (or viable) condition, is transplanted into another individual—the heart transplant recipient is also the heart transplant donor. This procedure is referred to as a "domino heart transplant." Annually, approximately 4000 patients are listed for a heart transplant, but only about 2300 donor hearts become available for transplantation each year. There were 2127 heart transplants done in 2005.[3]

Intestine

The intestine is the portion of the gastrointestinal (GI) tract that extends from the stomach to the anus. It is divided into two major sections, the small intestine and the large intestine. The small intestine, composed of the upper intestine, jejunum, and ileum, is about 20 feet (610 cm) in length. It functions to provide extensive food digestion and absorption of nutrients. Drug metabolism also takes place in the small intestine. The large intestine, composed of the cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum, is wider than the small intestine but is only about 6 feet in length. Its major function is the absorption of water and excretion of solid waste materials. Some reasons for intestine transplants include:

- Functional bowel problems (e.g., **Hirschsprung's disease,** neuronal intestinal dysplasia, pseudo-obstruction, protein-losing enteropathy, microvillous inclusion disease)
- Retransplantation after a previous graft failure
- Short-gut syndrome (e.g., intestinal artresia, necrotizing enterocolitis, intestinal volvulus, massive resection secondary to inflammatory bowel disease, tumors, mesenteric thrombosis)

An intestine transplant may involve the use of an entire intestine or just a shortened segment. Most intestine transplants completed in the United States have involved the transplant of the full organ and often are performed in conjunction with a liver transplant. Although most intestine transplants involve organs harvested from a deceased donor, recent advances in the field now have made it possible for living-donor intestinal segment transplants. There were 178 intestinal transplant recipients (171 deceased donors, 7 living donors) in 2005.[3]

Kidneys

The kidneys are located on the posterior part of the abdomen on either side of the spine, below the diaphragm, and behind the liver and stomach. They are bean-shaped and weigh approximately 150 grams (0.33 lb) each. The primary function of the kidneys is excretion. They work to excrete waste products through a series of steps involving glomerular filtration, secretion, and reabsorption. The kidneys also have several endocrine (e.g., production of erythropoietin and renin) and metabolic (e.g., vitamin D activation and drug metabolism) functions.

Prevalence of Kidney Disease

Over 20 million Americans have chronic kidney disease (CKD), with another 20 million considered at increased risk for the development of kidney disease. End-stage renal disease (ESRD) constitutes only a small portion of those CKD patients, with over 450,000 patients currently diagnosed with ESRD throughout the United States. The ESRD population continues to increase, with projections estimating that more than 660,000 people will carry a diagnosis of ESRD by 2010. All patients with ESRD should be considered for renal transplantation if they are healthy enough to undergo the transplant surgery. A successful kidney transplant may offer advantages in terms of both quality and duration of life compared with other renal replacement therapies (i.e., hemodialysis and peritoneal dialysis). It is also more effective than dialysis from a medical and economic perspective. Some reasons for kidney transplant include:

- Congenital, familial, and metabolic disorders (e.g., congenital obstructive uropathy, **Fabry's disease, medullary cystic disease,** and nephrolithiasis)
- Diabetes mellitus (DM)
- Glomerular diseases (e.g., anti–glomerular basement membrane disease, focal segmental glomerularsclerosis, IgA nephropathy, hemolytic uremic syndrome, systemic lupus erythematosus, **Alport's syndrome,** amyloidosis, membranous nephropathy, and **Goodpasture's syndrome**)
- Hypertension (HTN)
- Neoplasm (e.g., renal cell carcinoma and **Wilms' tumor**)
- **Polycystic kidney disease** (PCKD)
- Renovascular disease
- Retransplantation after a previous graft (allograft) failure
- Tubular and interstitial diseases (e.g., analgesic nephropathy, drug-induced nephritis, oxalate nephropathy, **radiation nephritis, acute tubular necrosis,** and **sarcoidosis**)

Most kidney transplant procedures are heterotopic, where the kidney is implanted above the pelvic bone and attached to the patient's iliac artery and vein. The ureter of the transplant kidney is attached directly to the recipient's bladder or native ureter. The native kidneys usually are not removed, and data have shown that under most circumstances, removal of the native kidneys does not influence patient survival and **allograft survival**. Special circumstances, however, such as renal cell carcinoma and PCKD, may necessitate native kidney removal.[1,3] There were 16,477 (9914 deceased donors, 6563 living donors) kidney transplants and 903 simultaneous kidney-pancreas procedures done in 2005.[3]

Liver

The liver is the largest of the abdominal organs, weighing 1 to 2.5 kg (2.2–5.5 lb), and is located under the diaphragm on the right side of the upper abdomen. The liver is composed of two soft, wedge-shaped lobes with eight segments. This organ plays a vital role in several processes, including carbohydrate, lipid,

and xenobiotic metabolism; synthesis of plasma proteins; and production of several clotting factors and glycogen storage.[1,3] Some reasons for liver transplant include:

- Acute hepatic necrosis (e.g., chronic or acute hepatitis B or C)
- Biliary atresia
- Cholestatic liver disease/cirrhosis (e.g., primary biliary cirrhosis)
- Metabolic disease (e.g., **Wilson's disease,** primary oxalosis, and hyperlipidemia)
- Neoplasms (e.g., hepatoma, cholangiocarcinoma, hepatoblastoma, and bile duct cancer)
- Non-cholestatic cirrhosis (e.g., alcoholic cirrhosis, postnecrotic cirrhosis, and drug-induced cirrhosis)
- Retransplantation after a previous graft failure

A liver transplant may involve the use of the entire organ or a segment of the liver. In most cases, the full organ (deceased donor) is used. In recent years, segmental transplants have been gaining popularity. This procedure requires donation of the right hepatic lobe, which accounts for nearly 60% of the overall liver mass. This type of procedure is possible because the liver can regenerate; therefore, both the donor and recipient, in theory, will have normal liver volumes shortly after the transplant procedure.[1,3] There were 6445 (6122 deceased donors, 323 partial-lobe living donors) liver transplants done in 2005.[3]

Lungs

Functions of the Lungs

The lungs are a pair of highly resilient, spongy organs located in the thoracic cavity beneath the rib cage. These organs can be divided into five lobes. The left lung has two lobes, and the right lung has three lobes. Their principal functions are gas exchange, the transport of oxygen from the atmosphere into the bloodstream in exchange for carbon dioxide, and control of hydrogen ion concentration. Some reasons for lung transplant include:

- α_1-Antitrypsin deficiency
- Congenital disease (e.g., **Eisenmenger's syndrome**)
- Cystic fibrosis
- Emphysema/chronic obstructive pulmonary disease
- Idiopathic pulmonary fibrosis
- Primary pulmonary hypertension
- Retransplantation after a previous graft failure

Lung transplants may involve deceased donation of two lungs or a single lung. More recently, lobar lung transplants from blood group–compatible living donors have been performed for a small segment of the population. In a lobar transplant, a lobe of the donor's lung is removed, sized appropriately for the recipient's thoracic dimensions, and transplanted. Most of the lobar transplants have been performed on cystic fibrosis patients. On rare occasions, a simultaneous heart-lung transplant occurs. This type of procedure is reserved for patients with severe pulmonary and cardiac disease. There were 1408 (1407 deceased donors, 1 living donor) lung transplants and 33 simultaneous heart-lung transplant procedures done in 2005.[3]

Pancreas

The pancreas is a small retroperitoneal organ located behind the stomach on the posterior abdominal wall.[1,3] The pancreas has both exocrine and endocrine functions. The exact nationwide prevalence of all diseases of the pancreas has not been fully quantified; however, DM, both types 1 and 2, affect nearly 21 million people in the United States alone. Some reasons for pancreas transplants include:

- DM (e.g., types 1 and 2, DM secondary to chronic pancreatitis, and DM secondary to cystic fibrosis)
- Pancreatic cancer
- Retransplantation after a previous graft failure

Transplant of a pancreas may involve either the entire organ or a pancreas segment. Currently, whole-organ transplant is the most common procedure, with a portion of the duodenum often transplanted along with the pancreas. Living donors are often the source of segmental transplants. In recent years, isolation and transplantation of beta islet cells alone have been completed, although at the time of this publication this procedure is still considered experimental.

Some people suffering from DM also may be afflicted with ESRD. A small percentage of these patients may undergo a simultaneous pancreas-kidney (SPK) transplant, which may be accomplished using organs from deceased or living donors. There were 541 pancreas transplants and 903 SPK procedures done in 2005.[3]

PATHOPHYSIOLOGY

Major Histocompatibility Complex

The primary target of the immune response against a transplanted organ is the Major Histocompatibility Complex (MHC).[1,2] The MHC is a region of highly polymorphic genes located on the short arm of chromosome 6. The human MHC is referred to as human leukocyte antigen (HLA). Human leukocyte antigens are a set of glycoprotein products that are expressed on the surfaces of almost all cells. These proteins are involved in immune recognition, which is the discrimination of self from non-self, and are also the principal antigenic determinants of allograft rejection.[1,2] The protein products of the HLA have been classified into two major groups, class I and II:

- *Class I.* These molecules are expressed on the surfaces of all nucleated cells and are recognized by CD8+ cells, also known as cytotoxic T cells. There are three subclasses of MHC class I molecules called HLA-A, HLA-B, and HLA-C.
- *Class II.* These molecules are expressed solely on the surfaces of antigen-presenting cells (APCs). The APCs serve to

stimulate CD4+ cells, also known as helper T cells. There are three subclasses of MHC class II molecules called HLA-DP, HLA-DQ, and HLA-DR.

T and B Lymphocytes

Lymphocytes are one of five kinds of white blood cells. Mature lymphocytes are astonishingly diverse in their functions. The most abundant of the lymphocytes are T lymphocytes (also called T cells) and B lymphocytes (also called B cells).

T Lymphocytes

❶ *T cells are the chief components initiating the immune response against the allograft. The activity of T cells is mediated largely through the synthesis and release of interleukin-2 (IL-2).* There are three recognized subclasses of T cells:

- Cytotoxic T cells (CD8+) promote target-cell destruction by activating cellular **apoptosis** or aggressively killing the target cell via the release of cytotoxic proteins.
- Helper T cells (CD4+) are the great communicators of the immune response. Once activated, they proliferate and secrete cytokines that regulate **effector cell** function. Some helper T cells secrete cytokines that recruit cytotoxic T cells, B cells, or APCs, whereas others secrete cytokines that turn off the immune response once an antigen has been destroyed.
- Regulatory T cells, or suppressor T cells, suppress the activation of an immune response. The activity of these cells in organ transplant is not well elucidated.

B Lymphocytes

B cells play a large role in the humoral immune response. In humans, B cells are produced and mature in the bone marrow. However, the abbreviation "*B*" does not stand for bone marrow. It stands for the bursa of Fabricius, an organ unique to birds, where B cells originally were discovered to mature.

The human body produces several types of B cells. Each B cell is unique, with a distinctive cell surface receptor protein that binds to only one particular antigen. Once B cells encounter their antigen and receive a cytokine signal from helper T cells, they can further differentiate into one of two cells, plasma B cells and memory B cells. Plasma B cells secrete antibodies that induce the destruction of target antigens through a process known as **opsonization.** Memory B cells play an important role in long-term immunity. Once formed to a specific antigen, memory B cells are capable of responding rapidly to subsequent exposures to their target antigen.

Antigen-Presenting Cells

❷ *An APC is a cell that displays a foreign antigen complex with MHC on its cell surface. Its major responsibility is to present these foreign antigens to T cells. T cells can identify this complex using their T-cell receptors (TCRs). There are three main types of APCs: dendritic cells, macrophages, and activated B cells.* Dendritic cells (DCs) are present in tissues that are in contact with the environment, such as the skin and the lining of the nose, lungs, stomach, and intestines. They are responsible for antigen **phagocytosis.** After phagocytosis, they express the foreign antigen on their cell surfaces and then migrate to the lymphoid tissues to interact with T and B cells to initiate the immune response. The main role of macrophages is the removal of pathogens and necrotic debris. However, like DCs, macrophages also phagocytize antigens and express them on their cell membranes to present to T cells in order to initiate an immune response. The first time an antigen is encountered, the DCs and macrophages act as the primary APCs. However, if the same antigen is encountered again, memory B cells become the most important APC because they initiate the immune response quickly after antigen presentation. It appears that both the DCs and macrophages have the most activity in terms of **allorecognition.**

Allorecognition

❶❷ *Recognition of the antigens displayed by the transplanted organ (alloantigens) is the prime event that initiates the immune response against the allograft.* There are currently two accepted pathways for T cell allorecognition:

- *Direct pathway.* Donor APCs migrate out of the allograft into the recipient's lymph nodes and present donor MHC molecules to the TCRs of the recipient's T cells.
- *Indirect pathway.* Recipient APCs migrate into the graft and phagocytize alloantigens. The donor MHC molecules then are expressed on the cell surfaces of the recipient's APCs and presented to recipient T cells in the lymph nodes.

T-Cell Activation

Whether it is by the direct or indirect pathway, in order for a T cell to become activated against a transplanted organ, two interactions, or signals, must take place between the APCs and the recipient's T cells.[1,2] Signal 1 is the interaction of the TCRs with the foreign antigens presented by the APCs. The second, co-stimulatory signal, known as Signal 2, is an interaction between one of several co-stimulatory receptors and paired ligands on the cell surfaces of the APCs and T cells, respectively. This interaction is of the utmost importance because Signal 1 in the absence of Signal 2 induces T cell **anergy.**

Once activated, T cells undergo clonal expansion (they multiply) under the influence of cytokines, specifically IL-2. These steps elicit an anti–donor T cell response that results in graft destruction.

Mechanisms of Acute Rejection

After activation, cytotoxic T cells emerge from lymphoid organs to infiltrate the graft and trigger the immune response. These cells have been shown to induce graft destruction via two mechanisms: (1) secretion of the cytotoxic proteins perforin and granzyme B, and (2) induction of cellular apoptosis

through interaction with various cell surface receptors. Besides the cytotoxic T cells, several other cell lines may play a role in allograft destruction, including B cells, granulocytes, and natural killer cells.

Types of Rejection

Hyperacute Rejection

Hyperacute rejection is an immediate recipient immune response against the allograft owing to the presence of preformed recipient antibodies directed against the donor's HLA. In other words, hyperacute rejection may occur when preformed donor-specific antibodies are present in the recipient at the time of the transplant. This type of reaction generally occurs within minutes of the transplant. The organ must be removed immediately to prevent a severe systemic response. Patients at highest risk for hyperacute rejection include any patient that has preformed HLA or ABO blood group antibodies, including patients with a history of previous organ transplants or multiple blood transfusions, as well as mothers receiving transplanted organs from their children. Hyperacute rejection has been largely eliminated owing to routine surveillance testing completed prior to the transplantation.

Acute Rejection

Acute rejection is a cell-mediated process that generally occurs within 5 to 90 days of the transplant procedure; however, it can occur at any time after transplantation. This reaction is mediated through alloreactive T cells, as outlined previously. Organ-specific signs and symptoms of acute rejection are listed in Table 52–2.

Humoral Rejection

Also known as antibody-mediated rejection, humoral rejection is the process of creating graft-specific antibodies.[1,4] This type of rejection occurs less frequently than cell-mediated acute rejection. Humoral rejection is characterized by deposition of immunoglobulins and complement in allograft tissues. Treatment for this type of rejection is not well defined, yet several reports have shown that treatments such as plasmapheresis, immunoglobulin therapy, rituximab, and/or antithymocyte globulin may be effective.

Chronic Rejection

Chronic rejection traditionally has been thought of as a slow, insidious form of acute rejection resulting in worsening organ function over time. The exact immunologic processes of chronic rejection are poorly understood; however, many believe that both the cell-mediated humoral immune systems (antibody-mediated) and drug-induced toxicities play a vital role in chronic allograft dysfunction. Currently, retransplantation is the only effective treatment option for chronic allograft dysfunction.[1,5]

Host-Graft Adaptation

The term host-graft adaptation describes a decreased immune response against the allograft over time.[2] This phenomenon is evident by the reduced incidence of acute rejection episodes seen months after the transplant procedure. In theory, host-graft adaptation is thought to be secondary to a weakened T-cell response to the donor antigens when patients are receiving maintenance immunosuppression.[2] Host-graft adaptation allows for acceptance of allograft (low rejection rate) despite the low intensity of immunosuppression.

TABLE 52–2. Organ-Specific Signs and Symptoms of an Acute Rejection Episode[1, 3]

Organ	Clinical Symptoms	Laboratory Signs
Heart	Fever, lethargy, weakness, SOB, DOE, hypotension, tachycardia, atrial flutter, ventricular arrhythmias	Leukocytosis, endomyocardial biopsy positive for mononuclear infiltrates
Kidney	Fever, graft tenderness and swelling, decreased urine output, malaise, hypertension, weight gain, edema	Increased SCr, BUN, leukocytosis, renal biopsy positive for lymphocytic infiltration
Intestine	Fever and GI symptoms (e.g., bloating, cramping, diarrhea, increased stomal output)	There are no reliable biochemical markers for intestine transplant rejection, but biopsies may be helpful
Liver	Fever, lethargy, change in color or quantity of bile in patients w/ biliary T-tube, graft tenderness and swelling, back pain, anorexia, ileus, tachycardia, jaundice, ascites, encephalopathy	Abnormal LFTs, increased bilirubin, alkaline phosphatase, transaminases, biopsy positive for mononuclear cell infiltrate with evidence of tissue damage
Lung	Fever, impaired gas exchange, SOB, malaise, anxiety	Decreased FEV, infiltrate on CXR, biopsy positive for lymphocytic infiltration
Pancreas	Fever, graft tenderness and swelling, abdominal pain, ileus, malaise	Increased FBS, leukocytosis, decreased human C-peptide and urinary amylase levels

BUN, blood urea nitrogen; CXR, chest x-ray; DOE, dyspnea on exertion; FBS, fasting blood sugar; FEV, forced expiratory volume; GI, gastrointestinal; LFTs, liver function tests; SCr, serum creatinine, SOB: shortness of breath.

Tolerance

Tolerance is the process that allows organ-specific antigens to be accepted as self.[2,6] This would mean that the immune system would cease to respond to the allograft, and immunosuppressive medications would not be necessary. Immune tolerance has not been accomplished successfully in humans.[2,6]

TREATMENT

Desired Outcome

The major focus of transplant therapy is to achieve long-term patient and allograft survival.[2,7] Short-term outcomes (i.e., acute rejection rates and 1-year graft survival) have improved significantly since the first successful transplant owing to an improved understanding of the immune system and enhancements in surgical techniques, organ procurement, immunosuppression, and posttransplant care. Despite the success in improving short-term outcomes, the overall frequency of graft loss remains higher than desired.[1,2]

It is imperative that transplant practitioners be aware of the specific advantages and disadvantages of available immunosuppressants, as well as their adverse drug reaction and drug-drug interaction (DDI) profiles.

There are three stages of medical immunosuppression: (1) induction therapy, (2) maintenance therapy, and (3) treatment of acute rejection episodes. ❸ *The goal of pharmacotherapy in transplantation is to induce immunosuppression with resulting long-term allograft and patient survival while minimizing the complications of suppressing the immune system. Overall, the immunosuppressive regimens use multiple medications that work on different targets of the immune system.* Please refer to Table 52–3 for a list of currently available immunosuppressive agents.

Immunosuppressive Therapies: Induction Therapy

❹ *The goal of induction therapy is to provide a high level of immunosuppression in the critical early posttransplant period, when the risk of acute rejection is highest.*[2,7–10] This stage of immunosuppression is often initiated intraoperatively or immediately postoperatively and generally is concluded within the first 7 to 10 days of transplantation. Induction therapy is not a mandatory stage of recipient immunosuppression. However, since acute rejection is a major concern in solid-organ transplant recipients and its impact on chronic rejection is undeniable, induction therapy is used often to optimize outcomes.[2,7–10]

Goals of Induction Therapy

The induction agents are highly immunosuppressive and, when given prior to some organ transplants (e.g., kidney transplant), allow for significant reductions in acute rejection episodes and improved 1-year graft survival. Also, owing to their unique pharmacologic effect, these agents often are considered essential for use in patients at high risk for poor short-term outcomes, such as patients with preformed antibodies, a history of previous organ transplants, multiple HLA mismatches, or transplantation of organs with prolonged cold ischemic time or from expanded-criteria donors. Specifically, in renal transplant recipients, induction therapy plays an important role in preventing early-onset calcineurin inhibitor–induced nephrotoxicity. With the use of induction agents, initiation of calcineurin inhibitors can be delayed until the graft regains a modicum of function.[7,9,10]

The improved short-term outcomes gained from induction therapy come with a degree of risk. By using these highly immunosuppressive agents, particularly the antilymphocyte antibodies (ALAs), muronomab-CD3 (OKT-3), and the antithymocyte antibodies, the body loses much of its innate ability to mount a cell-mediated immune response, which increases the risk of opportunistic infections and cancer.[7,10]

Currently Available Induction Therapies

Basiliximab and Daclizumab

Basiliximab and daclizumab are considered monoclonal antibodies. Daclizumab is a humanized antibody that is approximately 10% murine and 90% human, whereas basiliximab is a chimeric antibody that is approximately 30% murine and 70% human.[9,11] These agents bind with high affinity to the IL-2 receptor, where they act as CD25 receptor antagonists. These receptors are present on almost all activated T cells. Their role in induction therapy involves inhibiting IL-2-mediated activation of lymphocytes, which is an important step for the clonal expansion of T cells.

The dose of basiliximab is 20 mg intravenously (IV) given within 2 hours prior to the transplant, followed by a second 20 mg dose on postoperative day 4.[7,9,11] This dosing schedule can be used for both children weighing 35 kg (77 lb) or more and adults. Two 10 mg doses with the same dosing schedule should be used for children weighing less than 35 kg (77 lb). No specific dosage adjustments is needed in renal or hepatic impairment.[7,9,11]

The Food and Drug Administration (FDA) approved dose of daclizumab is 1 mg/kg within 24 hours of transplant surgery and then 1 mg/kg administered every 2 weeks after surgery for a total of five doses.[7,9,11] No dose adjustment is necessary in renal impairment, but no data are available for dose adjustments in hepatic dysfunction. Several trials have shown that a shorter dosing regimen of daclizumab, two doses given in a similar manner as basiliximab, may be as safe and effective as the full five-dose course.[12,13]

The most common adverse reaction with daclizumab is hyperglycemia, with clinical studies showing that a total of 32% of patients developed hyperglycemia.[9,11] Most of the high glucose levels occurred the day after transplantation or in

TABLE 52–3. Currently Available Immunosuppressive Agents[2, 7, 11]

Generic Name (Brand Name)	Common Adult Dosage	Common Adverse Effects	AWP (per Dose or per Dosage Form)
Induction Therapy Agents			
Lymphocyte immune globulin, antithymoglobulin equine (ATGAM®)	15 mg/kg IV × 3–14 days	Flu-like symptoms, chills, rigors, fever, rash, myelosuppression	$21,797–$101,720
Antithymocyte Globulin Rabbit (Thymoglobulin®)	1.5 mg/kg IV × 3–14 days	Flu-like symptoms, chills, rigors, fever, rash, myelosuppression	$5,434–$25,358
OKT-3 (Orthoclone OKT-3®)	5 mg IV × 7–14 days	Headache, hypertension, pulmonary edema, tremor, fever, aseptic meningitis, hypersensitivity reactions	$6,935–$13,871
Daclizumab (Zenapex®)	1 mg/kg IV × 5 doses	Hyperglycemia (only after infusion)	$6,907
Basiliximab (Simulect®)	20 mg IV × 2 doses	None reported compared with placebo	$3,401
Maintenance Immunosuppressants (Capsules and Tablets)[a]			
Cyclosporine (Sandimmune®, Neoral®, Gengraf®)	4–5 mg/kg by mouth twice a day	Neurotoxicity, gingival hyperplasia, hirsutism, hypertension, hyperlipidemia, glucose intolerance, nephrotoxicity, electrolyte abnormalities	Sandimmune: 25 mg = $1.74 100 mg = $6.93 Neoral: 25 mg = $1.53 100 mg = $6.11 Gengraf: 25 mg = $1.38 100 mg = $5.50
Tacrolimus (Prograf®)	0.05–0.075 mg/kg by mouth twice a day	Neurotoxicity, alopecia, hypertension, hyperlipidemia, glucose intolerance, nephrotoxicity, electrolyte abnormalities	1 mg = $3.97 5 mg = $19.74 0.5 mg = $1.98
Azathioprine (Imuran®)	1–2.5 mg/kg by mouth once a day	Myelosuppression, gastrointestinal disturbances, pacreatitis	50 mg = $1.30
Mycophenolate mofetil (CellCept®)	0.5–1.5 g by mouth twice a day	Myelosuppression, gastrointestinal disturbances	250 mg = $3.11 500 mg = $6.21
Enteric-coated MPA (Myfortic®)	720 mg by mouth twice a day	Myelosuppression, gastrointestinal disturbances	180 mg = $2.53 360 mg = $5.05
Sirolimus (Rapamune®)	1–10 mg by mouth once a day	Hypertriglyceridemia, myelosuppression, mouth sores, hypercholesterolemia, gastrointestinal disturbances, impaired wound healing, lymphocele, pneumonitis	1 mg = $6.57 2 mg = $13.15 5 mg = 32.87
Prednisone (Deltasone®)	Maintenance: 2.5–20 mg by mouth once a day	Mood disturbances, psychosis, cataracts, hypertension, fluid retention, peptic ulcers, osteoporosis, muscle weakness, impaired wound healing, glucose intolerance, weight gain, hyperlipidemia	2.5 mg = $0.07 5 mg = $0.04 10 mg = $0.06 20 mg = $0.11

[a]Only listing capsules and tablets (other routes such as liquids, injection or dermal excluded from this listing).
AWP, average wholesale price; IV, intravenous; MPA, mycophenolic acid; OKT-3, muronomab-CD3.

patients with preexisting DM. All other adverse events in the daclizumab clinical trials showed no statistically significant difference compared with placebo. The incidence of all adverse reactions with basiliximab was similar to placebo in clinical trials.[9,11]

Lymphocyte Immune Globulin, Antithymoglobulin Equine (ATG)

ATG contains antibodies against several T-cell surface markers, including CD2, CD3, CD4, CD8, CD11a, and CD18. After binding to these cell surface markers, ATG promotes T-cell

depletion through opsonization and complement-mediated T cell lysis.[7,8,11] The common dosing strategy for ATG when used for induction therapy is 10 to 30 mg/kg per day IV for 3 to 14 days. The first dose usually begins shortly before or after transplantation.[7,8,11]

After T cell lysis, there is a cytokine release. Owing to this phenomenon, ATG is associated with several adverse reactions.[7,8,11] The most common include fever (63%), chills (43%), headache (35%), back pain (43%), nausea (28%), diarrhea (32%), dizziness (25%), malaise (4%), and myelosuppression [**leukopenia** (30%) and **thrombocytopenia** (44%)]. Overall incidence of opportunistic infections is 27%, with **cytomegalovirus (CMV) disease** occurring in 11% of patients.[7,8,11]

Antithymocyte Globulin Rabbit

Antithymocyte globulin induces T cell clearance, but more important, it alters T cell activation, homing, and cytotoxic activities. Compared with ATG, this agent causes less T cell lysis owing to its multiple mechanisms of immunosuppression. It is also believed that antithymocyte globulin plays a role in inducing T cell apoptosis. Antithymocyte globulin has been dosed at 1 to 4 mg/kg per day (typically dosed at 1.5 mg/kg per day) and usually is administered for 3 to 10 days after transplantation.[7,8,11] Many renal transplant centers aim to initiate the first dose intraoperatively to help reduce organ reperfusion injury.

Adverse reactions are common and may include fever (63%), chills (57%), headache (40%), nausea (37%), diarrhea (37%), malaise (13%), dizziness (9%), leukopenia (57%), thrombocytopenia (37%), and generalized pain (46%).[7,8,11] The incidence of infection is 37%, with CMV disease occurring in 13% of patients. There are no reported drug-drug interactions (DDIs) with the use of antithymocyte globulin at this time.[7,8,11]

Muronomab-CD3

Muronomab-CD3 (OKT-3) is a murine monoclonal antibody that targets the CD3 receptor. The CD3 receptor is only found on activated T cells and medullary thymocytes.[10,11,14] After binding with the CD3 receptor, complement-mediated T cell lysis occurs rapidly. This agent is dosed at 5 mg/day. This dose is given daily for 10 to 14 days. Lower doses have been used successfully in liver transplant recipients.[14]

Owing to its ability to cause widespread T cell lysis after the first dose, OKT-3 has several severe adverse effects that manifest within 3 hours after administration.[10,11,14] These adverse reactions often are referred to as the first-dose effect and usually are secondary to cytokine release. The adverse-reaction profile of OKT-3 includes fever (77%), chills (43%), dyspnea (16%), nausea (32%), vomiting (25%), diarrhea (37%), and tachycardia (26%). One of the major complications of OKT-3 is the development of severe pulmonary edema.[11,15,16] In reported cases of this complication, patients were fluid overloaded at the time of the initial dose. Another problematic adverse reaction is the development of nephropathy.[11,17]

Comparative Efficacy: Induction-Therapy Agents

Improvements in short-term outcomes gained from the use of induction therapies cannot be denied. Despite these improvements, use of induction therapy has not affected long-term allograft function or survival. There are a few studies that help to delineate the ideal induction-therapy agent. For example, studies comparing antithymocyte globulin and ATG show that antithymocyte globulin is more effective in lowering acute rejection rates and improving 1-year allograft survival.[18] Conversely, studies evaluating the use of basiliximab versus antithymocyte globulin demonstrate similar short-term efficacy between both



Patient Encounter, Part 1: The Medical History, Physical Examination, and Diagnostic Tests

JJ is a 52-year-old woman who presents to your transplant center for a living, related renal transplant.

PMH

ESRD secondary to PCKD and failed previous transplant. One prior renal transplant that occurred in 1995 (received kidney from husband), which failed secondary to chronic allograft nephropathy in 2004 (presumably from multiple rejection episodes within the first few years after transplant). For the previous transplant, the patient was maintained on cyclosporine, mycophenolate, and prednisone.
Hypertension
Hyperlipidemia
Insomnia

FH

Father died of a myocardial infarction at age 53, whereas mother is alive and living with HTN, systemic lupus erythematosus, DM, and osteoporosis at the age of 75.

SH

The patient works as a secretary. Was a heavy tobacco user (25 pack-years) but quit 3 years ago. She denies alcohol and IV drug use.

Admission meds

Calcitriol 0.25 mg by mouth once a day
Calcium acetate 1334 mg by mouth three times a day
Ferrous sulfate 325 mg by mouth once a day
Epoetin Alfa 4000 units intravenously every hemodialysis session
Simvastatin 20 mg by mouth once a day at bedtime
Metoprolol 100 mg by mouth twice a day
Aspirin 81 mg by mouth once a day

Allergies

"Codeine causes upset stomach."
"Penicillin causes hives."
"Sulfa causes rash."

- Identify your treatment goals for JJ.
- Create a plan for induction therapy (i.e., would you recommend induction therapy? If so, why? Which agent?).

groups.[19] When choosing an agent for induction therapy, one must weigh the risks versus the benefits. For the most part, the ALAs (OKT-3, ATG, and antithymocyte globulin) are considered to be most effective but are associated with a higher incidence of infectious disease and cancer.

Immunosuppressive Therapies: Maintenance Therapy

❹ *The goals of maintenance immunosuppression are to further aid in preventing acute rejection episodes and to optimize patient and graft survival.* Anti-rejection medications require careful selection and dosage titration to balance the risks of rejection with the risks of adverse events. Common maintenance immunosuppressive agents can be divided into four basic medication classes:

- Calcineurin inhibitors (cyclosporine and tacrolimus)
- Antiproliferatives [azathioprine and the mycophenolic acid (MPA) derivatives]
- Target of rapamycin (ToR) inhibitors (sirolimus)
- Corticosteroids (prednisolone derivatives and dexamethasone)

❸ *Maintenance immunosuppression generally is achieved by combining two or more medications from the different classes to maximize efficacy by specifically targeting unique components of the immune response.* Figure 52–1 presents a schematic representation of these different drug mechanisms, and Fig. 52–2 shows an example protocol for administration of immunosuppressive medications after transplantation. This method of medication selection also helps to minimize adverse events by choosing agents with different adverse-event profiles. Immunosuppressive regimens vary between organ types and transplant centers, but most often they include a calcineurin inhibitor with an adjuvant agent (antimetabolite with or without corticosteroids). Selection of appropriate immunosuppressive regimens should be patient-specific. The transplant practitioner must take into account the patient's preexisting disease states, medication regimens, and preferences.

Calcineurin Inhibitors

❺ *Cyclosporine and tacrolimus belong to a class of immunosuppressants called the calcineurin inhibitors. These agents are considered by many to be the cornerstone of medical immunosuppression. The calcineurin inhibitors work by complexing with cytoplasmic proteins (cyclosporine with cyclophylin and tacrolimus with FK binding protein 12). These complexes then inhibit calcineurin phosphatase, which results in reduced IL-2 gene transcription. The final outcome is a decrease in IL-2 synthesis and a subsequent reduction in T cell activation.*[7,11,20,21]

Cyclosporine

Cyclosporine USP was first approved by the FDA in 1983 but was associated with a variable oral absorption. The development

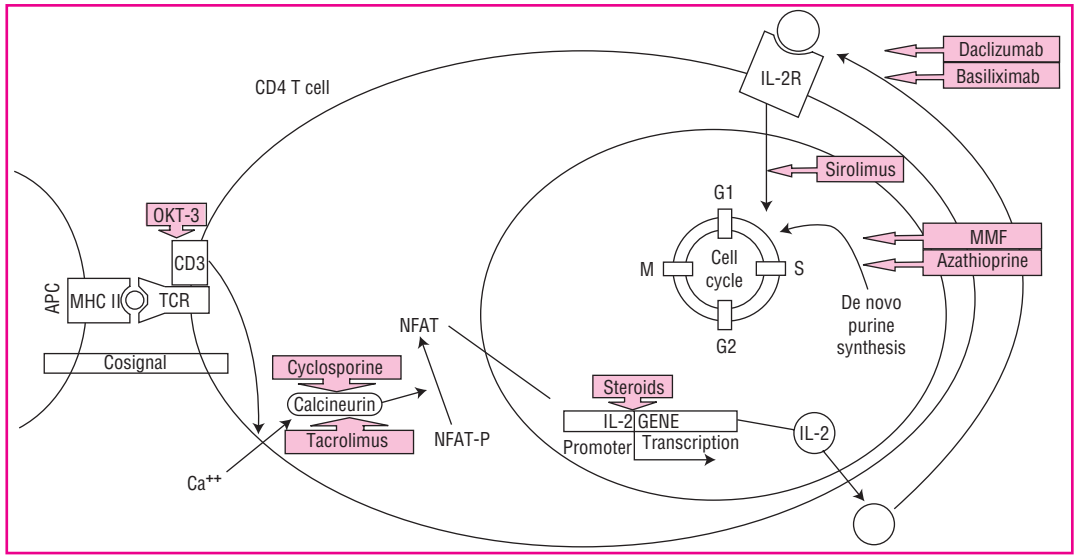


FIGURE 52–1. Stages of CD4 T-cell activation and cytokine production with identification of the sites of action of different immunosuppressive agents. Antigen–major histocompatibility complex (MHC) II molecule complexes are responsible for initiating the activation of CD4 T cells. These MHC-peptide complexes are recognized by the T-cell recognition complex (TCR). A co-stimulatory signal initiates signal transduction with activation of second messengers, one of which is calcineurin. Calcineurin removes phosphates from the nuclear factors (NFAT-P), allowing them to enter the nucleus. These nuclear factors specifically bind to an interleukin-2 (IL-2) promoter gene facilitating IL-2 gene transcription. Interaction of IL-2 with the IL-2 receptor (IL-2R) on the cell membrane surface induces cell proliferation and production of cytokines specific to the T cell.
APCs, antigen-producing cells; MMF, mycophenolate mofetil; OKT-3, muronomab-CD3. (Adapted from Mueller XM. Drug immunosuppressive therapy for adult heart transplantation: I. Immune response to allograft and mechanism of action of immunosuppressants. Ann Thorac Surg 2004; 77: 354–362, with permission.)

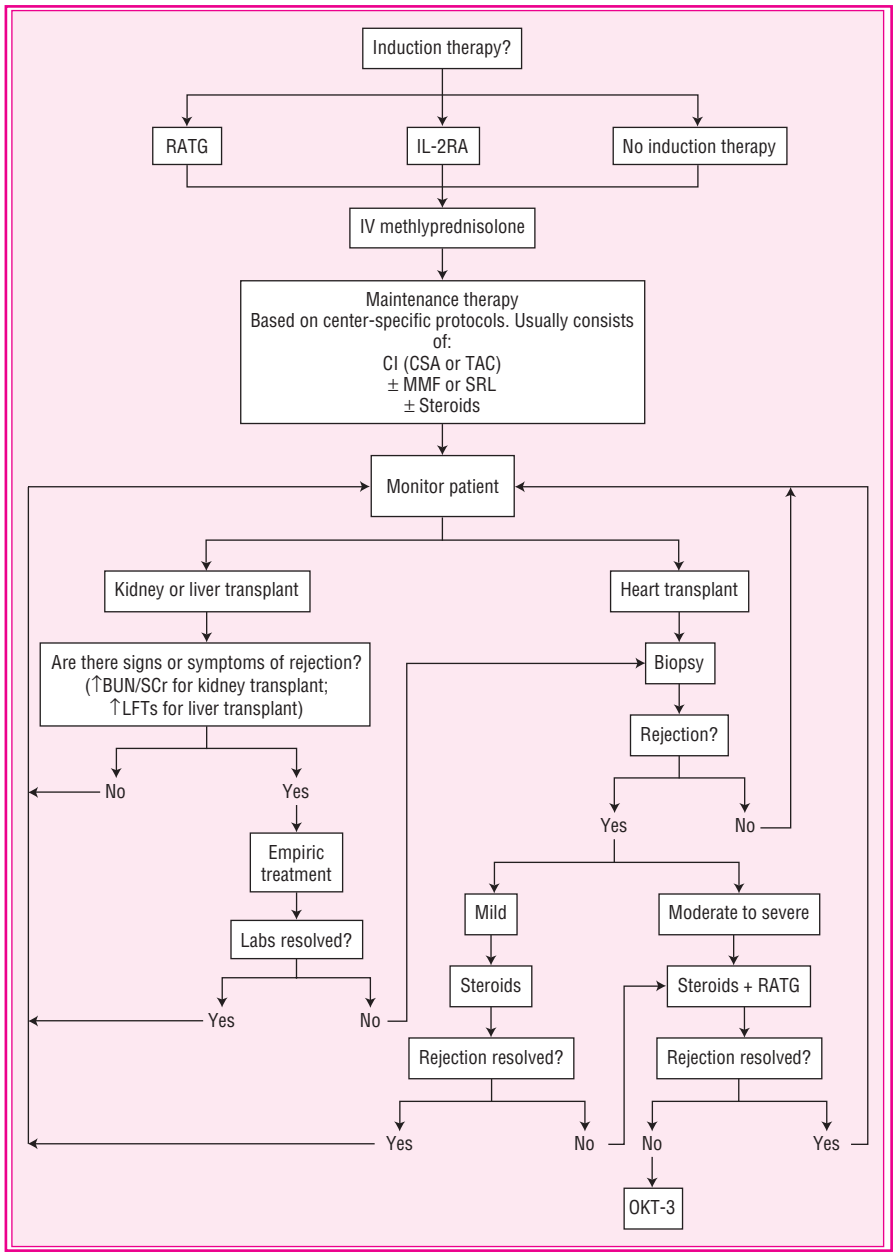


FIGURE 52–2. Center-specific protocols may use RATG, an IL-2RA, or no induction therapy. In any situation, patients receive IV methylprednisolone prior to, during, or immediately following the transplant operation. The patient then will begin the maintenance immunosuppressive regimen. The center-specific protocol will specify which calcineurin inhibitor (cyclosporine or tacrolimus) is used in combination with mycophenolate mofetil or sirolimus with or without steroids. Patients then are monitored for signs and symptoms of rejection. If rejection is suspected, a biopsy can be done for definitive diagnosis, or the patient may be treated empirically for rejection. Empirical treatment generally involves administration of high-dose corticosteroids. If signs and symptoms of rejection are resolved with empirical therapy, the patient will continue to be monitored according to the center-specific protocol. If rejection is confirmed by biopsy, treatment may be based on the severity of rejection. High-dose corticosteroids are used most frequently for mild to moderate rejection. RATG can be used for moderate to severe rejections or steroid-resistant rejections. Severe rejection episodes that are not resolved with steroids or RATG are treated with OKT-3.
BUN, blood urea nitrogen; CI, calcineurin inhibitor; CSA, cyclosporine; IL-2RA, interleukin 2 receptor antagonist; LFTs, liver function tests; MMF, mycophenolate mofetil; OKT-3, muronomab-CD3; RATG, rabbit antithymocyte immunoglobulin; SCr, serum creatinine; SRL, sirolimus; TAC, tacrolimus. (Reprinted from Johnson HJ, Schonder KS. Solid-organ transplantation. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1613–1643, with permission.)

of a newer formulation, cyclosporine microemulsion USP, introduced in 1994, allowed for a more consistent drug exposure owing to a more reliable pharmacokinetic profile.[22] Cyclosporine microemulsion is the formulation of choice for most transplant centers that use cyclosporine for maintenance immunosuppression owing to the aforementioned benefit. The two formulations are not interchangeable.

The usual adult oral dose of cyclosporine ranges from 4 to 18 mg/kg per day in two divided doses.[11] Appropriate selection of the starting dose usually depends on the organ type, the patient's preexisting disease states, and other concomitant immunosuppressive agents used. Cyclosporine microemulsion is available as 25 and 100 mg individually blister-packed capsules and an oral solution. An IV formulation is also available. When converting a patient from oral to IV administration, the dosage should be reduced to approximately one-third the oral dose.[11]

Cyclosporine whole-blood trough concentrations traditionally have been obtained to help monitor for efficacy and safety. Therapeutic trough levels (C_0) may range from 50 to 400 ng/mL (41–329 mmol/L). Target levels should be individualized for each patient, usually depending on the organ transplanted, the patient's condition, and the time since transplant and type of assay [high-performance liquid chromatography (HPLC), TDX, or monoclonal antibody]. Newer studies suggest that monitoring of concentrations at 2 hours postdose (C_2) correlates better with toxicity and efficacy than C_0.[23]

Tacrolimus

Tacrolimus (also known as FK506) is the second calcineurin inhibitor and was approved by the FDA in 1997. Even though cyclosporine and tacrolimus both belong to the same general medication class, there are several differences between the two. For example, some studies suggest that tacrolimus-based regimens are associated with improved short-term survival when compared with cyclosporine-based regimens.[24] However, newer data suggest that there is no significant difference in acute rejection rates between cyclosporine and tacrolimus.[25]

Oral starting doses of tacrolimus range from 0.1 to 0.2 mg/kg per day in two divided doses. Tacrolimus is available in 0.5, 1, and 5 mg capsules and as an injectable.[11] The IV formulation usually is avoided owing to the risk of anaphylaxis because of its castor oil component. Tacrolimus C_0 whole-blood levels should be monitored (12 hours after the last administered dose) and maintained between 5 and 15 ng/mL; again, desired serum concentrations depend on the transplanted organ, the patient's condition, and the time since transplant.[11] A once-daily modified formulation of tacrolimus is being studied currently.

Adverse Drug Reactions

❺ *One of the major drawbacks of calcineurin inhibitors is their ability to cause acute and chronic nephrotoxicity.* Acute nephrotoxicity has been correlated with high calcineurin inhibitor doses and usually is reversible. Chronic toxicity, however, typically is irreversible and is linked to chronic drug exposure. Table 52–4 expands on the more common calcineurin inhibitor–induced adverse events.

Comparative Efficacy: Calcineurin Inhibitors

Several studies have assessed the clinical efficacy of cyclosporine versus tacrolimus. Most of the studies have shown similar long-term patient and allograft survival, whereas some renal transplant studies have demonstrated improved renal function in tacrolimus-treated patients. The most significant difference between the two agents appears to be their adverse-reaction profiles (Table 52–4).

Antiproliferatives

These agents generally are considered to be adjuvant to the calcineurin inhibitors or possibly sirolimus. ❻ *The antiproliferatives azathioprine and the mycophenolic acid (MPA) derivatives inhibit T cell proliferation.*

Azathioprine

Azathioprine was originally approved by the FDA in 1968 as an adjunct immunosuppressant for use in renal transplant recipients. It is available in oral and IV dosage forms.[11] Prior to the advent of cyclosporine, the combination of azathioprine and corticosteroids was the mainstay of immunosuppressive therapy. Over the past 10 years, the use of azathioprine has declined markedly due in large part to the success of the MPA derivatives, which are more specific inhibitors of T cell proliferation. Azathioprine is a pro-drug for 6-mercaptopurine (6-MP), a purine analog. 6-MP acts as an antimetabolite and inhibits DNA replication with a resulting reduction in T-cell proliferation.[11] The typical oral dose of azathioprine for organ transplantation is 3 to 5 mg/kg once a day.[11] The IV and oral doses are equivalent (1:1 conversion). The maintenance dose usually is reduced to l to 2 mg/kg per day within a few weeks of transplantation. In patients with severely impaired renal function, dose reductions may be necessary because 6-MP and its metabolites are eliminated renally.[11] Trough concentrations of 6-MP are not monitored; however, most clinicians often monitor for signs of myelosuppression and liver dysfunction. ❻ *Myelosuppression (mainly leukopenia and thrombocytopenia) is a frequent dose-dependent and dose-limiting complication (greater than 50% of patients) that often prompts dose reductions.*[11] Other common adverse events include hepatotoxicity (2% to 10%) and GI problems (10% to 15%, mostly nausea and vomiting). Importantly, pancreatitis and veno-occlusive disease of the liver occur in fewer than 1% of patients following chronic azathioprine therapy.[11]

Mycophenolic Acid Derivatives

Mycophenolate mofetil was approved by the FDA in 1995, and enteric-coated mycophenolic acid was approved in 2004. Both agents are considered to be adjunctive immunosuppressants. Mycophenolic acid acts by inhibiting inosine monophosphate deydrogenase, a vital enzyme in the de novo pathway of purine synthesis. Inhibition of this enzyme prevents the proliferation of most cells that are dependent on the de novo pathway for purine synthesis, including T cells.[7,11,26–28]

Mycophenolate mofetil is available in 250 mg capsules and 500 mg tablets, an oral suspension (100 mg/mlL, in cherry syrup), and an injectable.[11] Usual doses of mycophenolate mofetil range from 1000 to 3000 mg/day in two to four divided doses. The conversion between oral and IV mycophenolate mofetil is 1:1. Enteric-coated mycophenolic acid is available in 180 and 360 mg tablets. For conversion between mycophenolate mofetil and enteric-coated MPA, 1000 mg mycophenolate mofetil is equivalent to 720 mg enteric-coated MPA.[26,29] The recommended starting dose of enteric-coated mycophenolic acid is 720 mg given twice daily.[11] It appears that conversion of mycophenolate mofetil to enteric-coated mycophenolic acid is safe, but more studies are needed to determine the exact role of enteric-coated MPA in the immunosuppressive armamentarium. Mycophenolic acid trough concentrations can be monitored, but they are not recommended routinely.

❻ *The most common adverse events associated with these agents are GI (18% to 54%, namely, diarrhea, nausea, vomiting, and gastritis) and myelosuppression (20% to 40%).*[7,11,26–28] Despite its enteric coating, to date, mycophenolic acid has shown no significant benefit in terms of reduction in GI adverse events compared with mycophenolate mofetil in renal transplant recipients.[26]

TABLE 52–4. Management of Common Adverse Effects of Calcineurin Inhibitors[1, 7, 11]

Adverse Effects	AZA	MMF	Steroids	CSA	TAC	SRL	IL-2RA	ATG	OKT-3	Management
Adrenal suppression			+							Taper doses slowly; administer every other day; patient identification card
Cataracts/glaucoma			+							Annual eye exams or as indicated
Hypertension[a]			++	++	++					Monitor blood pressure; sodium restriction and antihypertensive medications as needed
Tremor (fine hand)[b]				++	++					Adjust dose as needed
Gastrointestinal abnormalities	++ Nausea, vomiting	++ Diarrhea, nausea, abdominal pain	+ GI bleeding	+	++ Diarrhea, nausea, vomiting, anorexia					AZA: administer after meals; MMF: decrease or divide dose, administer with food; TAC/PRED: administer with food; ulcer prophylaxis
Respiratory abnormalities					++				+	TAC: pleural effusion, dyspnea; OKT-3: pulmonary edema
Nephrotoxicity				++	++	+				Monitor SCr/BUN; adjust dose and discontinue as needed
Headache				+	++					Check drug concentration; adjust dose
Hepatotoxicity	+			+	++					Monitor liver enzymes; AZA-associated toxicity is reversible and usually occurs within the first 6 months of therapy; adjust dose and discontinue as needed
Hyperlipidemia[a]			++	++	+	++				Dietary counseling; pharmacotherapy as needed
Glucose alterations[b]			++	+	++					Monitor glucose; adjust doses of hypoglycemics or immunosuppressants
Osteoporosis/aseptic necrosis			+/++							Annual bone exams; weight-bearing exercise
Personality changes			++							Patient and family education
Weight gain			++							Patient education; exercise
Acne			+	+						Dose reduction; increased hygiene; topical agents (e.g., retinoic acid)
Gingival hyperplasia				++						Patient education; appropriate dental hygiene; consider TAC
Hirsutism				++						Patient education; consider TAC
Pruritus					++					Treatment when appropriate
Thrombocytopenia	++	+			+	++				Monitor platelets
Leukocytosis			++		++					Monitor WBCs
Leukopenia	++	++		+		++				Monitor WBCs; dose-dependent and reversible with AZA/MMF
Hyperkalemia				+	++					Monitor serum electrolytes
Hypokalemia							+			
Hypomagnesemia				+	++					Monitor serum magnesium

[a]Tacrolimus is associated with hypertension and hyperlipidemia, but to a much lower extent than cyclosporine.
[b]Cyclosporine is associated with hyperglycemia and central nervous system (CNS) toxicities, but to a much lower extent than tacrolimus.
ATG, lymphocyte immune globulin, antithymoglobulin equine; AZA, azathioprine; BUN, blood urea nitrogen; CSA, cyclosporine; GI, gastrointestinal; IL-2RA, interleukin 2 receptor antagonist; MMF, mycophenalate mofetil; OKT-3, muronomonab-CD3; PRED, prednisone; SCr, serum creatinine; SRL, sirolimus; TAC, tacrolimus; WBC, white blood cell.
Adapted from DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005, Table 87–4, p. 1622.

Comparative Efficacy: Antiproliferatives

MPA derivatives have replaced azathioprine as the antiproliferative agent of choice in most organ transplant centers. The MPA derivatives generally are considered to provide a more specific immunosuppressive effect compared with azathioprine. Mycophenolate mofetil and enteric-coated mycophenolic acid have similar safety and efficacy data in renal transplant recipients.

Target of Rapamycin Inhibitors

Sirolimus

Sirolimus is currently the only FDA-approved ToR inhibitor. One of its derivatives, everolimus, is in phase III clinical trials and has been approved for use in some European countries.[30] Sirolimus is a macrolide antibiotic that has no effect on calcineurin phosphatase.[11,31,32] ❼ *Sirolimus inhibits T cell activation and proliferation by binding to and inhibiting the activation of the mammalian ToR, which suppresses cellular response to IL-2 and other cytokines (i.e., IL-4 and IL-15).*[11,31] Studies have shown that sirolimus may be used safely and effectively with either cyclosporine or tacrolimus as a replacement for either azathioprine or mycophenolate mofetil.[33] However, when using both sirolimus and cyclosporine as part of a patient's immunosuppressant therapy, because of a drug interaction between the two resulting in a marked increase in sirolimus concentrations, it is recommended to separate the sirolimus and cyclosporine doses by at least 4 hours. ❼ *Sirolimus also can be used as an alternative agent for patients who do not tolerate calcineurin inhibitors due to nephrotoxicity or other adverse events.*[34]

Sirolimus is available in 1 and 2 mg tablets and a 1 mg/mL oral solution. The current FDA-approved dosing regimen for sirolimus is a 6 mg loading dose followed by a 2 mg/day maintenance dose.[11] It was recommended that this agent not require therapeutic drug monitoring. However, many centers do check trough concentrations and adjust doses to reach goal concentrations.[35] Many clinicians who prescribe sirolimus use a loading dose of 5 to 15 mg/day for 1 to 3 days to achieve adequate immunosuppression more rapidly.[31,33,34] Maintenance doses of sirolimus usually range from 1 to 10 mg/day given once daily. Sirolimus blood C_0 (trough) levels should be obtained and then maintained at between 5 and 20 ng/mL depending on the institution-specific protocols.[35] Of note, sirolimus has a half-life of approximately 62 hours, which means that it will not reach steady state after dosage changes for several days.[11]

❼ *The most common adverse events reported with sirolimus are leukopenia (20%), thrombocytopenia (13% to 30%), and hyperlipidemia (38% to 57%).*[11,31] Other adverse effects include delayed wound healing, anemia, diarrhea, arthralgias, rash, and mouth ulcers. Sirolimus has an FDA black-box warning in newly transplanted liver and lung recipients.[11] In liver transplant recipients, use of sirolimus immediately after transplant is associated with an increased risk of hepatic artery thrombosis, graft loss, and death. In lung transplant recipients, bronchial anastomotic dehiscence, including some fatal cases, has been noted in patients treated with sirolimus, tacrolimus, and corticosteroids.

Corticosteroids

Traditional triple-therapy immunosuppressive regimens have consisted of a calcineurin inhibitor, an antiproliferative or ToR inhibitor, and corticosteroids. In recent years, many protocols have focused on corticosteroid sparing or avoidance. Avoidance or sparing of corticosteroids has been supported in the literature, although more studies are needed to better characterize which patients should follow these protocols.[36–39]

❽ *Corticosteroids have various effects on immune and inflammatory response systems, although their exact mechanism of immunosuppression is not fully understood. It is generally believed that at high doses, the agents are directly lymphotoxic, and at lower doses, the corticosteroids act by inhibiting the production of various cytokines that are necessary to amplify the immune response.*[11]

The most commonly used corticosteroids are methylprednisolone (IV and oral) and prednisone (oral), although prednisolone and dexamethasone also have been shown to be effective for organ transplantation. Corticosteroid doses vary by center-specific protocols, organ type, and patient characteristics. A typical taper would include an IV 100 to 500 mg bolus of methylprednisolone at the time of transplant and then a taper over 5 to 7 days to a maintenance dose of prednisone 20 mg/day or complete cessation.[2,7] It is important for practitioners to know that approximately 4 mg methylprednisolone is equivalent to 5 mg prednisone and 0.75 mg dexamethasone.[11] At most transplant centers, therapeutic drug monitoring of corticosteroids is not employed. ❽ *Corticosteroids are associated with a variety of acute and chronic toxicities. The most common adverse events have been summarized in Table 52–5.*

Maintenance Immunosuppressive Therapies: Common Drug-Drug Interactions

❾ *As the number of medications that a patient takes increases, so does the potential for DDIs.* Disease severity, patient age, and organ dysfunction are all risk factors for increased DDIs. In general, DDIs can be broken down into two categories: (1) pharmacokinetic interactions and (2) pharmacodynamic interactions.

Given the large number of medications consumed by transplant recipients, it is no surprise that this patient population is at high risk for DDIs. Pharmacokinetic DDIs often are considered the major problem with some of the maintenance immunosuppressants. Due to their narrow therapeutic index, DDIs involving immunosuppressant agents may be significant and could result in toxicities and/or decreased effect. In other words, pharmacokinetic interactions can result in increased concentrations of one or more agents, increasing the risk for toxic side effects, or in lowered or sub-therapeutic drug concentrations, possibly leading to allograft rejection.

TABLE 52–5. Common Adverse Events Associated with Corticosteroids[11]

Body System	Adverse Event
Cardiovascular	Hyperlipidemia Hypertension
Central nervous system	Anxiety Insomnia Mood changes Psychosis
Dermatologic	Acne Diaphoresis Ecchymosis Hirsutism Impaired wound healing Petechiae Thin skin
Endocrine/metabolic	Cushing's syndrome Hyperglycemia Sodium and water retention
Gastrointestinal	Gastritis Increased appetite Nausea, vomiting, diarrhea Peptic ulcers
Hematologic	Leukocytosis
Neuromuscular/skeletal	Arthralgia Impaired growth Osteoporosis Skeletal muscle weakness
Ocular	Cataracts Glaucoma
Respiratory	Epistaxis

Corticosteroids, Cyclosporine, Tacrolimus, and Sirolimus

Cyclosporine, tacrolimus, and sirolimus are substrates of the cytochrome P-450 3A (CYP3A) isozyme system and P-glycoprotein (P-gp) transport protein.[11] The cytochrome P-450 (CYP) isozyme system is responsible for the oxidative biotransformation of many medications. The majority of the CYP-mediated metabolism takes place in the liver, but CYP is also expressed in the intestine, lungs, kidneys, and brain. Two types of interactions usually occur with medications metabolized via the CYP enzyme system: inhibitory interactions and inducing interactions. Enzyme inhibition occurs when there is enzyme inactivation or mutual competition of substrates at a catalytic site. This usually results in a reduction of drug metabolism leading to increased whole-blood trough concentrations and prolonged half-lives of all medications involved. Enzyme induction interactions are just the opposite and occur when there is increased synthesis or decreased degradation of CYP enzymes. This type of interaction can produce decreased concentrations of medications.

Cyclosporine, tacrolimus, and sirolimus are all metabolized via the CYP3A4 pathway; therefore, it would be anticipated that they would experience similar pharmacokinetic DDIs. Table 52–6 details some clinically relevant DDIs that occur with calcineurin inhibitors and sirolimus due to inhibition or induction of the CYP enzyme system.

One of the most often overlooked DDIs in transplant recipients is the effect corticosteroids have on drug metabolism.[40] Corticosteroids are CYP3A enzyme inducers, meaning that they may reduce the whole-blood trough concentrations of cyclosporine, tacrolimus, and sirolimus.[11] This is usually not a noteworthy interaction because the doses of cyclosporine, tacrolimus, and sirolimus can be titrated to achieve target trough concentrations. However, this DDI has been problematic during steroid withdrawal protocols and is evident by increased immunosuppressant trough concentrations after complete steroid withdrawal.

Most pharmacokinetic interactions in transplantation occur due to interactions with the CYP enzyme system; however, several interactions have been shown to occur via alternative mechanisms. One of the most notable is that seen between tacrolimus and some of the prokinetic agents. Cisapride and metoclopramide have been shown to increase the absorption of tacrolimus by enhancing gastric emptying.[41]

P-glycoprotein, a plasma membrane transport protein, is present in the gut, brain, liver, and kidneys.[42] This protein provides a biologic barrier by eliminating toxic substances and xenobiotics that may accumulate in these organs. P-glycoprotein plays an important role in the absorption and distribution of many medications. Medications that are CYP3A4 substrates, inhibitors, or inducers are also often affected by P-glycoprotein; therefore, the potential for even more DDIs exists in transplant recipients.[42]

Azathioprine and the Mycophenolic Acid Derivatives

Azathioprine, mycophenolate mofetil, and enteric-coated MPA are not metabolized through the CYP isozyme system; therefore, they do not experience the same DDI profiles as cyclosporine, tacrolimus, and sirolimus. Azathioprine's major DDIs involve allopurinol, angiotensin-converting enzyme (ACE) inhibitors, aminosalicylates (e.g., mesalamine and sulfasalazine), and warfarin.[11] The interaction with allopurinol is seen frequently and has clinical significance. Allopurinol inhibits xanthine oxidase, the enzyme responsible for metabolizing azathioprine. Combination of azathioprine and allopurinol has resulted in severe toxicities, particularly myelosuppression. It is recommended that concomitant therapy with azathioprine and allopurinol be avoided, but if combination therapy is necessary, the azathioprine doses must be reduced to one-third or one-fourth of the current dose. Use of azathioprine with the ACE inhibitors or aminosalicylates also can result in enhanced myelosuppression.[11] Some case reports exist demonstrating that warfarin's therapeutic effects may be decreased by azathioprine.[43–45]

Most of the interactions with mycophenolate mofetil and enteric-coated MPA are due to reductions in intestinal absorption. Aluminum-, magnesium-, or calcium-containing antacids decrease the peak level and overall exposure of MPA from either of the preparations.[11] If a patient requires liquid antacids, they should be administered at least 4 hours before

TABLE 52–6. Potential Drug-Drug Interactions with the Calcineurin Inhibitors and Sirolimus Mediated Through the CYP3A4 Isozyme[11]

Substrates[a]		Inducers[b]	Inhibitors[c]
Alfentanil	Lidocaine	Carbamazepine	Cimetidine
Alprazolam	Loratadine	Dexamethasone	Clarithromycin
Amiodarone	Lovastatin	Ethosuximide	Clotrimazole
Amlodipine	Nevirapine	Isoniazid	Delavirdine
Atorvastatin	Nicardipine	Nevirapine	Diltiazem
Cilostazol	Nifedipine	Phenobarbital	Erythromycin
Cisapride	Omeprazole	Phenytoin	Fluconazole
Chlorpromazine	Paclitaxel	Prednisone	Fluoxetine
Clonazepam	Propafenone	Rifabutin	Fluvoxamine
Cocaine	Progesterone	Rifampin	Grapefruit Juice
Cortisol	Quetiapine	St. John's Wort	Indinavir
Cyclophosphamide	Quinidine		Itraconazole
Dantrolene	Sertraline		Ketoconazole
Dapsone	Simvastatin		Miconazole
Diazepam	Tamoxifen		Nefazodone
Disopyramide	Testosterone		Nelfinavir
Enalapril	Triazolam		Ritonavir
Estradiol	Venlafaxine		Saquinavir
Estrogen	Vinblastine		Troleandomycin
Etoposide	Warfarin		Verapamil
Felodipine	Zolpidem		Voriconazole
Flutamide			Zafirlukast

[a]Substrates of the CYP3A4 isozyme will compete with cyclosporine, tacrolimus, and sirolimus for metabolism; therefore, concentrations of both medications may be increased (usually by less than or equal to 20%).
[b]Inducers of the CYP3A4 isozyme will enhance the metabolism of cyclosporine, tacrolimus, and sirolimus; therefore, concentrations of these medications may be decreased.
[c]Inhibitors of the CYP3A4 isozyme will decrease the metabolism of cyclosporine, tacrolimus, and sirolimus; therefore, concentrations of these medications may be increased.
CYP3A4, cytochrome P-450 system 3A isozyme.

or after the MPA derivatives. Cholestyramine has been shown to decrease overall MPA exposure.[46,47] This interaction is due to the ability of cholestyramine to inhibit the enterohepatic recirculation of MPA. Through a similar mechanism, cyclosporine has been shown to reduce the overall exposure to MPA derivatives.[48] Recent studies have shown lower MPA levels in cyclosporine-based immunosuppression regimens than in tacrolimus-based regimens.

In addition to the numerous pharmacokinetic interactions seen with the maintenance immunosuppressants, there also exists the possibility for pharmacodynamic interactions. An in-depth review of pharmacodynamic interactions with maintenance immunosuppressive agents goes beyond the scope of this chapter. However, it is important to note that the addition of nephrotoxic agents, such as amphotericin B, aminoglysides (e.g., gentamicin, tobramicin, or amikacin), and non-steroidal anti-inflammatory drugs (NSAIDs; e.g., naproxen, ibuprofen, or ketorolac) may potentiate the nephrotoxic effects of the calcineurin inhibitors. The use of myelosuppressive agents, such as cotrimoxazole and valganciclovir, also could enhance myelosuppression when combined with azathioprine or the MPA derivatives.

The potential exists for multiple DDIs in transplant recipients owing to the complexity of their medication regimens. Practitioners must be diligent in reviewing all medications for potential DDIs. In addition to reviewing prescription medications, it is essential to question patients about the use of both non-prescription and complementary and alternative medications because these products also have the potential for significant interactions.

Treatment of Acute Rejection Episodes

Reduction in severity of the immune response and prevention of irreversible graft injury are the chief aims of acute rejection episode treatment. Treatment strategies include: (1) using high-dose corticosteroids (dosage is later tapered); (2) using short-term treatment with induction agents such as ATG or OKT-3; (3) increasing the dosage of the patient's immunosuppressant maintenance therapy; or (4) adding another immunosuppressant



Patient Encounter, Part 2

1. Identify your treatment goals for JJ in terms of maintenance immunosuppressants.
2. Create a plan for maintenance therapy for JJ, making sure to compare and contrast the pros and cons of the different maintenance immunosuppressants.
3. Identify the potential DDIs that may exist with the addition of the maintenance immunosuppressants to the medications that JJ is currently taking.

such as sirolimus to the patient's regimen. Choice of treatment varies by medical center and type of transplant; however, acute rejection generally is treated with a course of high-dose methylprednisolone (250–1000 mg/day IV for 3 days), which is usually sufficient to ameliorate the rejection episode. If the acute rejection episode is resistant to the initial course of steroids, a second course may be administered, or the patient then may begin therapy with antithymocyte globulin (1.5 mg/kg per day for 3 to 14 days). Acute rejection refractory to these treatments may require OKT-3. However, the use of OKT-3 to treat acute rejection has fallen out of favor due to the severe short- and long-term adverse events associated with its use.

Management of Immunosuppressive Drug Complications

Opportunistic Infections

❾ *Solid-organ transplant recipients are at increased risk of infectious diseases, which is a major cause of early morbidity and mortality.* The prevalence of posttransplant infection depends on several factors, including clinical risk factors, environmental exposures, and the degree of immunosuppression. Anti-infectives are prescribed universally in this population, and their use can be split into three different categories:

- *Prophylaxis*—antimicrobials given to prevent an infection
- *Empirical*—preemptive therapy based on clinical suspicion of an active infection
- *Treatment*—antimicrobials given to manage a documented infection

Within the first-year posttransplantation, infection and rejection are the most frequently encountered complications. The risk of infection is associated with the overall level of immunosuppression. Thus, the risk of infection is greatest during the first 3 months after transplantation and during intense immunosuppression treatment, such as seen when treating rejection episodes. The information in this section is designed only to highlight prophylaxis options used routinely in organ transplant recipients. Table 52–7 lists the agents used

TABLE 52–7. Prophylactic Options for *Pneumocystis jiroveci* Pneumonia and CMV[50,51]

Medication	Dosing	Common Adverse Events
Anti-*Pneumocystis* Prophylaxis		
Sulfamethoxazole-trimethoprim (SMZ-TMP, cotrimoxazole)	One SS tablet by mouth once a day[a] One DS tablet by mouth once a day[a] One DS tablet by mouth every M/W/F[a]	Hyperkalemia Myelosuppression Nephrotoxicity Neutropenia Photosensitivity Rash
Pentamadine	300 mg inhaled every 3–4 weeks	Bronchospasm Cough Hypoglycemia or hyperglycemia
Dapsone	50–100-mg tablet by mouth once a day	Hepatotoxicity Myelosuppression Nephritis
Atovaquone	1500 mg suspension by mouth once a day	Elevated liver transaminases Nausea Rash
Anti-cytomegalovirus		
Valganciclovir	450–900 mg by mouth once a day[a]	Stomach upset (8–41%) Myelosuppression (2–27%) Headache (9–22%)
Ganciclovir	5 mg/kg IV every day, or 1000 mg by mouth three times a day[a]	Stomach upset (13–40%) Myelosuppression (5–40%) Rash (10–15%)
Valacyclovir	1–2 g by mouth four times a day[a]	Stomach upset (1–15%) Myelosuppression (less than 1%) Headache (14–35%)
CMV IgG and polyvalent IVIG	The maximum recommended total dosage per infusion is 150 mg/kg beginning within 72 hours of transplantation Follow-up doses and time intervals depend on the type or organ transplanted	Stomach upset (1–6%) Fevers and chills (1–6%) Flushing (1–6%)

[a]Dose adjustment required in renal insufficiency.
CMV, cytomegalovirus; DS, double-strength (800 mg SMZ, 160 mg TMP); IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; M/W/F, Monday, Wednesday and Friday; SS, single-strength (400 mg SMZ, 80 mg TMP).

for the prevention of *Pneumocystis jiroveci* pneumonia and CMV disease. Table 52–8 presents special pharmacotherapy considerations in transplant recipients.

Pneumocystis jiroveci Pneumonia

❾ *Without prophylaxis,* Pneumocystis jiroveci *(formerly* Pneumocystis carinii*) pneumonia occurs in 5% to 15% of transplant recipients.*[49] Anti-*Pneumocystis* prophylaxis is enormously helpful and generally is used in all organ transplant recipients. The duration of prophylaxis usually is 3 to 12 months after transplant but may be prolonged in highly immunosuppressed patients (i.e., active CMV disease and treatment for rejection) or liver or lung recipients.[50] Sulfamethoxazole-trimethoprim is the preferred agent for prophylaxis. One of its major advantages is its relatively broad spectrum of activity. Not only is it effective against *Pneumocystis* pneumonia, but it also has activity against toxoplasmosis and other common bacterial infections. Patients with sulfa allergies, glucose-6 phosphate dehydrogenase (G6PD) deficiency, or an inability to tolerate sulfamethoxazole-trimethoprim should be given one of the second-line treatments.[11] Unfortunately, the second-line agents are antiparasitics and have no meaningful activity against common bacteria. These agents include dapsone, atovaquone, and pentamidine.

Cytomegalovirus

CMV is the most concerning opportunistic pathogen in transplantation due to its association with poor outcomes.[51] **CMV infection** is present in 30% to 97% of the general population, but CMV disease typically is restricted to immunocompromised hosts.[52] The risk of CMV disease is highest among CMV-naive recipients who receive a CMV-positive organ (donor+/recipient–).[51] Other factors that augment the risk of CMV disease include organ type (lung and pancreas recipients are at highest risk) and immunosuppressive agents (ALA use increases risk). CMV disease characteristically occurs within the first 3 to 6 months after transplantation, but delayed-onset disease has been seen in patients receiving antiviral prophylaxis.[51]

Several antivirals have proven efficacy in preventing and treating CMV[51] (Table 52–7). Valacyclovir and valganciclovir, prodrugs of acyclovir and ganciclovir, respectively, have improved bioavailability compared with their parent compounds and offer the advantage of less frequent dosing. CMV prophylaxis classically is continued for the first 100 days or longer after transplantation.[52,53] Both IV ganciclovir and oral valganciclovir may be used for preemptive therapy or for treatment of established CMV disease. The adverse events are similar among these agents and include myelosuppression and GI effects.[11]

Invasive Fungal Infections

Fungal infections are an important cause of morbidity and mortality in solid-organ transplant recipients. Immunologic (e.g., immunosuppressants and CMV infection), anatomic (e.g., tissue ischemia and damage), and surgical (e.g., duration of surgery and transfusion requirements) factors contribute to the risk for invasive fungal infections. Mucocutaneous candidiasis (i.e., oral thrush and esophagitis) is associated with corticosteroid and ALA use. Oral nystatin or clotrimazole troches are effective prophylactic options for the prevention of thrush. However, clotrimazole inhibits the CYP3A system in the gut and can alter immunosuppressive levels (concentrations).[11] The use of systemic fungal prophylaxis, such as oral fluconazole, is controversial owing to the potential for DDIs and the risk of developing resistance. The choice of agents depends on the fungal risk in that particular population. For example, liver and intestine transplant recipients are at high risk for candidiasis; therefore, the use of medications that cover the *Candida* species is crucial, such as the triazole antifungals (e.g., fluconazole or itraconazole) or the echinocandins (e.g., caspofungin or micafungin). Lung transplant recipients are at high risk for aspergillosis; therefore, it is imperative to use antifungal prophylaxis that covers the *Aspergillus* species, such as the echinocandins or polyenes (e.g., amphotericin B or lipid-based amphotericin B products).[54]



Patient Encounter, Part 3

1. Identify your treatment goals for JJ in terms of antimicrobial prophylaxis.
2. Create a plan for JJ's antimicrobial prophylaxis, making sure to compare and contrast the pros and cons of the different agents for this patient.

Hypertension

❾ *Cardiovascular disease has been identified as one of the leading causes of death in organ transplant recipients.*[55] Posttransplant hypertension (HTN) is associated with an increase in cardiac morbidity and patient mortality in all transplant patients and is also an independent risk factor for chronic allograft dysfunction and loss.[56] Based on all the available posttransplant morbidity and mortality data, it is imperative that posttransplant HTN be identified and managed appropriately.

There are several underlying mechanisms responsible for posttransplant HTN. Some causes of HTN in transplant recipients may include renal dysfunction, increased sensitivity to endothelin-1 and angiotensin, increased density of glucocorticoid receptors in the vascular smooth muscle, and decreased production of vasodilatory prostaglandins.[57] However, one of the most easily recognized causes of posttransplant HTN is the use of corticosteroids and calcineurin inhibitors.[58,59] Corticosteroids usually cause sodium and water retention,[57] thus increasing blood pressure, whereas calcineurin inhibitors are associated with a number of effects that may result in HTN, including

TABLE 52–8. Special Pharmacotherapy Considerations in Transplant Recipients

Problem	Pharmacotherapy	Special Considerations
Infection		
CMV	See Table 52–7	
Perioperative prophylaxis	Bowel decontamination	Donor culture results Penicillin allergy: vancomycin
Pneumocystis jiroveci prophylaxis	See Table 52–7	Sulfa allergy
Fungal		
Prophylaxis Treatment	Nystatin, clotrimazole, fluconazole, itraconazole, ketoconazole, Amphotericin B	Inhibit P-450 3A4; monitor CSA and TAC levels; decrease doses Consider liposomal products; decrease or stop CSA or TAC to minimize nephrotoxicity Remember to adjust doses of renally eliminated drugs (e.g., acyclovir, ganciclovir, TMP-SMX)
Hyperkalemia	Restrict dietary intake; dialysis	May be exacerbated by CSA or TAC or ACEIs, acidosis, or RI; fludrocortisone acetate 0.1 mg orally every day twice daily for refractory hyperkalemia
Hyperglycemia		
Diabetes pretransplant	Insulin Oral hypoglycemics	Glucocorticoids, TAC, and CSA also increase hypoglycemic requirements; insulin requirements will increase with improving renal function
	Metformin	Avoid in those with RI
Posttransplant diabetes	Insulin	Risk factors: obesity, family history, African-American race, cadaveric kidney, TAC greater than CSA
	Oral hypoglycemics	May resolve/improve as immunosuppressive doses decrease
Ulcer prophylaxis	H_2-receptor antagonists Sucralfate Proton pump inhibitors	Adjust dose in those with RI; decreased TAC absorption; if RI, caution aluminum content; no RI, caution hypophosphatemia
Hyperlipidemia	Diet	CSA greater than TAC; consider switch to TAC; discontinue or hold SRL
	HMG-CoA reductase inhibitors (statins)	CSA/TAC may increase statin levels; start at lowest dose Monitor for muscle cramps, CPK levels and LFTs
	Gemfibrozil	Adjust dose in those with RI Caution with concomitant statin
	Ezetemibe	Often used in combination with a statin
Hypertension	Calcium channel blockers	Diltiazem, verapamil inhibit CSA/TAC metabolism Dihydropyridines may potentiate CSA-gingival hyperplasia
	ACE inhibitors; ARBs	May exacerbate hyperkalemia; monitor K^+, SCr to assess for renal allograft vascular disease; may be useful in posttranplant erythrocytosis (hematocrit greater than 55%)
Osteoporosis	Oral calcium supplementation (1000–5000 mg/day)	If daily intake less than 1000 mg elemental calcium
	Oral vitamin D Calcifediol (1000 IU/day) Calcitriol (0.5 mcg/day)	Documented deficiency If kidney functioning If kidney not functioning
	Hormone-replacement therapy	Post-menopausal women without contraindications
	Calcitonin or oral bisphosphonates	Documented loss in bone mineral density greater than 3% Data lacking for bisphosphonates in patients with RI
Malignancy		
Prevention	Minimize immunosuppressant doses; avoid sun exposure (sunblock, hats, clothing); routine self-exams (skin, lymph nodes); yearly gynecologic/prostate exams	AZA particularly associated with skin cancers CSA/TAC may be associated with lymphoproliferative disorders (lymphomas)
Treatment	Discontinue or minimize immunosuppressants Surgical, radiologic, or antineoplastic therapy	Do not abruptly withdraw corticosteroids

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; AZA, azathioprine; CMV, cytomegalovirus; CPK, creatinine phosphokinase; CSA, cyclosporine; HMG-CoA, 3-hydroxy 3-methylglutaryl coenzyme A reductase; K^+, potassium; LFTs, liver function tests; RI, renal insufficiency; SCr, serum creatinine; SRL, sirolimus; TAC, tacrolimus; TMP-SMX, trimethoprim-sulfamethoxazole.

Adapted from DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005, Table 87–10, p. 1637.

reduced glomerular filtration rate (GFR) and renal blood flow (RBF), increased systemic and intra-renal vascular resistance, sodium retention, reduced concentrations of systemic vasodilators (e.g., prostacyclin and nitric oxide), and increased concentrations of vasoconstrictive thromboxanes.[60]

Although tacrolimus therapy is associated with increasing blood pressure, studies have found that tacrolimus has less dramatic effects on GFR and RBF than cyclosporine. In some clinical trials, tacrolimus caused less severe HTN and required significantly fewer antihypertensive medications at both 24 and 60 months after transplantation than cyclosporine.[61–63] Thus conversion from cyclosporine-based immunosuppression to tacrolimus-based immunosuppression may be one way to minimize blood pressure increases in transplant recipients. Conversion to sirolimus also may be an alternative to the calcineurin inhibitors in patients with difficult-to-treat HTN because sirolimus therapy is less associated with increased blood pressure. Additionally, withdrawal or tapering of steroid therapy may be an effective strategy for lowering blood pressure.

Treatment

❾ *Controlling HTN after transplantation is essential in preventing cardiac morbidity and mortality and prolonging graft survival.* The target blood pressure in kidney transplant recipients should be less than 130/80 mm Hg. This goal blood pressure may not be suitable for all organ transplant recipients. In such cases, the guidelines detailed in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VII) should be followed.

Nonpharmacologic Therapy: Lifestyle Modifications

In order to achieve a goal blood pressure, lifestyle modifications, including diet, exercise, sodium restriction, and smoking cessation, are recommended.[63] Unfortunately, lifestyle modifications alone often are inadequate to control HTN in this high-risk population, and antihypertensive medications usually are needed.

Antihypertensive Agents

There is no single class of antihypertensive medications recognized as the ideal agent. Numerous factors must be considered when determining appropriate treatment for a given patient, including the safety and efficacy data of the available agents, patient-specific situations, and potential comorbidities and medication cost. A large majority of patients often require multiple medications to achieve their goal blood pressure. This conclusion is supported by the recommendations of JNC-VII, where combination therapy is regarded as an appropriate first-line therapy.

β-Blockers and thiazide diuretics have proven benefits in reducing cardiovascular disease–associated morbidity and mortality.[55] Tolerability permitting, these agents are to be considered first-line therapies in most transplant recipients. The ACE inhibitors and angiotensin-receptor blockers (ARB) have definite benefits in patients with nephropathy and are believed to have renoprotective effects in most patients. Due to their ability to cause an initial bump in serum creatinine, these agents should be used cautiously when employed in combination with the calcineurin inhibitors. The dihydropyridine calcium channel blockers have demonstrated an ability to reverse the nephrotoxicity associated with cyclosporine and tacrolimus (Table 52–8). In general, antihypertensive therapy should focus on agents with proven benefit in reducing the progression of cardiovascular disease and should be chosen on a patient-specific basis.[55] See Chapter 2 for further recommendations for treating HTN.

Hyperlipidemia

❾ *Hyperlipidemia is seen in up to 60% of heart, lung, and renal transplant patients and greater than 30% of liver transplant patients.*[64–66] As a result of elevated cholesterol levels, transplant recipients are not only at an increased risk of atherosclerotic events, but emerging evidence also shows an association between hyperlipidemia and allograft vasculopathy.[66] Hyperlipidemia, along with other types of cardiovascular disease, is now one of the primary causes of morbidity and mortality in long-term transplant survivors.[67]

Elevated cholesterol levels in transplant patients are due to a culmination of factors such as age, genetic disposition, renal dysfunction, DM, proteinuria, body weight, and immunosuppressive therapy. Many of the immunosuppressive agents can produce elevations in serum lipid levels.

Treatment

❾ *Lowering cholesterol has been shown to decrease severe rejection and transplant vasculopathy significantly and to improve 1-year survival in heart transplant recipients.*[68] Although these results cannot be extrapolated to other transplant populations, they do demonstrate the potential benefits of aggressive cholesterol-lowering in organ transplant recipients. Due to the high prevalence of cardiovascular disease among organ transplant recipients, most health care practitioners consider these patients to fall in the highest-risk category for lipid-lowering as established by the National Cholesterol Education Panel (NCEP) III guidelines. These guidelines recommend a low-density lipoprotein cholesterol (LDL-C) level of less than 100 mg/dL (2.6 mmol/L).[69]

Nonpharmacologic Therapy: Lifestyle Modifications

Generally, lowering cholesterol in patients begins with therapeutic lifestyle changes. These changes are initiated either alone or in conjunction with lipid-lowering drug therapy depending on baseline cholesterol levels and other risk factors. Therapeutic lifestyle changes entail a reduction in saturated fat and cholesterol intake and an increase in moderate physical activity.[69] As with hypertension, lifestyle modifications alone

rarely are effective enough to achieve a goal LDL-C level.[66] Modifications of the immunosuppressive regimen and use of cholesterol-lowering medications often are warranted in this patient population.

Immunosuppressive Regimen Modifications

Tacrolimus has shown the propensity to cause less severe hyperlipidemia when compared with cyclosporine. Thus conversion from cyclosporine-based immunosuppression to tacrolimus-based immunosuppression may be one way to counteract this disease in transplant recipients.[66] Studies demonstrate that steroid withdrawal in renal transplant patients lowered total cholesterol by 17% and LDL-C by 16%; unfortunately, an 18% decrease in high-density lipoprotein (HDL) levels also was noted in these patients.[66]

Cholesterol-Lowering Agents

Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are considered to be first-line therapy for reducing LDL-C in the general population.[66,70–73] However, there is some uncertainty about the pathogenesis of cardiovascular disease in transplant recipients and whether statin therapy will have similar effectiveness in organ transplant recipients. Statins have shown definite advantages when used in heart transplantation, including a reduction in LDL-C and major adverse cardiac events (MACE), as well as an apparent cardioprotective effect. In renal transplant recipients, statins are known to lower LDL-C levels and reduce the incidence of some cardiac events; however, the ability to lower MACE may not be evident in this patient population. Despite these mixed results, statins still are considered the primary therapeutic option for hyperlipidemia in all organ transplant recipients.[66] It is important to note that statins used in combination with calcineurin inhibitors have resulted in an increased risk for muscle weakness and rhabdomyolysis. Thus close monitoring is necessary in transplant patients who are taking a calcineurin inhibitor and a statin. Monitoring should include periodic assessment of liver enzymes and creatine kinase [CK, or creatine phosphokinase (CPK)] levels, as well as assessment for muscle weakness (Table 52–8).

Fibric acid derivatives are an excellent choice for lowering triglycerides but are not as effective as statins at lowering LDL-C.[66] These agents, in conjunction with statins, play a role in treating patients with both elevated LDL-C and triglycerides. Nicotinic acid is very effective at improving the lipid panel, with excellent results in lowering LDL-C, as well as increasing HDL. However, patient tolerability issues are of concern with this agent. Bile acid sequestrants should be avoided in organ transplant recipients due to their high incidence of GI adverse events, as well as their propensity for pharmacokinetic DDIs with immunosuppressants. Although some clinical trials demonstrated that cyclosporine increased ezetimibe serum concentrations, ezetimibe appears to be an effective cholesterol-lowering agent, especially when combined with a statin. Future studies are needed to establish ideal regimens involving the antihyperlipidemic and immunosuppressive medications in order to decrease morbidity and mortality and, ultimately, prevent cardiovascular events.[66] See Chapter 9 for further guidance in treating hyperlipidemia.

New-Onset Diabetes Mellitus after Transplantation

❾ *New-onset DM after transplantation (NODAT) is a serious complication that often is underestimated by transplant practitioners.*[74] Kasiske and colleagues attempted to quantify the cumulative incidence of NODAT in renal transplant recipients and found that 8% of patients developed NODAT at 3 months after transplantation, 13% at 12 months, and



Patient Encounter, Part 4

JJ has recovered from her transplant procedure and now is doing relatively well. She returns to your clinic 1 month after the transplant.

Labs

Na: 141 mEq/L (141 mmol/L)
K: 4.9 mEq/L (4.9 mmol/L)
Cl: 100 mEq/L (100 mmol/L)
CO_2: 22 mEq/L (22 mmol/L)
BUN: 22 mg/dL (7.9 mmol/L)
SCr: 1.2 mg/dL (106.1 μmol/L)
Glucose: 89 mg/dL (4.9 mmol/L)
Lipid panel: TC = 271 mg/dL (7.0 mmol/L);
LDL-C = 180 mg/dL (4.7 mmol/L)
HDL = 30 mg/dL (0.8 mmol/L); TG = 325 mg/dL (3.7 mmol/L)

VS: BP = 154/95 mm Hg (152/88 mm Hg repeated);
HR = 60 beats/minute

Meds

Tacrolimus 3 mg by mouth twice a day
Mycophenolate mofetil 1000 mg by mouth twice a day
Prednisone 10 mg by mouth once a day
Bactrim SS 1 tablet daily
Nystatin 5 mL swish and swallow four times daily
Valganciclovir 450 mg by mouth once a day
Vitamin D 800 IU by mouth once a day
Calcium carbonate 1250 mg by mouth twice a day separated from food and mycophenolate
Simvastatin 20 mg by mouth once a day at bedtime
Metoprolol 100 mg by mouth twice a day
Amlodipine 10 mg by mouth once a day
Aspirin 81 mg by mouth once a day

- Identify why JJ is taking each medication listed.
- What are some treatment options, in addition to metoprolol 100 mg twice daily and amlodipine 10 mg daily, for JJ's elevated blood pressure?
- Design a monitoring plan for JJ's therapy.

22% at 36 months.[74] Even more alarming is that recent studies have revealed an overwhelming prevalence of impaired glucose tolerance, which is also accepted as a risk factor for long-term morbidity and mortality.[74] New-onset DM is associated with increases in cardiovascular events and an approximately 22% higher risk of mortality. Patients with NODAT are also more likely to suffer acute rejection episodes and infectious complications than patients without NODAT.[74,75]

Prevention

New-onset DM prevention consists mainly of identifying patients at risk before transplantation and controlling modifiable risk factors both before and after transplantation.[74] The major modifiable risk factors are choice of immunosuppressive therapy and body mass index (BMI). For example,

- *Immunosuppressive medications.* Steroid minimization and possibly withdrawal are effective strategies for the prevention of NODAT. Also, patients with worsening blood glucose levels after transplantation who are receiving tacrolimus may benefit from conversion to cyclosporine.[74]
- *BMI.* A reduction in body weight is always recommended in obese patients prior to the transplant procedure to help lower their NODAT risk.[74]

Treatment

Lifestyle modifications are always in order in patients who have developed or those who are at increased risk of developing NODAT.[74] Insulin therapy and oral hypoglycemic agents are used often (Table 52–8) in patients in whom lifestyle modifications alone have not controlled blood glucose levels. See Chapter 40 for appropriate treatment regimens for diabetes.

Neoplasia

Skin Cancer

Skin cancer remains the most common malignancy after organ transplantation. Skin cancers occur at rates from 3.4-fold (melanoma) up to 84-fold (Kaposi's sarcoma) higher in organ transplant recipients when compared with the general population.[77] A number of studies have shown that transplant recipients are at higher risk of cancer as a result of taking immunosuppressants after organ transplantation. The incidence of these types of cancers increases with time after transplantation, with one study showing a prevalence rate of 35% among patients within 10 years of transplant.[78] More alarming than the high prevalence is the activity of these cancers in the patient on maintenance immunosuppression. Skin cancers in transplant recipients tend to grow more rapidly and are more likely to metastasize.[77]

The most common risk factors for skin cancer development after transplantation include increased age, excessive ultraviolet (UV) light exposure, high degree of immunosuppression, Fitzpatrick skin types I, II and III, history of skin cancers, and infection by human papillomavirus.[77]

It is of the utmost importance that transplant practitioners be vigilant about educating their patients about excessive exposure to the sun.[77] Patients should be warned about the risk of skin cancer and be advised on simple methods to limit their risk:

- Use of protective clothing (e.g., long-sleeve shirts and long pants and dark-colored clothing).
- Use of sunscreen daily that is applied to all sun-exposed skin.
- Use of sunscreen with sun protection factor (SPF) 30 or higher is recommended.

Posttransplant Lymphoproliferative Disorders

❾ *Posttransplant lymphoproliferative disorders (PTLDs) are a major complication in patients following organ transplantation.*[79] The incidence of PTLD is 1% for renal patients, 2% for cardiac patients, 2% for liver patients, and 9% for heart-lung patients. The risk of developing non-Hodgkin's lymphoma is 28- to 49-fold higher in solid-organ transplant recipients than in the general population. Another independent risk factor is the presence of Epstein-Barr virus (EBV).[79–81] Lymphomas are the most common form of lymphoproliferative disease found in transplant recipients.[79]

The incidence of disease depends on certain factors. These factors include the type of organ transplanted, the age of the transplant recipient, the degree of immunosuppression, the type of immunosuppression, and exposure to EBV.[79,81] The mortality rate in these patients is about 50%, with most patients dying shortly after diagnosis. It also has been demonstrated that the risk of developing PTLD is greater in the population of patients who are EBV-seronegative at the time of transplant.[81]

Another risk factor for the development of PTLD is the type of immunosuppressive regimens used. Immunosuppressive regimens using ALAs have been proven to increase the risk of PTLD.[79]

Treatment

Treatment for PTLD is still controversial; however, the most common treatment options include reduction of immunosuppression, chemotherapy,[11,82] and anti-B cell monoclonal antibodies.[79]

PTLDs continue to be a long-term complication of prolonged immunosuppression. Current treatment options are all associated with certain risks. Prevention is the most effective treatment for PTLD. A better understanding in the future of the disease process and the risk factors involved with the development of PTLD will aid in the prophylaxis and treatment of this disorder.

OUTCOME EVALUATION

- Successful outcomes in solid-organ transplantation generally are measured in terms of several separate end points: (1) preventing acute rejection; (2) increasing 1-year graft survival; (3) preventing immunosuppressive drug complications; and (4) improving long-term allograft and patient survival.

- The short-term goals after organ transplantation revolve around reducing the incidence of acute rejection episodes and attaining a high graft survival rate. By accomplishing these goals, transplant clinicians hope to attain good allograft function to allow for an improved quality of life. These goals can be achieved through the appropriate use of medical immunosuppression and assessing the therapeutic and toxic monitoring parameters associated with each medication employed.
- Monitor transplant recipients for adverse drug reactions, drug-drug interactions, and compliance with their therapeutic regimen.
- The long-term goals after organ transplantation are to maximize the functionality of the allograft and to prevent complications of immunosuppression, which lead to improved patient survival.
- Clinicians must follow patient responses to immunosuppressant therapy, including identifying and treating the adverse sequelae associated with lifelong immunosuppression, such as cardiovascular disease, malignancy, infection, and osteoporosis, among others.
- Emphasize the importance of limiting drug misadventures and ensuring medication compliance with the therapeutic regimen to maximize desired outcomes and minimize adverse events.



Patient Care and Monitoring

The early management of transplant recipients:

1. Review any available diagnostic and laboratory data to evaluate the function of the allograft and the health of the recipient.
2. Assess the patient's current medication regimen, including

   Induction therapy agent:
   - Assess for appropriate dose and duration of therapy.
   - Therapeutic monitoring parameters (organ function)
   - Adverse-events monitoring parameters (Table 52–3)

   Maintenance immunosuppressive agents:
   - Assess for appropriate dose and duration of therapy.
   - Therapeutic monitoring parameters (organ function)
   - Adverse-events monitoring parameters (Tables 52–3 to 52–5)

   Anti-infective prophylaxis:
   - Assess suitability of chosen prophylactic agents (e.g., drug allergies, CMV donor, and recipient serostatus).
   - Therapeutic monitoring parameters (e.g., does the patient have any signs and/or symptoms of the infectious disease?)
   - Adverse-events monitoring parameters (Table 52–7)

   Medications used for comorbidities:
   - Assess appropriate selection of these medications for pharmacokinetic and pharmacodynamic DDIs (Table 52–6), need (e.g., do renal transplant recipients need to continue to take erythropoietin?), and efficacy.
   - Therapeutic monitoring parameters
   - Adverse-events monitoring parameters (Tables 52–7 and 52–8)
3. Evaluate the patient for the presence of adverse drug reactions, drug allergies, or DDIs.
4. Develop patient-specific short- and long-term therapeutic goals.
5. Provide patient education in regard to the organ transplant, the complications associated with transplantation, the need for lifestyle modifications to reduce the risk of the complications (e.g., wear sunscreen, low-sodium diet), and drug therapy.
6. Stress the importance of adherence with their therapeutic regimen.

The outpatient management of transplant recipients:

1. Obtain a thorough history of prescription, non-prescription, and complementary and alternative medication use.

   Maintenance immunosuppressive agents:
   - Assess for appropriate dose and duration of therapy.
   - Therapeutic monitoring parameters (organ function)
   - Adverse-events monitoring parameters (Tables 52–3 to 52–5)

   Anti-infective prophylaxis:
   - Assess suitability of chosen prophylactic agents (e.g., drug allergies, CMV donor, and recipient serostatus).
     - Does the patient need continued prophylaxis therapy?
     - When do you stop prophylaxis?
   - Therapeutic monitoring parameters (e.g., does the patient have any signs and/or symptoms of the infectious disease?)
   - Adverse-event monitoring parameters (Tables 52–7 and 52–8)

   Medications used for comorbidities:
   - Assess appropriate selection of these medications for pharmacokinetic and pharmacodynamic DDIs (Table 52–6), need, and efficacy.
   - Therapeutic monitoring parameters (drug- and disease-specific)
   - Adverse-events monitoring parameters (drug-specific) (Tables 52–7 and 52–8)
2. Evaluate the patient for the presence of adverse drug reactions, drug allergies, or DDIs.
3. Reassess your patient-specific short- and long-term therapeutic goals.
4. Continue with patient education in regard to the complications associated with transplantation, the need for lifestyle modifications to reduce the risk of complications (e.g., wear sunscreen, low-sodium diet), and drug therapy.
5. Emphasize the importance of adherence with the therapeutic regimen.
6. Assess patients' quality-of-life measures such as physical, psychological, and social functioning and well-being.

ABBREVIATIONS

ACE: angiotensin-converting enzyme
ACE-I: angiotensin-converting enzyme inhibitor
ALA: antilymphocyte antibodies (includes OKT-3, ATG, and antithymocyte globulin)
ANF: atrial natriuretic factor
APC: antigen-presenting cell
ARB: angiotensin-receptor blocker
ATG: lymphocyte immune globulin, antithymoglobulin equine
AWP: average wholesale price
AZA: azathioprine
BMI: body mass index
BUN: blood urea nitrogen
C_0: trough concentration
C_2: drug concentration 2 hours postdose
CCB: calcium channel blocker
CD4+: helper T cells
CD8+: cytotoxic T cells
CI: calcineurin inhibitor
CK: creatine kinase
CKD: chronic kidney disease
CMV: cytomegalovirus
CNS: central nervous system
CPK: creatine phosphokinase
CSA: cyclosporine
CXR: chest x-ray
CYP: cytochrome P-450 system
CYP3A: cytochrome P-450 system 3A isozyme
DC: dendritic cell
DDI: drug-drug interaction
DM: diabetes mellitus
DOE: dyspnea on exertion
DS: double strength
EBV: Epstein-Barr virus
ESRD: end-stage renal disease
FBS: fasting blood sugar
FDA: Food and Drug Administration
FEV: forced expiratory volume
GFR: glomerular filtration rate
GI: gastrointestinal
G6PD: glucose-6-phosphate dehydrogenase
HDL: high-density lipoprotein
HLA: human leukocyte antigen
HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A reductase
HTN: hypertension
IgG: immunoglobulin G
IL-2: interleukin-2
IL-2RA: interleukin-2 receptor antagonist
IV: intravenous
IVIG: intravenous immunoglobulin
JNC-VII: Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
K: potassium
LDL-C: low-density lipoprotein cholesterol
LFT: liver function test
MACE: major adverse cardiovascular events
MHC: major histocompatibility complex
MMF: mycophenolate mofetil
6-MP: 6-mercaptopurine
MPA: mycophenolic acid
NCEP: National Cholesterol Education Panel
NFAT-P: nuclear factor
NODAT: new-onset DM after transplant
NSAIDs: non-steroidal anti-inflammatory drugs
NYHA: New York Heart Association
OKT-3: muronomonab-CD3
PCKD: polycystic kidney disease
P-gp: P-glycoprotein
PRED: prednisone
PTLD: posttransplant lymphoproliferation disorder
RATG: rabbit antithymocyte immunoglobulin
RBF: renal blood flow
RI: renal insufficiency
SCr: serum creatinine
SOB: shortness of breath
SPF: sun protective factor
SPK: simultaneous pancreas-kidney
SRL: sirolimus
SS: single strength
TAC: tacrolimus
TC: total cholesterol
TCR: T-cell receptor
TG: triglycerides
TMP-SMX: trimethoprim-sulfamethoxazole
ToR: target of rapamycin
UV: ultraviolet
WBC: white blood cell

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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53 Osteoporosis

Beth Bryles Phillips



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Explain the association between osteoporosis and morbidity and mortality.
2. Identify risk factors that predispose patients to osteoporosis.
3. Describe the pathogenesis of fractures.
4. List the criteria for the diagnosis of osteoporosis.
5. Recommend appropriate lifestyle modifications to prevent bone loss.
6. Compare and contrast the effect of available treatment options on reduction of fracture risk.
7. Recommend an appropriate treatment regimen for a patient with osteoporosis, and develop a monitoring plan for the selected regimen.
8. Educate patients on osteoporosis and drug treatment, including appropriate use, administration, and adverse effects.

Key Concepts

❶ The most important risk factors for fracture are low bone mineral density and a personal history of adult fracture.

❷ A standardized approach for diagnosing osteoporosis is recommended using central dual-energy x-ray absorptiometry (DXA) measurements.

❸ Both pharmacologic and nonpharmacologic therapies for osteoporosis are aimed at preventing fractures and their complications, maintaining or increasing bone mineral density, preventing secondary causes of bone loss, and improving morbidity and mortality.

❹ All postmenopausal women with a personal history of osteoporotic fracture and/or low bone mineral density with risk factors for osteoporosis should receive treatment for osteoporosis.

❺ Adequate calcium and vitamin D intake is essential in the prevention and treatment of osteoporosis. Calcium and vitamin D supplements to meet requirements should be added to all drug therapy regimens for osteoporosis.

❻ Bisphosphonates are first-line therapy for postmenopausal osteoporosis owing to their established efficacy in preventing hip and vertebral fractures.

❼ Alendronate should be considered first-line treatment for primary osteoporosis in men owing to its proven benefit in reducing fractures and relative safety.

❽ For glucocorticoid-induced osteoporosis, bisphosphonate therapy is recommended in all patients who are starting treatment with glucocorticoids (prednisone greater than or equal to 5 mg/day or equivalent) for at least 3 months. For patients receiving chronic glucocorticoids (prednisone greater than or equal to 5 mg/day or equivalent), bisphosphonate therapy is also recommended if the bone mineral density is low or there is a history of fracture.

Osteoporosis is a common and often silent disorder associated with significant morbidity and mortality and reduced quality of life. It is associated with increased risk and rates of bone fracture and is responsible for over 1.5 million fractures in the United States annually, resulting in direct health care costs of over $17 billion.[1] As the population ages, these numbers are expected to increase. It is estimated that postmenopausal Caucasian women have a 50% lifetime chance of developing an osteoporosis-related fracture.[1] Common sites of fracture include the spine, hip, and wrist, although almost all sites can be affected. Only a fraction of patients with osteoporosis receive optimal treatment.

Osteoporosis is a disabling disorder with enormous impact. In addition to the initial pain associated with a new fracture, several adverse long-term complications can occur, including chronic pain, loss of mobility, depression, nursing home placement, and death. Patients with vertebral fractures may experience chronic pain, height loss, **kyphosis,** and decreased mobility

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owing to limitations in bending and reaching. Multiple vertebral fractures may lead to restrictive lung disease and alter abdominal anatomy. Patients with hip fractures have added risks associated with surgical intervention to repair the fracture. Some patients never recover fully or regain preinjury independence; mortality is common within 1 year of hip fracture.

EPIDEMIOLOGY AND ETIOLOGY

Osteoporosis is the most common skeletal disorder, and approximately one in five Caucasian women in the United States has the disease. The prevalence of vertebral fracture in postmenopausal women is greater than 20%.[2] Only one in three patients with osteoporosis has been diagnosed, and only one in seven will receive treatment.[2]

Osteoporosis can be classified as either primary (no known cause) or secondary (caused by drugs or other diseases). Primary osteoporosis is found most often in postmenopausal women and aging men, but it can occur in other age groups as well.

The prevalence of osteoporosis varies by age, gender, and race/ethnicity. The risk of fracture increases exponentially with each decade in age over 50.[3] Residents of nursing homes may be at an even higher risk of fracture. Both men and women lose bone as they age. However, women have accelerated bone loss surrounding menopause owing to loss of estrogen. Men have some protection from osteoporosis owing to their large bone mass and size and the absence of menopause. Fragility fractures of the hip and spine are common among men, especially as age increases. Men comprise 20% of the Americans with osteoporosis. Secondary causes of osteoporosis are found more commonly in men with fragility fractures.

Most hip fractures occur in postmenopausal Caucasian women; they also have the highest incidence of fracture when adjusted for age.[4] The incidence of osteoporosis and low bone mass is highest in Caucasian women, followed by Asian, Hispanic, and African-American women, respectively.[4]

TABLE 53–1. Risk Factors for Osteoporosis

White or Asian ethnicity
Positive family history of osteoporosis
Female sex
Advanced age
Small body frame (less than 58 kg or 128 lbs)
Smoking
Inactivity or excessive exercise
Excessive alcohol use
Poor nutrition
Low calcium intake
Low 25-hydroxyvitamin D levels
Hormonal deficiencies (e.g., hypogonadal state)
Inflammatory disorders
Organ transplantation
Medical disorders (e.g., chronic renal disease, anorexia nervosa, endocrine disorders)
Drugs (e.g., glucocorticoids, anticonvulsants, aromatase inhibitors)

Many of the risk factors for osteoporosis and osteoporotic fractures are predictors of low bone mineral density, such as age and ethnicity (Table 53–1). ❶*The most important risk factors for fracture are low bone mineral density, personal history of adult fracture, age, and family history of osteoporotic fracture.* Other important risk factors for osteoporosis and osteoporotic fractures include menopausal status, smoking status, and low body weight. As bone mineral density decreases, the risk of fracture increases. However, the threshold at which individual patients develop a fracture varies, and other factors may play a role in fracture susceptibility. One such factor that can influence the development of fracture is falling.

Osteoporosis also can develop from secondary causes such as concurrent disease states and drugs (Table 53–2).

TABLE 53–2. Medical Conditions and Drugs Associated with Osteoporosis or Low Bone Mass

Medical Conditions	Drugs
Alcoholism	Anticonvulsants (phenytoin, phenobarbital)
Chronic renal disease	Aromatase inhibitors (anastrazole, exemestane, letrozole)
Cushing's syndrome	Cytotoxic drugs (e.g., methotrexate, cisplatin)
Cystic fibrosis	Glucocorticoids
Diabetes mellitus	Gonadotropin-releasing hormone analogs (e.g., leuprolide acetate, nafarelin, gosarelin)
Eating disorders	Heparin
Gastrointestinal disorders (e.g., gastrectomy, malabsorption syndromes)	Immunosuppressants (e.g., tacrolimus)
Hematologic disorders (e.g., hemophilia)	Lithium
Hyperparathyroidism	Medroxyprogesterone acetate
Hyperthyroidism	Thyroid supplements (due to overreplacement)
Hypogonadal states	Total parenteral nutrition
Organ transplantation	
Skeletal cancer (e.g., myeloma)	



Patient Encounter, Part 1: Patient History

A 74-year-old woman with a history of chronic obstructive pulmonary disease (COPD) and gastroesophageal reflux disease (GERD) presents to the clinic for follow-up. She reports intermittent daytime and nighttime sweating that comes on suddenly. She reports soaking her bed sheets when this occurs. She had a hysterectomy at age 20 and has never taken estrogen replacement. She reports good relief of reflux symptoms on her current regimen. She started taking a calcium supplement approximately 2 years ago on the suggestion of her friend because she has never gotten much calcium in her diet. She states that she does not like milk and never drank it even as a child. She occasionally eats some dairy products such as cheese and ice cream approximately once per week.

PMH
- COPD
- GERD
- S/P total abdominal hysterectomy and bilateral salpingoophorectomy at age 20
- Chronic smoking

FH
Father died at age 85 with Alzheimer's dementia; mother died at age 86 with history of colon cancer and osteoporotic fractures of the hip and spine; brother alive and well at age 71.

SH
Retired elementary school teacher; smokes 1 pack per day for the last 50 years; does not drink alcohol.

Meds
- Albuterol inhaler 2 puffs four times daily
- Ipratropium inhaler 2 puffs four times daily
- Omeprazole 20 mg daily
- Calcium carbonate 500 mg daily
- Multivitamin daily

- Do any symptoms suggest the presence of osteoporosis?
- What risk factors for osteoporosis does this patient have?
- What are her calcium and vitamin D requirements?
- How could she incorporate more calcium into her diet?

Approximately one-third to one-half of osteoporosis cases in men and half of all cases in perimenopausal women are due to secondary causes.[4] Common secondary causes in men include hypogonadism, glucocorticoid use, and alcoholism. The most common cause of drug-induced osteoporosis is glucocorticoid use.

PATHOPHYSIOLOGY

The human skeleton consists of both cortical and trabecular bone. Cortical bone is dense and compact and is responsible for much of bone strength. It is the most common type of bone and accounts for approximately 80% of the skeleton. It is generally found on the surfaces of long and flat bones. Trabecular or cancellous bone has a spongelike appearance and generally is found along the inner surfaces of long bones and throughout the vertebrae, pelvis, and ribs.

Under normal circumstances, the skeleton undergoes a dynamic process of **bone remodeling.** Bone tissue responds to stress and injury through continuous replacement and repair. This process is completed by the basic multicellular unit, which includes both **osteoblasts** and **osteoclasts.** Osteoclasts are involved with **resorption** or breakdown of bone and continuously create microscopic cavities in bone tissue. Osteoblasts are involved in bone formation and continuously mineralize new bone in the cavities created by osteoclasts. Until peak bone mass is achieved between the ages of 25 and 35, bone formation exceeds bone resorption for an overall increase in bone mass. Trabecular bone is more susceptible to bone remodeling in part owing to its larger surface area.

In osteoporosis, an imbalance in bone remodeling occurs. Most commonly, osteoclastic activity is enhanced, resulting in overall bone loss. However, a reduction in osteoblastic activity and reduced bone formation also can occur in certain types of osteoporosis. Bone remodeling accelerates during menopause, and up to 15% of bone is lost during the first 5 years after menopause. After this initial decline, bone loss continues to occur but at a much slower rate of up to 1% per year. The resulting bone loss and change in bone quality predispose patients to low-impact or **fragility fractures.**

CLINICAL PRESENTATION AND DIAGNOSIS



Presentation of Osteoporosis

General
Many patients with osteoporosis are asymptomatic unless they experience a fragility fracture.

Symptoms
Symptoms of fragility fracture include pain at the site of the fracture and immobility.

Signs
- Height loss (greater than 2 cm or 0.78 inches)
- Spinal kyphosis ("dowager's hump")
- Fragility fracture, especially of the hip or spine

Laboratory Tests
Only useful to rule out secondary causes of osteoporosis

Diagnostic Tests
Bone densitometry using dual-energy x-ray absorptiometry (DXA) reveals a *T*-score at least –2.5 SD below the mean.

Diagnosis

Osteoporosis has been defined by the World Health Organization (WHO) as a disease characterized by low bone density and weakening of bone tissue associated with an increase in fragility and vulnerability to fracture.[5] Because bone strength cannot be measured directly, an assessment of bone mineral density is used, which represents 70% of bone strength. Low bone mineral density has been associated with an increased risk of fractures. X-rays are useful only in identifying patients suspected of sustaining a fracture and are not recommended for the diagnosis of osteoporosis.

Measurement of Bone Mineral Density

Bone mineral density can be measured at various sites throughout the skeletal system and by various methods. The site of measurement can be either central (hip and/or spine) or peripheral (heel, forearm, or hand). Dual-energy x-ray absorptiometry (DXA) can be used to measure central and peripheral sites of bone mineral density. Quantitative ultrasound, peripheral quantitative computed tomography, radiographic absorptiometry, and single-energy x-ray absorptiometry are used to measure peripheral sites.

❷ *The WHO recommends a standardized approach to measuring bone mineral density for the diagnosis of osteoporosis using central measurement of bone mineral density by DXA.*[4] Central DXA is recommended for diagnosis owing to inconsistencies in *T*-scores measured between different sites and by different methods.[2] Current standards of practice consist of measuring bone mineral density at the lumbar spine and hip, although the WHO suggests that the hip is the preferred site for diagnosis.[3,5]

Peripheral bone mineral density measurements cannot be used for diagnosis because they do not correlate with central measurements. However, they are useful in identifying patients who are candidates for central DXA and who are at increased risk of fracture.[5] It also may be useful in patients who have had multiple fractures or in low-risk patients. Additionally, peripheral measurement of bone mineral density generally is less expensive than central DXA and is easily accessible. Instruments used for peripheral bone densitometry are portable, which allows bone density to be measured in pharmacies and health-fair screening booths.

Once the bone mineral density report is available, *T*-scores and *Z*-scores are useful tools in interpreting the data. The *T*-score is the number of standard deviations from the mean bone mineral density in healthy young white women. Osteoporosis is defined as a *T*-score at least –2.5 standard deviations below the mean (Table 53–3). **Osteopenia,** or low bone mass that eventually may lead to osteoporosis, is defined as a *T*-score between –2.5 and –1.0 standard deviations below the mean. The International Society for Clinical Densitometry recommends use of the WHO definition and *T*-scores for diagnosis of osteoporosis in postmenopausal women and men over age 65 and in men between the ages of 50 and 65 if other risk factors are present.[6]

TABLE 53–3. World Health Organization Definition of Osteoporosis

Skeletal Disorder	*T*-Score[a]
Normal	less than or equal to 1.0
Osteopenia	greater than 1.0 to less than or equal to 2.5
Osteoporosis	greater than 2.5

[a]*T*-score is the number of standard deviations below the mean bone mineral density in young adults.

The *Z*-score is a similar measure that is corrected for age and sex of the patient. The *Z*-score is defined as the number of standard deviations from the mean bone mineral density of age- and sex-matched controls. In premenopausal women, men under age 50, and patients who may have secondary causes for low bone mineral density, *Z*-scores may be more clinically relevant in evaluating bone mineral density.

Screening

Screening for low bone density is an effective way to identify individuals at risk for osteoporotic fracture. Much of the data regarding interpretation of bone mineral density were derived from postmenopausal women. As such, interpretation of measurements on individuals outside this group is difficult. The United States Preventive Services Task Force (USPSTF), National Osteoporosis Foundation (NOF), and American Association of Clinical Endocrinologists (AACE) recommend routine bone mineral density screening for all women over age 65.[1,2,7] Outside this group, however, differences exist in recommendations among various guidelines.

In general, osteoporosis screening is not recommended in premenopausal women owing the unclear association between low bone mineral density and fracture risk in this population. The USPSTF recommends that all women over age 65 and women between the ages of 60 and 65 with multiple risk factors be screened routinely.[7] The NOF and AACE recommend screening for postmenopausal women with multiple risk factors.[1,2] Additionally, the AACE recommends screening in women receiving long-term corticosteroids, women with secondary causes of osteoporosis that would benefit from treatment, and women over age 40 who have sustained a fracture.[2] The International Society for Clinical Densitometry recommends bone mineral density testing in men over age 70 or those with a medical condition or drug therapy associated with low bone mass or a history of fragility fracture.[8]

Laboratory Evaluation

Laboratory assessment has little value in diagnosing osteoporosis, but it can be beneficial in identifying or excluding

secondary causes of bone loss, such as hyperparathyroidism, low 25-hydroxyvitamin D levels, hyperthyroidism, hypogonadism, or cancer.[3] Biochemical markers of bone turnover such as pyridinoline, deoxypyridinoline, and *N*-telopeptides and *C*-telopeptides of type I collagen cross-links have been associated with an increased fracture risk in some trials. Variations in the normal ranges of these tests may be related to age, gender, food, and diurnal variation, making interpretation of these tests difficult.[2] For these reasons, biochemical markers of bone turnover are not recommended for the diagnosis of osteoporosis.

TREATMENT

Desired Outcomes

❸ *Pharmacologic and nonpharmacologic therapies are aimed at the following goals: (1) preventing fractures and their complications, (2) maintaining or increasing bone mineral density, (3) preventing secondary causes of bone loss, and (4) reducing morbidity and mortality associated with osteoporosis.*

Nonpharmacologic Therapy

The primary goal of nonpharmacologic therapy for osteoporosis is to prevent fractures. Strategies include maximizing peak bone mass, reducing bone loss, and using precautions to prevent falls leading to fragility fractures.

Modification of Risk Factors

Some osteoporosis risk factors (see Table 53–1) are nonmodifiable, including family history, age, ethnicity, sex, and concomitant disease states. However, certain risk factors for bone loss may be minimized or prevented by early intervention, including smoking, low calcium intake, poor nutrition, inactivity, heavy alcohol use, and vitamin D deficiency. In order to prevent certain risk factors and maximize peak bone mass, efforts must be directed toward osteoporosis prevention at an early age.

Nutrition

Good nutrition is essential for intake of sufficient nutrients and maintenance of appropriate weight. Dietary calcium intake is important for achieving peak bone mass and maintaining bone density. Adequate dietary intake of vitamin D is essential for calcium absorption. Table 53–4 lists calcium and vitamin D requirements for different age groups. Good dietary sources of calcium include dairy products, fortified juice, cruciferous vegetables (e.g., broccoli and kale), salmon, and sardines (Table 53–5). The most common source of vitamin D comes from exposure to sunlight. Ultraviolet rays from the sun promote the synthesis of vitamin D_3 (cholecalciferol) in the skin. This generally occurs within 15 minutes of sunlight exposure. Vitamin D also may be found in some dietary sources, including fortified milk, egg yolks, saltwater fish, and liver.

Exercise

Exercise can be beneficial in preventing fragility fractures. Weight-bearing exercise such as walking, jogging, dancing, and climbing stairs can help to build and maintain bone strength. Muscle-strengthening or resistance exercises can help to improve and maintain strength, agility, and balance, which can reduce falls.[1] It is important to develop and maintain a lifelong routine of weight-bearing and resistance exercise because the benefits on bone can be lost after cessation of the exercise program.[1]

Falls Prevention

Another crucial step in avoiding fragility fractures is prevention of falls. Patients with frailty, poor vision, or hearing loss and those taking medications affecting balance are at higher risk for falling and subsequent fragility fractures.[1,2]

TABLE 53–4. Recommended Daily Calcium and Vitamin D Intake

	Elemental Calcium (mg)		Vitamin D (IU)
Adolescents/Young Adults		Age less than 50	200
Age 11–24	1200–1500	Age 51–70	400
Men		Age greater than 70	600
Age 25–65	1000	High-risk individuals[a]	800
Age greater than 65	1500		
Women			
Age 25–50	1000		
Age 51–65 (postmenopausal)			
On estrogens	1000		
Not on estrogens	1500		
Age greater than 65	1500		
Pregnant and nursing	1200–1500		

[a]Elderly, chronically ill, housebound, or institutionalized persons.
IU, international units.

TABLE 53–5. Calcium-Rich Foods[a]

1 cup skim milk
1 cup soy milk (calcium-fortified)
1 cup yogurt
1½ ounces cheddar cheese
1½ ounces jack cheese
1½ ounces Swiss cheese
1½ ounces part-skim mozzarella
4 tablespoonfuls grated Parmesan cheese
8 ounces tofu
1 cup greens (collards, kale)
2 cups broccoli
4 ounces almonds
2 cups low-fat cottage cheese
3 ounces sardines with bones
5 ounces canned salmon
1 cup orange juice (calcium-fortified)

[a]Foods containing approximately 300 mg of elemental calcium.

A number of medications have been associated with an increased risk of falling, including drugs affecting mental status such as antipsychotics, benzodiazepines, tricyclic antidepressants, sedative-hypnotics, anticholinergics, and corticosteroids. Some cardiovascular and antihypertensive drugs also can contribute to falls, especially those causing orthostatic hypotension.[9]

Efforts to decrease the risk of falling include balance training, muscle strengthening, removal of hazards in the home, installation of fall-reduction measures such as handrails in the home, and discontinuation of predisposing medications.[1,2,10] Additionally, the use of hip protectors is an effective way to prevent hip fractures, although adherence to this measure is poor, and some patients may not be amenable to wearing them at all.[10]



Patient Encounter, Part 2: Physical Examination and Diagnostic Tests

ROS

(+) hot flashes, 5-cm height loss (about 2 inches) since middle age; (–) back pain

PE

- **General:** Well-developed Caucasian woman in no acute distress
- **VS:** 122/66, P 77, RR 16, T 36.3°C (97.3°F), weight 55.4 kg (122 lbs), height 5 ft, $3^1/_2$ in (162 cm)
- **Chest:** Decreased breath sounds bilaterally; air movement decreased; no rales or rhonchi
- **CV:** RRR, normal S_1, S_2; no murmurs, rubs, or gallops
- **Abd:** Soft, nontender, nondistended; normal bowel sounds, no hepatosplenomegaly
- **Exts:** No clubbing, cyanosis or edema

Labs

Within normal limits

Other

- Bone densitometry by DXA
- BMD of left hip: 0.544 g/cm^2; *T*-score –3.3
- BMD of lumbar spine: 0.683 g/cm^2; *T*-score: –3.3

- What signs of osteoporosis are present in this patient?
- What are the goals of pharmacologic and nonpharmacologic therapy?
- List three nonpharmacologic interventions important in her treatment plan.
- What factors support drug treatment of osteoporosis?
- What type of calcium supplement would you recommend for this patient? Why?

Pharmacologic Treatment

Treatment decisions regarding initiation of therapy for osteoporosis can be complex. ❹ *Patients meeting criteria for osteoporosis (T-score below –2.5) or other high-risk patients with a history of osteoporotic fracture gain significant benefit from treatment. Drug therapy should be initiated in these patients.*

In other patients with osteopenia, it is not clear who derives the most benefit from treatment.[10] The criterion defining osteopenia (*T*-score between –1 and –2.5 standard deviations below the mean) is broad, and the threshold for fracture risk is uncertain. Current guidelines support drug therapy in patients with osteopenia and risk factors for osteoporosis because drug therapy was effective in reducing fracture risk in this population in clinical trials. The AACE recommends consideration of drug therapy in postmenopausal women with fragility fractures and low bone mineral density, women who meet the criteria for osteoporosis, women with a *T*-score below –1.5 in the presence of risk factors, and women who continue to experience bone loss or fragility fractures despite nonpharmacologic measures.[2] The NOF recommends treating women with a history of a vertebral or hip fracture, *T*-score below –2.0, or *T*-score below –1.5 in the presence of risk factors.[1]

Calcium and Vitamin D

❺ *Adequate calcium and vitamin D intake are essential for preventing and treating osteoporosis. Calcium and vitamin D supplements to meet requirements should be added to all drug therapy regimens for osteoporosis.* When the calcium supply is insufficient, calcium is taken from bone stores to maintain the serum calcium level. Calcium plays an important role in maximizing peak bone mass and decreasing bone turnover and slowing bone loss. Calcium supplementation also may correct the hyperparathyroidism seen commonly in elderly patients. Vitamin D is crucial for calcium absorption and maintenance of bone.

Calcium and vitamin D supplementation increases bone mineral density, and the combination decreases the risk of hip and vertebral fractures. Additionally, vitamin D supplementation decreases nonvertebral fractures in older men and women living independently.[11] Because of the effects of calcium on

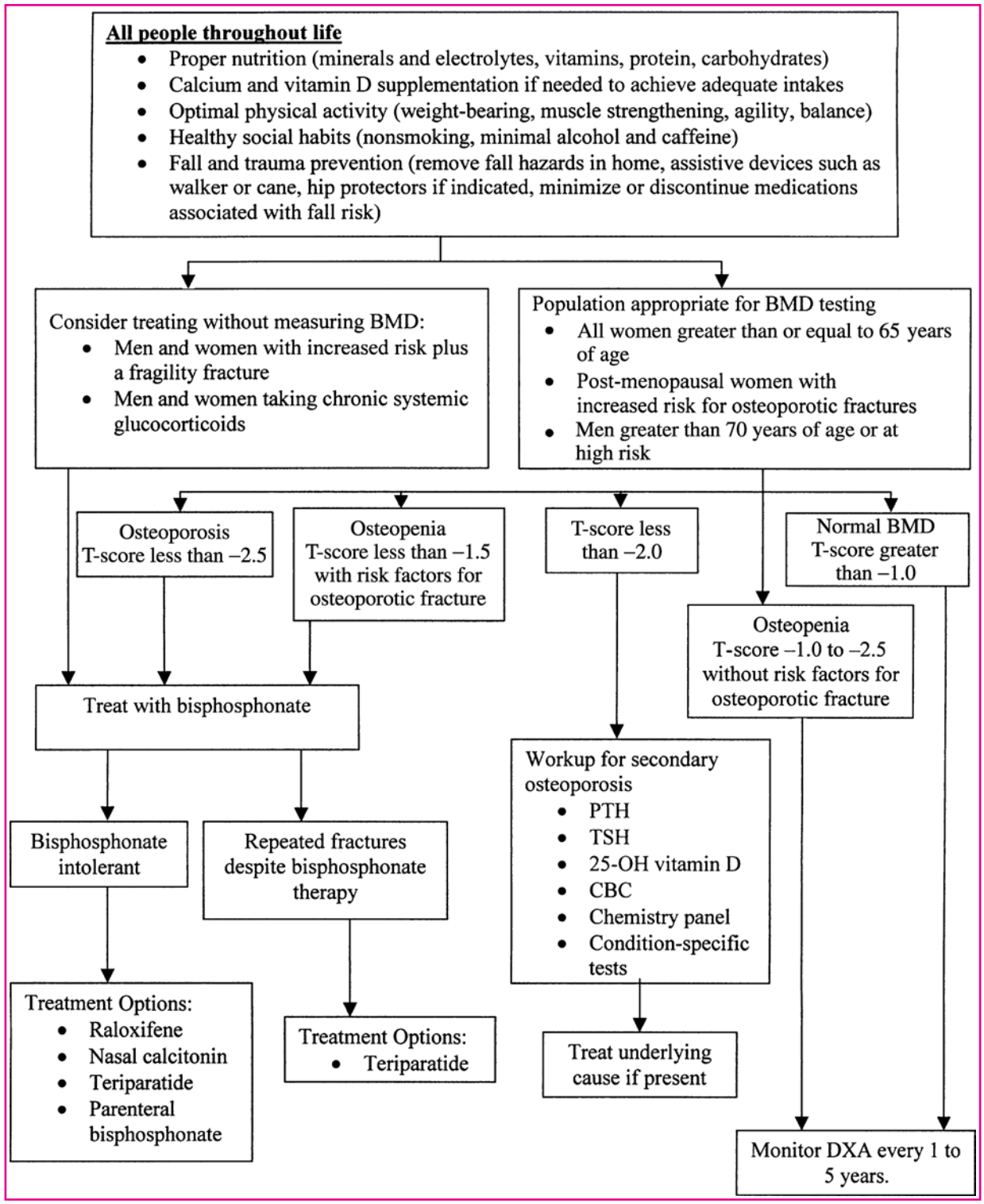


FIGURE 53–1. Algorithm for preventing osteoporotic fractures. BMD, bone mineral density; CBC, complete blood count; DXA, dual-energy x-ray absorptiometry; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone. (Adapted from DiPiro JT, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill, 2005, Figure 88–4, p. 1652, with permission.)

bone, adequate calcium intake and supplementation are key components for all participants of well-designed clinical trials evaluating osteoporosis interventions.

Daily calcium and vitamin D requirements are highest in postmenopausal women and elderly men: 1500 mg elemental calcium and 400 to 800 IU vitamin D (see Table 53–4). When these requirements cannot be achieved by diet alone, appropriate calcium and/or vitamin D supplementation is recommended.

For example, elderly patients living in nursing homes will not be able to meet vitamin D requirements and will need supplementation. Vitamin D deficiency is common in elderly patients owing to decreased exposure to sunlight and subsequent decreased vitamin D synthesis in the skin, decreased gastrointestinal absorption of vitamin D, and reduction in vitamin D_3 synthesis. Individuals living in northern climates also have decreased exposure to sunlight and are less likely to achieve vitamin D requirements.

Calcium supplements are available in a variety of calcium salts and dosage forms. Calcium requirements are listed in terms of elemental calcium. However, many product labels list calcium content in the salt form, so the percent of elemental calcium must be known to calculate the elemental calcium content per tablet.

Some calcium products contain lead.[12] While the clinical significance and long-term risks are unknown, it is best to use supplements without a high lead content. Because of the number of calcium supplements available, patients may find it overwhelming to choose a supplement. Health care providers can help patients find a suitable and tolerable supplement with good absorption and high elemental calcium content, necessitating fewer tablets per day. Table 53–6 lists widely available supplements with elemental calcium and vitamin D content.

A number of factors can limit calcium absorption, and special consideration must be given to calcium dosing to maximize absorption. Large amounts of calcium taken at once cannot be absorbed. Supplement doses should be limited to 500 to 600 mg of elemental calcium per dose. Calcium intake greater than 2500 mg/day should be avoided due to increased risk of toxicity, including **hypercalciuria** and **hypercalcemia.**

Calcium carbonate should be taken with food to maximize absorption. Elderly patients or patients receiving proton pump inhibitors or H_2-receptor antagonists may have added difficulty absorbing calcium supplements because of reduced stomach acidity. Better absorption may occur in this setting with calcium citrate because an acid environment is not needed for absorption; it may be taken with or without food.

Common adverse effects of calcium salts include constipation, bloating, cramps, and flatulence. Changing to a different salt form may alleviate symptoms for some patients. Calcium salts may reduce the absorption of levothyroxine, iron and some antibiotics, such as tetracycline and fluoroquinolones.

Vitamin D is often combined in varying amounts with calcium salts. A multiple vitamin is another good source of vitamin D. Most multivitamins contain 400 IU per tablet. Vitamin D is also available as a single entity. Doses above 2000 IU/day should be avoided owing to the risk of hypercalciuria and hypercalcemia. Ergocalciferol (vitamin D_2) and

TABLE 53–6. Calcium and Vitamin D Content of Common Supplements[a]

Product (% Elemental Calcium)	Elemental Calcium per Tablet (mg)	Vitamin D per Tablet (IU)
Calcium Carbonate (40%)		
Tums® 500 mg	200	—
Tums E-X® 750 mg	300	—
Tums ULTRA® 1000 mg	400	—
Os-Cal 500®	500	—
Os-Cal 500 + D®	500	200
Os-Cal Ultra®	600	200
Caltrate 600®	600	—
Caltrate 600 + D®	600	200
Caltrate 600 + Soy®	600	200
One-A-Day Women's Multivitamin®	450	400
Rolaids® 550 mg	220	—
Viactiv®	500	100
Calcium Citrate (24%)		
Citracal®	200	—
Citracal 250 mg + D®	250	62.5
Citracal + D®	315	200
Calcium Phosphate, Tribasic (39%)		
Posture–D	600	125
Calcium Lactate (13%)	85	—
Calcium Gluconate (9%)	60	—

[a]Some calcium supplements may contain lead, and many products have not been tested. Tums E-X and Tums Ultra do not contain appreciable amounts of lead.[11]

cholecalciferol (vitamin D_3) are available in higher doses and generally are reserved for patients with vitamin D deficiency.

Bisphosphonates

❻ *Bisphosphonates are first-line therapy for osteoporosis owing to their established efficacy in preventing hip and vertebral fractures.* They are also the most commonly prescribed therapy for osteoporosis. They decrease bone resorption by binding to the bone matrix and inhibiting osteoclast activity. They remain in the bone for a prolonged period and are released very slowly. These effects increase bone mineral density. Several bisphosphonates are available currently, including alendronate, etidronate, ibandronate, pamidronate, risedronate, tiludronate, and zoledronic acid. Alendronate, risedronate, and ibandronate are oral agents approved by the United States Food and Drug Administration (FDA) for use in osteoporosis. Table 53–7 contains comparative dosing and cost information for the bisphosphonates.

In placebo-controlled clinical trials, alendronate, ibandronate, and risedronate increased bone mineral density by up to 5% to 8% in the lumbar spine and up to 3% to 5% in the hip.[13–16] Additional data suggest that bone mineral density continues to increase with long-term therapy of 7 to 10 years.[17,18] Although increases in bone mineral density have been reported at other sites, most of the clinically significant fractures occur in the hip or spine, and these sites have become clinically important measures in the trials. These increases in bone mineral density are an important marker of treatment effects and are related to the benefits found in larger trials of decreased fracture risk.

Large, well-designed trials have proven the benefits of bisphosphonate therapy in preventing vertebral and nonvertebral fractures. Several studies have found decreases in vertebral fracture risk by as much as 40% to 50% with alendronate and risedronate.[13,14,19–21] Data suggest a similar reduction with ibandronate on vertebral fractures.[16,22] Alendronate and risedronate decrease the incidence of hip and nonvertebral fractures as well.[14,19,23]

Several studies have evaluated the long-term efficacy and safety of bisphosphonates in postmenopausal women. One study evaluated the use of alendronate over a 10-year period and found no difference in adverse effects between women who received alendronate for 10 years and women who discontinued alendronate after 5 years. Women who discontinued alendronate after 5 years continued to experience sustained increases in bone mineral density compared with baseline values and a reduction

TABLE 53–7. Dosage Regimens and Cost of Prescription Agents for Osteoporosis

Drug	Product Size	Usual Dose	Administration	Monthly Cost[a]
Bisphosphonates				
Alendronate	5-, 10-, 35-, 70-mg tablets; 70-mg oral solution	Postmenopausal osteoporosis or osteoporosis in men: 10 mg orally once daily or 70 mg orally once weekly Glucocorticoid-induced osteoporosis: 5 mg orally once daily for men and women; 10 mg once daily for postmenopausal women not on estrogen	Take after an overnight fast with 6 to 8 oz plain water while sitting or standing upright at least 30 minutes prior to morning meal; do not lie down for 30 minutes after administration; do not take with other medications or fluids; do not chew or suck on the tablet	$70 for 70-mg weekly tablet
Ibandronate	2.5-, 150-mg tablets	Treatment or prevention of postmenopausal osteoporosis: 2.5 mg orally daily or 150 mg orally once monthly	Same as alendronate except administer at least 1 hour prior to morning meal and refrain from lying down for 1 hour after administration	$76 for 150-mg tablet
Risedronate	5-, 35-mg tablet	Osteoporosis or glucocorticoid-induced osteoporosis: 5 mg orally daily or 35 mg orally once weekly	Same as alendronate	$68 for 35-mg weekly tablet
Selective Estrogen Receptor Modulators				
Raloxifene	60-mg tablet	60 mg daily	May be taken with or without food	$85 for 60-mg tablet
Calcitonin				
Calcitonin	200 IU/0.9 mL, 3.75-mL nasal spray	Nasal spray: 200 IU daily	Nasal spray: Alternate nostrils on a daily basis	$93 per 3.75-mL nasal spray
Recombinant Human Parathyroid Hormone				
Teriparatide	250 mcg/mL, 3-mL prefilled pen	20 mcg SQ daily	Inject into thigh or abdominal wall; keep pen refrigerated	$590 per prefilled pen

[a]Monthly cost from drugstore.com; accessed February 6, 2006.
IM, intramuscularly; SQ, subcutaneously.

in fracture rates.[17] Another study found sustained increases in bone mineral density after discontinuation of alendronate, albeit less than in those who continued longer-term alendronate therapy.[24] A 7-year follow-up study with risedronate found continued increases in bone mineral density and no increase in adverse effects in women receiving alendronate for 7 years compared with women receiving risedronate for 2 years.[18]

The safety of long-term bisphosphonates has been evaluated in clinical trials. A number of case reports have highlighted serious adverse effects. Concern exists over the use of chronic bisphosphonate therapy due to reports of nonvertebral atraumatic fractures and jaw **osteonecrosis.**[25–27] One report described nonvertebral atraumatic fractures in nine patients and delayed fracture healing in four of those patients while receiving alendronate therapy for 3 to 8 years. Bone biopsies in all patients revealed severely suppressed bone turnover, which may have caused bone weakening owing to suppression of osteoclastic activity.[25,26] Another report described 63 cases of jaw osteonecrosis resistant to conservative measures and requiring surgical intervention in most cases.[27] Although a majority of the cases were reported in cancer patients who had received intravenous bisphosphonate, some of the cases were reported in women who had received oral bisphosphonates for osteoporosis.[27]

Oral bisphosphonates are poorly absorbed (less than 5%). Taking them in the presence of food or calcium supplementation further reduces absorption. After absorption, bisphosphonate uptake to the primary site of action is rapid and sustained. Once attached to bone tissue, bisphosphonates are released very slowly. These drugs are not metabolized and are excreted renally. They are not recommended for use in patients with renal insufficiency.

The most notable adverse effects associated with the bisphosphonates are gastrointestinal, ranging from relatively mild nausea, vomiting, and diarrhea to more severe esophageal irritation and esophagitis. Common adverse reactions reported in clinical trials include dyspepsia, abdominal pain, nausea, and esophageal reflux. Clinically significant adverse events include esophageal ulceration, erosions with bleeding, perforation, stricture, and esophagitis. Upper gastrointestinal adverse effects have been reported in up to 20% of patients.[14,20,23,28] However, in some studies, the incidence is no different from that for placebo.[20,23] Many gastrointestinal events are related to inappropriate administration. An evaluation of the Fracture Intervention Trial data found certain factors, including advanced age, previous upper gastrointestinal tract disease, and nonsteroidal anti-inflammatory drug use, increased the risk for gastrointestinal adverse events.[29] In addition to appropriate administration, once-weekly administration of oral bisphosphonates may decrease the risk of adverse gastrointestinal effects.

Proper drug administration is important for optimal absorption and prevention of adverse effects. Oral bisphosphonates should be taken 30 to 60 minutes prior to the first meal or food in the morning after an overnight fast with 6 to 8 oz of water (or 2 oz with the oral solution). Patients should remain upright and refrain from lying down for 30 to 60 minutes after administration. The tablets should be swallowed whole without chewing or sucking. Administration should be with water only and not combined with other fluids. Bisphosphonates should not be taken with other medications or dietary supplements. Bisphosphonates are not recommended for use in patients with esophageal abnormalities, hypocalcemia, and renal insufficiency or failure (creatinine clearance less than35 mL/minute).

There is considerable interest in using injectable bisphosphonates, such as pamidronate and zoledronic acid, in patients unable to tolerate or absorb oral bisphosphonates. Zoledronic acid in particular has a potential advantage of once-yearly dosing. Currently, neither drug has received FDA approval for this indication. Ibandronate has recently been approved for this indication.

Selective Estrogen Receptor Modulators

Raloxifene is a selective estrogen receptor modulator (SERM) that has estrogen-like activity on bones and cholesterol metabolism and estrogen antagonist activity in breast and endometrium. SERMs reduce bone resorption and decrease overall bone turnover. The related SERMs tamoxifen and toremifene have partial agonist and antagonist activity at various estrogen receptors. However, the latter agents are limited to the treatment of breast cancer; potential adverse effects preclude further study for long-term use in osteoporosis.

Raloxifene increases bone mineral density and reduces fracture rates. In trials of 1 to 3 years, raloxifene increased vertebral and hip bone mineral density by 2% to 3% and 1% to 2%, respectively.[30-32] In the Multiple Outcomes for Raloxifene Evaluation (MORE) trial, raloxifene decreased the risk of vertebral fractures by 30% in postmenopausal with at least one prior fracture.[30] No significant reduction in nonvertebral fractures was reported.

In addition to effects on bone, raloxifene may have effects in breast tissue and on the cardiovascular system. A secondary end point of the MORE trial evaluated the effects of raloxifene on the primary prevention of breast cancer and found a significant reduction in all types of breast cancer.[33] Raloxifene decreases total and low-density lipoprotein (LDL) cholesterol,[34] and studies are evaluating its effect on reducing the risk of cardiovascular disease.[35]

Adverse effects of raloxifene include hot flashes, leg cramps, and increased risk of venous thromboembolism. Hot flashes are very common and may be intolerable in postmenopausal women who are already predisposed to experiencing them. A more serious adverse effect is a threefold increased risk of venous thromboembolism that was found in patients treated in the MORE trial.[30] A previous history of venous thromboembolism is a contraindication to therapy.

Hormone-Replacement Therapy

Estrogen, either alone or in combination with a progestin, as hormone-replacement therapy (HRT) has a long history as an effective treatment of osteoporosis. The Women's Health Initiative (WHI) trial found a 33% reduction in both vertebral and hip fractures and a 23% reduction in other fractures in postmenopausal women receiving conjugated estrogen and medroxyprogesterone.[36] However, data from the WHI and another well-designed trial, the Hormone and Estrogen/progestin Replacement Study (HERS), found significant risks associated with HRT, including a higher incidence of breast cancer and venous thromboembolism.[36,37] For these reasons, the AACE no longer recommends estrogen or HRT for the treatment of osteoporosis.

Calcitonin

Calcitonin is a naturally occurring mammalian hormone that plays a major role in regulation of calcium levels. It inhibits bone resorption by binding to osteoclast receptors. Compared with mammalian calcitonin, salmon calcitonin has high potency and extended duration of action. Although commercial formulations of calcitonin-salmon actually are synthetic and not derived from salmon, they contain the same amino acid sequence as calcitonin of salmon origin.

Calcitonin is available in injectable and intranasal formulations. It cannot be administered orally owing to inactivation by gastric fluids. The parenteral formulation must be administered either subcutaneously or intramuscularly every other day. It is associated with significant adverse effects, including flushing, urinary frequency, nausea, vomiting, abdominal cramping, and irritation at the injection site. Additionally, the benefits of the parenteral formulation on bone may diminish over time owing to the formation of neutralizing antibodies.

The intranasal formulation is the preferred route of administration owing to ease of administration and fewer adverse effects, which mainly are local in nature. Adverse effects associated with the intranasal formulation include rhinitis, nasal irritation, and dryness. Hypersensitivity can develop with either formulation and should be considered before administering to patients with a suspected risk of hypersensitivity.

Perhaps the most benefit of calcitonin is in patients with or at risk for vertebral fractures. Nasal calcitonin increases vertebral bone mineral density by 1% to 3%.[38–40] One 5-year study found a 30% decrease in the risk of vertebral fractures.[38] Increases in hip bone mineral density and reductions in nonvertebral fractures have not been demonstrated.[38–40] Calcitonin may have analgesic effects in women with back pain from vertebral fractures.[41] However, enthusiasm for using calcitonin in this setting has waned in favor of managing fracture risk and pain separately.[10]

Anabolic Agents

Teriparatide, recombinant human parathyroid hormone(1–34), is the first anabolic agent approved by the FDA for treatment of osteoporosis. It is generally reserved for patients with moderate to severe osteoporosis. This agent differs from antiresorptive therapies in that it stimulates osteoblastic activity to form new bone with once-daily administration. Teriparatide also has many actions that are similar to endogenous parathyroid hormone, and continuous infusions actually stimulate osteoclastic activity and increase bone resorption. In one study, its bone-forming properties increased bone mineral density in the spine and hip by 9% and 3%, respectively. After 21 months of therapy, these increases led to 65% and 35% reductions in vertebral and nonvertebral fractures, respectively.[42]

The dose of teriparatide is 20 mcg given by subcutaneous injection once daily. It is available in a prefilled multiple-dose pen delivery system. Common adverse effects include nausea, headache, leg cramps, dizziness, injection-site discomfort, and hypercalcemia. Osteosarcoma has been observed in animal studies, but no cases have been reported in humans. However, this potential concern has led to the inclusion of a black-box warning in the product labeling. The warning states that teriparatide should not be used in patients at increased risk for osteosarcoma, including patients with Paget's disease of bone, unexplained elevations of alkaline phosphatase, prior radiation therapy involving the skeleton, and/or children and young adults with open epiphyses. Additionally, teriparatide should not be used in patients with preexisting hypercalcemia or skeletal radiation therapy. Patient-related concerns regarding the use of teriparatide include cost of therapy and need for subcutaneous injections. The labeling recommends treatment for a maximum of 2 years because it has not been studied for longer periods.

Combination and Sequential Therapy

Interest in combination antiresorptive therapies developed from the hope that using two agents with differing mechanisms for inhibiting bone resorption would result in greater increases in bone mineral density and reductions in fracture rates. Studies have evaluated the combination of bisphosphonates plus estrogen or raloxifene or estrogen plus calcitonin. Combination therapy produced greater increases in bone mineral density than single agents in some trials, but there was no further reduction in fracture risk. Combination therapy is also more expensive, and concern has been raised that significant reductions in bone turnover may promote bone that is more brittle.[25,43] The AACE does not recommend combination antiresorptive therapy for treating osteoporosis.

The combination of a bisphosphonate with anabolic therapy (teriparatide) should not be used because a well-controlled trial showed that women receiving the combination actually had smaller increases in bone mineral density than women receiving teriparatide alone.[44] However, sequential therapy with these agents may be more promising. In one study, women who received alendronate for 1 year directly after receiving parathyroid hormone for 1 year had greater

increases in bone mineral density than those receiving combination alendronate plus parathyroid hormone, alendronate monotherapy, or parathyroid hormone for 1 year followed by placebo for 1 year. Additionally, patients who received no therapy after 1 year of parathyroid hormone experienced decreases in bone mineral density.[45] Whether sequential therapy leads to reductions in fracture risk remains to be seen.

Other Therapies

Strontium ranelate is an oral agent possessing bone-forming and antiresorptive properties. Some data suggest significant reductions in vertebral fractures.[46] However, the benefit in nonvertebral fractures is unclear. This agent has not yet been approved for use by the FDA.

Sodium fluoride is an agent with bone-forming properties. Its use has fallen out of favor after data suggested an increased risk of fracture despite increases in bone mineral density. It is not currently available commercially in the United States.

Thiazide diuretics decrease urinary calcium excretion and may decrease bone turnover. However, their effects on bone mineral density and fracture rates have not been studied in controlled trials. Thiazide diuretics are not recommended solely for potential beneficial effects in osteoporosis.

Interest in the role of HMG-CoA reductase inhibitors (statins) in the treatment of osteoporosis came from bone-forming properties seen in animal studies. However, controlled clinical trials are needed.

Several studies have evaluated dietary supplements such as isoflavones, which are found in soy products and red clover. A well-controlled trial in more than 400 postmenopausal women evaluating a specific isoflavone, ipriflavone, found no benefits on bone mineral density or fracture rates after 3 years.[47] Nevertheless, because these therapies are available without prescription and are not regulated by the FDA, patients may choose to self-medicate with isoflavones. Lymphocytopenia appeared in several patients treated with ipriflavone in clinical trials. Additionally, ipriflavone should be used with caution in immunocompromised patients or those with renal disease. It may inhibit CYP1A2 and CYP2C9 and may interact with drugs metabolized by those pathways, such as warfarin.

Treatment of Special Populations

Premenopausal Women

Although most fragility fractures in women occur after age 50, certain groups of premenopausal women are at high risk for osteoporosis. The NOF recommends measuring bone mineral density in premenopausal women with risk factors in addition to sex and race, in whom treatment would be considered.[1] Premenopausal women at risk for osteoporosis should follow all nonpharmacologic recommendations for exercise and adequate calcium and vitamin D intake. Currently, no good data are available regarding pharmacologic therapy on fracture reduction in this population. Bisphosphonates should be used with caution in this population owing to pregnancy risks and uncertain long-term effects.

Men

Compared with postmenopausal osteoporosis, few clinical trials have been conducted evaluating therapies in men. Although alendronate and calcitonin have both been studied, only alendronate reduces fracture rates in men. Teriparatide also has been studied, but no data are available yet on fracture rates. At this time, alendronate and teriparatide are approved by the FDA for the treatment of osteoporosis in men. ❼ *Owing to proven benefit in reducing fractures and relative safety, alendronate should be considered first-line treatment for primary osteoporosis in men.* Teriparatide should be reserved as alternate therapy in this population.

Because secondary osteoporosis causes play a significant role in men, any secondary cause (e.g., **hypogonadism**) should be excluded or treated before considering other drug therapy.

Glucocorticoid-Induced Osteoporosis

Glucocorticoids play a significant role in bone remodeling. Exogenous glucocorticoid administration results in an increase in bone resorption, inhibition of bone formation, and change in bone quality. Glucocorticoids such as prednisone, hydrocortisone, methylprednisolone, and dexamethasone promote bone resorption through reduced calcium absorption from the gastrointestinal tract and increased renal calcium excretion. Bone formation is reduced through inhibition of osteoblasts. They also decrease estrogen and testosterone production.

Patients receiving long-term glucocorticoids are at increased risk of fracture. This risk is greater with higher doses and longer-term therapy. Most bone is lost during the initial 6 to 12 months of therapy, and bone mass continues to decline thereafter. Owing to the risk of bone loss and fractures, therapy is recommended for patients receiving long-term supraphysiologic doses of glucocorticoids.

In addition to nonpharmacologic measures, the American College of Rheumatology (ACR) has specific recommendations for prevention and treating patients receiving glucocorticoids.[48] Recommendations for optimal calcium and vitamin D intake are higher among patients receiving glucocorticoids. These recommendations include 1500 mg daily of elemental calcium and 800 IU daily of vitamin D for all adults receiving glucocorticoids. Patients should take a vitamin D–containing supplement to ensure that these requirements are being met.

❽ *The ACR recommends bisphosphonate therapy for all patients who are starting treatment with glucocorticoids (prednisone greater than or equal to 5 mg daily or equivalent) that will continue for 3 months or longer. For patients receiving chronic*

glucocorticoids (prednisone greater than or equal to 5 mg daily or equivalent), bisphosphonate therapy is also recommended if the bone mineral density is low or there is a history of fracture.[48] *Calcitonin may be used in patients who are intolerant of bisphosphonates.*

Gastrointestinal Disease

Various gastrointestinal disorders, including inflammatory bowel disease, celiac disease, and postgastrectomy states, are associated with osteoporosis due to impairment of calcium and vitamin D absorption, corticosteroid-induced bone changes, and chronic inflammatory states. The American Gastroenterological Association recommends bone mineral density measurement in high-risk patients and consideration of treatment for patients with a *T*-score below –2.5, history of vertebral compression fracture, or who are receiving long-term glucocorticoids.[49]

OUTCOME EVALUATION

- Evaluate patients for progression of osteoporosis, including signs and symptoms of new fragility fracture (e.g., localized pain), loss of height, and physical deformity (e.g., kyphosis). Patients should be assessed on an annual basis or more often if new symptoms present.
- Monitor for beneficial effects on bone density. The AACE recommends a follow-up DXA scan annually for the first 2 years after initiating drug therapy and every other year thereafter. Changes in bone mineral density may fluctuate from year to year.
- Assess patients for adverse effects of therapy.
- *Bisphosphonates:* Dyspepsia, esophageal reflux, esophageal pain or burning.
- *SERMs:* Hot flushes, signs or symptoms of thromboembolic disease (e.g., pain, redness, or swelling in one extremity; chest pain, and shortness of breath).
- *Calcitonin:* Nasal irritation or burning.
- *Teriparatide:* Nausea, headache, leg cramps, hypercalcemia.



Patient Encounter, Part 3: Development of a Treatment Plan

Considering all the information presented, develop a treatment plan for this patient. Include the following information: (1) goals of therapy, (2) detailed nonpharmacologic interventions, (3) recommendations for patient-specific drug therapy, including dose and frequency, (4) patient education about the chosen regimen, (5) monitoring plan for efficacy and adverse effects, and (6) consideration of alternative therapies if the initial therapy fails or is intolerable.



Patient Care and Monitoring

1. Assess patient risk factors for osteoporosis, with special attention to age, menopausal status, previous history of osteoporotic fracture, smoking status, low body weight, family history of osteoporotic fracture in first-degree relatives, and presence of secondary causes of osteoporosis.
2. Perform a thorough medication history, including prescription, over-the-counter, and alternative therapies. Pay special attention to any vitamins and calcium and vitamin D supplements the patient is taking.
3. Assess nonpharmacologic interventions for preventing osteoporotic fractures, including nutrition, weight-bearing and muscle-strengthening exercise regimens, and fall risk.
4. Determine average calcium intake from diet (see Table 53–5) and supplements (see Table 53–6). Compare with age-adjusted recommendations (see Table 53–4). Evaluate the patient's sources of vitamin D.
5. Review bone densitometry (i.e., central DXA) for the presence of low bone mass (i.e., *T*-score below –2.5 in the spine or hip for osteoporosis or *T*-score below –1.5 with presence of other significant osteoporosis risk factors).
6. Educate the patient about nonpharmacologic measures to prevent osteoporotic fractures.
7. If drug therapy is indicated, assess the patient for contraindications (e.g., esophageal disease or severe renal impairment for bisphosphonate therapy).
8. Educate the patient on the drug therapy selected, including drug name, dose, method of administration, common or serious adverse reactions, adherence, and monitoring. Pay special attention to administration instructions and monitoring for adverse effects. Include a discussion about the therapeutic goals and expectations (e.g., changes in individual *T*-scores may not necessarily correlate with benefit in fracture risk reduction).
9. Recommend appropriate calcium and vitamin D supplementation (see Table 53–6).
10. Develop a monitoring plan, including assessment of efficacy, adverse effects, nonpharmacologic measures to prevent fractures, and appropriate drug administration.

ABBREVIATIONS

AACE:	American Association of Clinical Endocrinologists
ACR:	American College of Rheumatology
BMD:	bone mineral density
DXA:	dual-energy x-ray absorptiometry
FDA:	Food and Drug Administration
HRT:	hormone-replacement therapy
NIH:	National Institutes of Health

NOF: National Osteoporosis Foundation
SERM: selective estrogen receptor modulator
SD: standard deviation
USPSTF: United States Preventative Services Task Force
WHI: Women's Health Initiative
WHO: World Health Organization

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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54 Rheumatoid Arthritis

Susan P. Bruce



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Identify risk factors for developing rheumatoid arthritis.
2. Describe the pathophysiology of rheumatoid arthritis, with emphasis on the specific immunologic components.
3. Discuss the comorbidities associated with rheumatoid arthritis.
4. Recognize the typical clinical presentation of rheumatoid arthritis.
5. Create treatment goals for a patient with rheumatoid arthritis.
6. Compare and contrast the available pharmacotherapeutic options, selecting the most appropriate regimen for a given patient.
7. Propose a patient education plan that includes nonpharmacologic and pharmacologic treatment measures.
8. Formulate a monitoring plan to evaluate the safety and efficacy of a therapeutic regimen designed for an individual patient with rheumatoid arthritis.

Key Concepts

❶ Comorbidities with the greatest impact on morbidity and mortality associated with rheumatoid arthritis are (1) cardiovascular disease, (2) infections, (3) malignancy, and (4) osteoporosis.

❷ Both osteoarthritis and rheumatoid arthritis are prevalent in the American population, but they differ significantly in presentation.

❸ The goals of treatment for rheumatoid arthritis are to (1) reduce or eliminate pain, (2) protect articular structures, (3) control systemic complications, (4) prevent loss of joint function, and (5) improve or maintain quality of life.

❹ Factors associated with poor outcomes are (1) early age of disease onset, (2) elevated erythrocyte sedimentation rate, (3) high titer of rheumatoid factor, (4) swelling of more than 20 joints, and (5) presence of extraarticular manifestations.

❺ It is imperative that the initiation of one or more disease-modifying antirheumatic drugs occurs in all patients within the first 3 months of diagnosis to reduce joint erosion.

❻ Most clinicians favor the "stepdown" approach to slow or reverse the early articular damage as soon as possible.

❼ Methotrexate is the disease-modifying antirheumatic drug of choice because of its documented efficacy and safety profile when monitored appropriately.

❽ The risk of infection in patients treated with biologic response modifiers must be considered when selecting and monitoring therapy.

❾ Patients of childbearing potential and their partners must be counseled to (1) use proper birth control while undergoing treatment for rheumatoid arthritis and (2) discontinue medications at least 3 months before conception.

❿ In addition to designing an individualized therapeutic regimen to control the progression of rheumatoid arthritis, the clinician must evaluate the presence of comorbidities and implement measures to control the increased risk.

Rheumatoid arthritis (RA) is a complex systemic inflammatory condition manifesting initially as symmetric swollen and tender joints of the hands and/or feet. Some patients may experience mild **articular** disease, whereas others may present with aggressive disease and/or extraarticular manifestations. The systemic inflammation of RA leads to joint destruction, disability, and premature death.

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EPIDEMIOLOGY AND ETIOLOGY

RA affects approximately 1% of the United States population and 1% to 2% of the world's population.[1,2] RA arises from an immunologic reaction, and there is speculation that it is in response to a genetic or infectious antigen. Risk factors associated with the development of RA include:

- Female gender (3:1 females to males)
- Increasing age (peak onset 35 to 50 years of age)
- Current tobacco smoking. Studies have identified a direct relationship between tobacco use and RA disease severity.[3] Tobacco users also have an increased risk of pulmonary manifestations of RA. This risk is reduced when a patient has remained tobacco-free for at least 10 years.
- Family history of RA. Genetic studies demonstrate a strong correlation between RA and the presence of major histocompatibility complex class II **human leukocyte antigens** (HLA), specifically HLA-DR1 and HLA-DR4.[4,5] HLA is a molecule associated with the presentation of antigens to T lymphocytes.
- Potential environmental exposures. The number of RA cases has increased during industrialization, although a specific link to environmental factors has not been determined.[6]
- Oral contraceptive use and high ingestion of vitamin D and tea are associated with a decreased risk of RA.[7]

PATHOPHYSIOLOGY

The characteristics of a **synovium** affected by RA are (1) the presence of a thickened, inflamed membrane lining called **pannus,** (2) the development of new blood vessels, and (3) an influx of inflammatory cells in the synovial fluid, predominantly T lymphocytes. The pathogenesis of RA is driven by T lymphocytes, but the initial catalyst causing this response is unknown. Understanding specific components of the immune system and their involvement in the pathogenesis of RA will facilitate understanding of current and emerging treatment options for RA. The components of most significance are T lymphocytes, cytokines, and B lymphocytes.[4,8]

T Lymphocytes

The development and activation of T lymphocytes are important to maintain protection from infection without causing harm to the host.[9] Activation of mature T lymphocytes requires two signals. The first is the presentation of an antigen by antigen-presenting cells to the T-lymphocyte receptor. Second, a ligand-receptor complex (i.e., CD80/CD86) on antigen-presenting cells binds to CD28 receptors on T lymphocytes. Once a cell successfully passes through all stages, the inflammatory cascade is activated.[10] Activation of T lymphocytes (1) stimulates the release of macrophages or monocytes, which subsequently causes the release of inflammatory cytokines, (2) activates osteoclasts, (3) activates the release of **matrix metalloproteinases** or enzymes responsible for the degradation of connective tissue, and (4) stimulates B lymphocytes and the production of antibodies.[4,9]

Cytokines

Cytokines, proteins secreted by cells, serve as intercellular mediators (see Table 54–1). An imbalance of proinflammatory

TABLE 54–1. Cytokines Involved in the Pathogenesis of Rheumatoid Arthritis[4,6]

Cytokine	Source	Activity
Proinflammatory		
TNF-α	Macrophages, monocytes, B lymphocytes, T lymphocytes, fibroblasts	Induces IL-1, IL-6, IL-8, GM-CSF; stimulates fibroblasts to release adhesion molecules
IL-1	Macrophages, monocytes, endothelial cells, B lymphocytes, activated T lymphocytes	Stimulates fibroblasts and chondrocytes to release matrix metalloproteinases
IL-6	T lymphocytes, monocytes, macrophages, synovial fibroblasts	Activates T lymphocytes, induces acute-phase response, stimulates growth and differentiation of hematopoietic precursor cells; stimulates synovial fibroblasts
IL-17	T lymphocytes in synovium	Synergistic effect with IL-1 and TNF leading to increased production of pro-inflammatory cytokines
Anti-inflammatory		
IL-4	CD4+ type 2 helper T lymphocytes	Inhibits activation of type 1 helper T lymphocytes, decreases production of IL-1, TNF-α, IL-6, IL-8
IL-10	Monocytes, macrophages, B lymphocytes, T lymphocytes	Inhibits production of IL-1, TNF-α, and proliferation of T lymphocytes

and anti-inflammatory cytokines in the synovium leads to inflammation and joint destruction.[8] Proinflammatory cytokines including interleukin 1 (IL-1), tumor necrosis factor α (TNF-α), IL-6, and IL-17 are found in high concentration in synovial fluid. The proinflammatory cytokines cause the activation of other cytokines and adhesion molecules responsible for the recruitment of lymphocytes to the site of inflammation. Anti-inflammatory cytokines and mediators (IL-4, IL-10, and IL-1 receptor antagonist) are present in the synovium, although concentrations are not high enough to overcome the effects of the proinflammatory cytokines.[4,8]

B Lymphocytes

In addition to serving as antigen-presenting cells to T lymphocytes, B lymphocytes may produce proinflammatory cytokines and antibodies.[5,10] Antibodies of significance in RA are **rheumatoid factors** (antibodies reactive with the Fc region of IgG) and antibodies against **cyclic citrullinated peptide (CCP)**.[5] Rheumatoid factors are not present in all patients with RA, but their presence is indicative of disease severity and likelihood of extraarticular manifestations.[10] CCPs are produced early in the course of disease. High levels of anti-CCP antibodies are indicative of aggressive disease and a greater likelihood of poor outcomes. Monitoring anti-CCP antibodies may be useful to predict the severity of disease and match aggressive treatment appropriately.[10]

Comorbidities Associated with Rheumatoid Arthritis

RA reduces a patient's average life expectancy by 3 to 10 years, but RA alone rarely causes death.[11,12] Instead, specific **comorbidities** contribute to premature death independent of safety issues surrounding the use of immunomodulating medications. ❶ *The comorbidities with the greatest impact on morbidity and mortality associated with RA are (1) cardiovascular disease, (2) infections, (3) malignancy, and (4) osteoporosis.*[11,12]

Cardiovascular

Half of all deaths in RA patients are cardiovascular-related.[11] Because a patient with RA experiences inflammation and swelling in his or her joints, it is likely that there is inflammation elsewhere, such as in the blood vessels, termed **vasculitis.** C-reactive protein (CRP), a nonspecific marker of inflammation, is associated with an increased risk of cardiovascular disease; CRP is elevated in patients with RA. Chronic systemic inflammation may contribute to the relationship between RA and cardiovascular disease, but the exact mechanism is still under investigation.[11,12]

Infection

RA alone leads to changes in cellular immunity and causes a disproportionate increase in pulmonary infection and sepsis.[11] Because medications that alter the immune system are linked to an increased risk of infection, it is difficult to distinguish between an increased risk of infection secondary to RA and the medications used to treat RA. Patients and clinicians must pay close attention to signs and symptoms of infection because of this increased risk.[11]

Malignancy

Patients with RA have an increased risk of developing **lymphoproliferative** malignancy (e.g., lymphoma, leukemia, and multiple myeloma) and a decreased risk of developing cancer of the digestive tract.[11,13] The relationship between RA and cancer is not clear. To confound the issue, medications for the treatment of RA may contribute to cancer risk. Patients presenting with new onset of symptoms (e.g., fevers, night sweats, chills, or anorexia) out of proportion with disease activity and patients not responding to conventional RA treatment should be evaluated further for lymphoproliferative malignancy.[11,13]

Osteoporosis

Osteoporosis associated with RA follows a multifaceted pathogenesis, but the primary mechanism likely is mediated by **osteoclast** activity.[12] The cytokines involved in the inflammatory process directly stimulate osteoclast and inhibit **osteoblast** activity. Additionally, arthritis medications can lead to increased bone loss. Bone mineral density should be evaluated at baseline and routinely using dual-energy x-ray absorptiometry.[11,12]



Patient Encounter, Part 1

AL is a 36-year-old woman presenting to her primary care physician with a 2-month history of pain and inflammation in her hands and feet. On questioning, she indicates that she experiences pain and stiffness for at least an hour in the morning. AL is an artist and avid runner, and she wonders if her activities are causing this pain.

- What information is suggestive of RA?
- What risk factors does she have for RA?
- What additional information is necessary to differentiate between osteoarthritis and RA?
- What additional information do you need before creating a treatment plan for this patient?

CLINICAL PRESENTATION AND DIAGNOSIS

❷ *Both osteoarthritis and RA are prevalent in the American population, but they differ significantly in presentation* (Table 54–2). Figure 54–1 illustrates the typical joint involvement for patients with RA and osteoarthritis.



Presentation of Rheumatoid Arthritis

General
- About 60% of patients develop symptoms gradually over several weeks to months.
- Patients may present with systemic findings, joint findings, or both.

Symptoms
- Nonspecific systemic symptoms may include fatigue, weakness, anorexia, and diffuse musculoskeletal pain
- Patients complain of pain in involved joints and prolonged morning joint stiffness.

Signs
- The metacarpophalangeal (MCP), proximal interphalangeal (PIP), metatarsophalangeal (MTP), and wrist joints are involved frequently.
- Joint involvement is usually symmetric.
- There is often limited joint function.
- Signs of joint inflammation are present (tenderness, warmth, swelling, and erythema).
- Low-grade fever may be present.
- Extraarticular manifestations:
  - Subcutaneous **nodules**
  - *Ocular:* **Keratoconjunctivitis sicca**, **scleritis**
  - *Pulmonary:* Interstitial fibrosis, pulmonary nodules, **pleuritis**, pleural effusions
  - *Vasculitis:* ischemic ulcers, skin lesions, **leukocytoclastic** vasculitis
  - *Neurologic:* Peripheral neuropathy, **Felty's syndrome**
  - *Hematologic:* Anemia, **thrombocytosis**

Laboratory Tests
- Positive rheumatoid factor (negative in up to 30% of patients)
- Elevated erythrocyte sedimentation rate (Westergren ESR: greater than 20 mm/hour men; greater than 30 mm/hour women)
- Elevated CRP (greater than 0.7 mg/dL or greater than 7 mg/L)
- *Complete blood count:* Slight elevation in white blood cell count with a normal differential; slight anemia, thrombocytosis
- Positive anti-CCP

Other Diagnostic Tests
- *Synovial fluid analysis:* Straw colored, slightly cloudy, 5000 to 25,000 WBCs/mm^3 (5–25 × 10^9/L), negative if cultured
- *Joint x-rays:* To establish baseline and evaluate joint damage
- *Magnetic resonance imaging:* May detect erosions earlier in the course of disease than x-rays but is not required for diagnosis.

Diagnosis[1]

Seven criteria must be met to diagnose RA appropriately:

1. Morning joint stiffness lasting more than 1 hour before disappearing
2. Involvement of three or more joint areas
3. Arthritis of hand joints
4. Symmetric joint involvement
5. Presence of rheumatoid nodules
6. Elevated rheumatoid factor
7. Radiographic changes

A patient may be diagnosed with RA if four or more of these are present. Criteria 1 through 4 must be present for at least 6 weeks. Criteria 5 through 7 must be observed by a clinician.

TREATMENT

Desired Outcomes

❸ *The goals of treatment in RA are to (1) reduce or eliminate pain, (2) protect articular structures, (3) control systemic complications, (4) prevent loss of joint function, and (5) improve or maintain quality of life.*[1,7]

General Approach to Treatment

The clinician must evaluate patient-specific factors and select appropriate treatment to maximize the care of an individual patient. ❹ *Factors associated with poor outcomes are (1) early age of disease onset, (2) elevated ESR, (3) high titer of rheumatoid factor, (4) swelling of more than 20 joints, and (5) presence of extraarticular manifestations.*[1] Thirty percent of all patients with RA have radiographic evidence of erosions at the time of diagnosis; therefore, all patients should be treated early and aggressively to reduce disease progression and to prevent joint erosions.[1] Aggressive treatment is defined as one or more disease-modifying antirheumatic drugs (DMARDs) at effective doses. Delaying treatment will result in more destructive disease that is very difficult to delay or reverse to preserve joint function. Specialty care by a rheumatologist may reduce the likelihood of disease progression and joint damage.[14]

Nonpharmacologic Therapy

All patients should receive education about the nonpharmacologic and pharmacologic measures to help manage RA. Empowered patients take an active role in care by participating in therapy-related decisions. Certain forms of nonpharmacologic therapy benefit all levels of severity, whereas others (i.e., surgery) are reserved for severe cases only.

Occupational and physical therapy may help patients to preserve joint function, extend joint range of motion, and strengthen joints and muscles through strengthening exercises. Patients with joint deformities may benefit from the use of mobility or assistive devices that help to minimize disability and allow continued activities of daily living. In situations where the disease has progressed to a severe form with extensive

TABLE 54–2. Comparison of Rheumatoid Arthritis and Osteoarthritis[6]

	Rheumatoid Arthritis	Osteoarthritis
Gender prevalence (women:men)	3 : 1	1 : 1
Peak age of onset	35–50	Greater than 65
Risk factor of obesity	No	Yes
Morning stiffness	Usually greater than or equal to 60 minutes	Usually less than 30 minutes
Involved joint distribution	Symmetric	Symmetric or asymmetric
Presence of inflammation	Local and systemic	None or mild, local
Erythrocyte sedimentation rate	Elevated	Normal
Synovial fluid	Leukocytosis, slightly cloudy	Mild leukocytosis
Systemic manifestations	Yes	No

joint erosions, surgery to replace or reconstruct the joint may be necessary.[1]

Pharmacologic Therapy

❺ *It is imperative that the initiation of one or more DMARDs occurs in all patients within the first 3 months of diagnosis to reduce joint erosion.* Figure 54–2 outlines the course of treatment according to the American College of Rheumatology (ACR) *Guidelines for Management of Rheumatoid Arthritis.*[1] Combination therapy may be initiated at the time of diagnosis or after an adequate trial of a DMARD initiated as monotherapy. Starting combination therapy initially is referred to as the *stepdown approach,* wherein one or more agents are discontinued once the disease is controlled. Adding a second or third agent after an adequate trial of DMARD monotherapy is considered a *step-up approach.* ❻ *Most clinicians favor the "step-down" approach to slow or reverse the early articular damage as soon as possible.*[7] The following medication classes are prescribed commonly for the treatment of RA: (1) non-steroidal anti-inflammatory drugs (NSAIDs), (2) glucocorticoids, (3) DMARDs, and (4) biologic response modifiers (BRMs). Table 54–3 highlights dosing, safety, monitoring, and patient counseling information for the common DMARDs and BRMs.

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs provide analgesic and anti-inflammatory benefits for joint pain and swelling. However, they do not prevent joint damage or change the underlying disease.[1] It is appropriate for a patient to begin taking an NSAID along with a DMARD for "bridge therapy" to provide symptomatic relief until the therapeutic effect of the DMARD is observed. Because of interpatient variability in response, patients may find relief from one NSAID and not another. For this reason, if a patient does not receive relief from one NSAID, it is acceptable to try a second one. Selecting another NSAID depends on multiple patient-specific factors including cardiovascular risk, potential for gastrointestinal-related adverse events, adherence to medication regimens, and insurance coverage or lack thereof. Clinicians must weigh these factors carefully to determine if the patient will benefit from another NSAID, if he or she should receive a cyclooxygenase-2 (COX-2) inhibitor, or if another medication class should be considered.

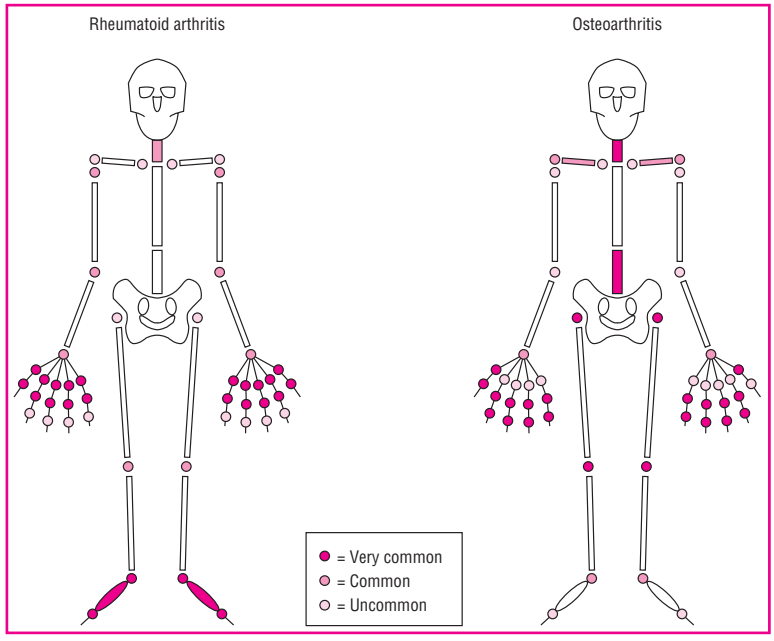


FIGURE 54–1. Patterns of joint involvement in rheumatoid arthritis. (From DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy*. 6th ed. New York: McGraw-Hill; 2005, Figure 89–3, p. 1673, with permission.)

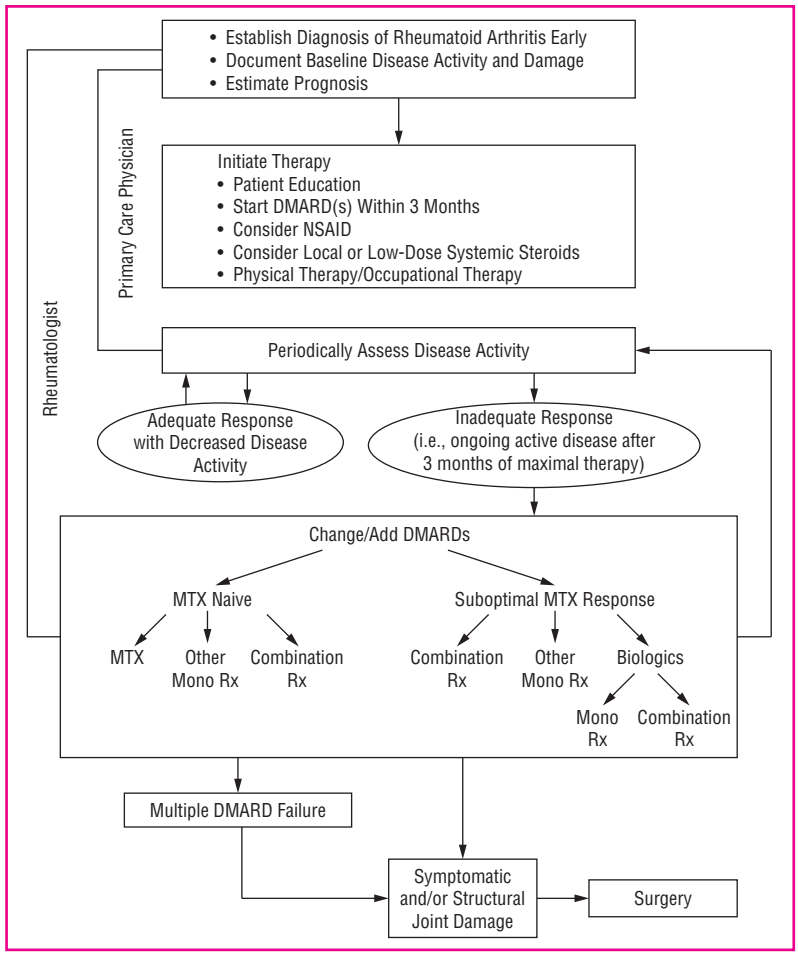


FIGURE 54–2. Outline of the management of rheumatoid arthritis. (From Guidelines for the management of rheumatoid arthritis: 2002 update. Arthritis Rheum 2002; 46(2):328–346, with permission.) DMARD, disease-modifying antirheumatic drug; NSAID, nonsteroidal antiinflammatory drug; MTX, methotrexate; Rx, therapy.

NSAID use is associated with an increased risk of gastrointestinal ulcers or hemorrhage, fluid retention, exacerbation of existing hypertension, and decreased renal function in certain patient populations.[7,15] Factors that place a patient at a higher risk of gastrointestinal-related adverse reactions include (1) history of peptic ulcer disease, (2) high doses of NSAIDs, (3) concomitant use of other medications with an increased risk of gastrointestinal hemorrhage or ulcers (e.g., anticoagulants, corticosteroids, use of multiple NSAIDs), (4) age greater than 75 years, and (5) serious underlying diseases.[1] If a patient is at an increased risk of NSAID-induced adverse reactions, gastroprotection should be considered by coinitiation of a proton pump inhibitor or histamine-2 receptor blocker or misoprostol. Misoprostol is effective in reducing the occurrence of gastric and duodenal ulcers. However, its tolerability is limited by adverse effects, specifically diarrhea. Histamine-2 receptor blockers effectively prevent duodenal ulcers (but not gastric ulcers) that occur more readily as a result of NSAID therapy. Proton pump inhibitors are the preferred gastroprotective agents due to achievement of a greater level of acid suppression, evidence of prevention of gastric and duodenal ulcers, and a tolerable adverse-effect profile.[16] Changing treatment to low-dose prednisone, a nonacetylated salicylate, or a COX-2 inhibitor is an additional option.[1]

NSAIDs may accentuate the increased risk of cardiovascular events inherent in patients with RA. Increases in blood pressure and fluid retention may exacerbate existing cardiovascular disease. With the evidence associating COX-2 inhibitors with cardiovascular disease, clinicians must carefully evaluate the potential risks of NSAID therapy against the potential benefits.[2] See Chap. 55 for additional discussion of NSAID therapy.

Glucocorticoids

Low-dose glucocorticoid treatment (prednisone less than or equal to 10 mg/day or equivalent) effectively reduces inflammation through inhibition of cytokines and inflammatory mediators and prevents disease progression.[15,17] The goal of glucocorticoid use is to minimize adverse drug events by keeping the doses low and using the drugs as infrequently as possible. Patients may receive glucocorticoids for a brief time as "bridge therapy" following DMARD initiation or via intraarticular injections to relieve symptoms of active disease. Patients taking doses more than 10 mg/day prednisone or equivalent are at an increased risk for clinically significant adverse reactions, especially bone loss leading to osteoporosis. Other glucocorticoid-related adverse reactions include Cushing's syndrome, peptic ulcer disease, hypertension,

TABLE 54–3. FDA-Approved DMARDs and BRMs for Treatment of Rheumatoid Arthritis[1,2,7,15,21,42]

Drug	Dose	Route	Time to Effect	ADRs	Monitoring	Counseling Points
Methotrexate	7.5–20 mg once weekly	Oral or IM	4–8 weeks	N, D, hepatotoxicity, alopecia, new-onset cough or SOB, MYL	CBC, creatinine, LFTs q 4–8 weeks Monitor for signs of infection	Concomitant use of folic acid Avoid alcohol Use contraception if childbearing potential
Hydroxychloroquine	200 mg bid	Oral	8–24 weeks	N, D, HA, vision changes, skin pigmentation	Eye exam every 12 mo.	
Sulfasalazine	1000 mg bid–tid	Oral	8–12 weeks	N, D, rash, yellow-orange discoloration, photosensitivity, MYL	CBC q 2–4 weeks for 3 mo. then q 3 mo.	Sunscreen use
Leflunomide (Arava)	100 mg daily for 3 days; then 20 mg daily	Oral	4–12 weeks	Hepatotoxicity, D, N, HTN, rash, HA, abdominal pain	CBC, creatinine, LFTs q mo. for 6 mo.; then q 4–8 weeks Monitor for signs of infection	Avoid alcohol Use contraception if childbearing potential
Etanercept (Enbrel)	25 mg twice weekly or 50 mg once weekly	SC injection	1–4 weeks	ISR	Monitor for infection	ISR—topical corticosteroids, antipruritics, analgesics, rotate injection sites Screen for tuberculosis
Infliximab (Remicade)	3–10 mg/kg at 0, 2, and 6 weeks; then q 8 weeks	IV infusion	1–4 weeks	IR (rash, urticaria, flushing, HA, fever, chills, nausea, tachycardia, dyspnea)	Monitor for infection	Screen for tuberculosis
Adalimumab (Humira)	40 mg every other week	SC injection	1–4 weeks	ISR	Monitor for infection	Screen for tuberculosis
Anakinra (Kineret)	100–150 mg daily	SC injection	2–4 weeks	HA, N, V, D, ISR	Monitor for infection	
Rituximab (Rituxan)	Two 1000-mg infusions separated by 2 weeks	IV infusion	4 weeks	IR	Monitor for infection	

N, nausea; D, diarrhea; HA, headache; SOB, shortness of breath; HTN, hypertension; LFTs, liver function tests; CBC, complete blood count; ISR, injection-site reactions; IR, infusion reactions; IV, intravenous; MYL, myelosuppression (watch for fever, symptoms of infection, easy bruisability, and bleeding); SC, subcutaneous.

weight gain, infection, mood changes, cataracts, dyslipidemia, and hyperglycemia.[2,17]

Disease-Modifying Antirheumatic Drugs

DMARDs are the mainstay of RA treatment because they modify the disease process and prevent or reduce joint damage. To differentiate between synthetic DMARDs and biologic DMARDs, the discussion is separated into DMARDs and BRMs. Although BRMs are considered disease-modifying agents, they are separated from traditional DMARDs because long-term data related to safety and efficacy are not as robust as with synthetic DMARDs. Until these data are available, it is difficult to justify using the medications interchangeably in clinical practice.

In addition to relying on safety and efficacy data, the initial DMARD choice depends on disease severity, patient characteristics (i.e., comorbidities, likelihood of adherence), cost, and clinician experience with the medication.[1,7] Methotrexate alone or in combination therapy is the initial treatment of choice for patients with aggressive disease. Patients with early, mild disease may receive monotherapy with sulfasalazine or hydroxychloroquine. Agents such as azathioprine, D-penicillamine, and gold salts are used rarely today because of concerns about toxicity and reduced efficacy.[1,15]

Methotrexate

❼ *Methotrexate is the DMARD of choice because of its documented efficacy and safety profile when monitored appropriately.*[1,15] Methotrexate exerts its anti-inflammatory effect through inhibition of dihydrofolate reductase, which causes the inhibition of purines and thymidylic acid, and by inhibiting the production of certain cytokines.[2] Unless the patient has contraindications to methotrexate, once-weekly doses should be initiated within 3 months of diagnosis and increased steadily until the patient has symptomatic improvement or a maximum dose of 20 mg/week is reached. Concomitant folic acid is given routinely to reduce the risk of folate-depleting reactions induced by methotrexate therapy (e.g., **stomatitis,** diarrhea, nausea, **alopecia, myelosuppression,** and elevations in liver function tests).[1,18] Serious adverse reactions include pulmonary fibrosis and hepatotoxicity. Patients should be counseled to avoid the use of alcohol, take folic acid as directed, adhere to the laboratory monitoring schedule, and immediately report symptoms of pulmonary fibrosis (e.g., cough or dyspnea) and hepatotoxicity (e.g., jaundice or abdominal pain). If monotherapy does not produce complete resolution of symptoms, methotrexate may be used in combination with other DMARDs. Combinations with evidence of efficacy and tolerability are methotrexate plus cyclosporine, methotrexate plus hydroxychloroquine and/or sulfasalazine, methotrexate plus leflunomide, and methotrexate plus infliximab or etanercept.[1,19]

Hydroxychloroquine and Sulfasalazine

The exact mechanism of action of these drugs is unknown, but both agents are fairly well tolerated. Hydroxychloroquine or sulfasalazine may be initiated on diagnosis of mild disease. Owing to their slow onset of action, each drug must be given at therapeutic doses for at least 6 months before it can be deemed a treatment failure. Hydroxycholorquine and sulfasalazine are relatively inexpensive compared with the new biologic agents. If patients do not respond to methotrexate monotherapy, adding one of these agents may provide the benefit necessary to reduce symptoms satisfactorily.[2]

Hydroxychloroquine may cause retinal toxicity, and patients must have their eyes examined at least annually to detect this abnormality. It is not associated with renal, hepatic, or bone marrow suppression and therefore may be an acceptable treatment option for patients with contraindications to other DMARDs because of their toxicities.

Starting sulfasalazine at low doses and titrating slowly will minimize the nausea and abdominal discomfort caused by the drug. Patients receiving sulfasalazine must undergo routine blood work to monitor for leukopenia.[1] Patients with a sulfa allergy should not receive sulfasalazine.

Leflunomide

Leflunomide inhibits dihydroorotate dehydrogenase, an enzyme within the mitochondria that supplies T lymphocytes with the necessary components to respond to cytokine stimulation.[20] Thus leflunomide inhibits the T-lymphocyte response to various stimuli and halts the cell cycle. Its efficacy is similar to that of moderate doses of methotrexate or sulfasalazine.[15] Because of its extended half life, leflunomide therapy begins with a loading dose followed by a maintenance dose. Patients with preexisting hepatic disease or a history of heavy alcohol ingestion should not receive leflunomide.[21] Leflunomide may be used in combination with methotrexate, but the added efficacy comes with a dramatic rise in the risk of hepatotoxicity. Liver function tests must be followed closely to prevent or minimize liver damage.[1] If therapy requires abrupt discontinuation (e.g., due to toxicity or pregnancy), administering cholestyramine will accelerate removal of leflunomide from the body.[19]

Biologic Response Modifiers

Biologic response modifiers (BRMs) are indicated in patients who have failed an adequate trial of DMARD therapy.[1] BRMs may be added to DMARD monotherapy (i.e., methotrexate) or replace ineffective DMARD therapy.[22] The decision to select a particular agent generally is based on the prescriber's comfort level with monitoring the safety and efficacy of the medications, the frequency and route of administration, the patient's comfort level or manual dexterity to self-administer subcutaneous injections, the cost, and the availability of insurance coverage.[23] In general, BRMs should be avoided in patients with serious infections, demyelinating disorders (e.g., multiple sclerosis or optic neuritis) or heart failure.[21]

Tumor Necrosis Factor Antagonists

Etanercept is a recombinant form of human tumor necrosis factor receptor.[24] Etanercept provides a therapeutic effect by binding to soluble TNF and preventing its binding with TNF receptors. It is administered subcutaneously once or twice weekly; noticeable symptomatic improvement is seen in 1 to

4 weeks. Etanercept is very effective as monotherapy or in combination with other DMARDs, except ANAKINRA.[24] There is no evidence to suggest a benefit to this combination, and there is an increased infection risk. The most common adverse reactions with etanercept are injection-site reactions. If such reactions are bothersome to patients, they should be advised to place ice on the injection site before and after administration or apply a topical anesthetic or corticosteroid to the affected area.[25]

Infliximab is a **chimeric** IgG1 monoclonal antibody that binds to soluble and bound TNF-α.[26] Methotrexate typically is given with it to suppress antibody production against the mouse-derived portion of the molecule. Infliximab is delivered via intravenous infusion every 4 to 8 weeks; however, patients may notice benefit within 1 to 4 weeks of receiving the first infusion. Infusion-related reactions including rash, urticaria, flushing, headache, fever, chills, nausea, tachycardia, and dyspnea may occur during treatment. Qualified health care personnel must be present during the infusion to respond to the infusion-related reactions, if they occur. If patients experience any of these symptoms, the reaction may be treated by (1) temporarily discontinuing the infusion, (2) slowing the infusion rate, or (3) administering corticosteroids or antihistamines.[25] Clinicians may prescribe pretreatment regimens with corticosteroids or antihistamines if the patient continues to experience infusion reactions.[25]

Adalimumab is a recombinant human IgG1 monoclonal antibody specific for human TNF.[27] Adalimumab binds to soluble and bound TNF-α. Patients may experience symptomatic relief in as early as 1 week. Adalimumab can be administered in combination with methotrexate or other DMARDs.[2]

Interleukin 1 Receptor Antagonist

Anakinra is a recombinant form of human IL-1 receptor antagonist. Anakinra inhibits the activity of IL-1 by binding to it and preventing cell signaling.[28] Patients must administer a subcutaneous injection every day, which may be less desirable than other treatment options. Anakinra may be used in combination with other DMARDs in patients not responding to or unable to tolerate DMARDs or TNF antagonists.[21] Anakinra should not be used in combination with TNF antagonists due to the increased risk of infection.[21]

Costimulation Blockers

Abatacept is the first agent in a new class of medications called *costimulation blockers.* Abatacept interferes with T-cell signaling, ultimately blocking T-cell activation and leading to anergy, or lack of response to an antigen.[29,30] Trials conducted in patients refractory to methotrexate and anti-TNF therapy demonstrated significant clinical benefit after administration of abatacept every 28 days with a dose approximating 10 mg/kg.[30] Adverse reactions reported in clinical trials were low and similar to those of placebo, with the exception of an increased incidence of headache, infections, and infusion-related reactions in the treatment group.[29,30] Abatacept is indicated as monotherapy or in combination with synthetic DMARDs. Its exact place in therapy is not yet clear; however, clinicians see a window of opportunity for patients who were intolerant to or did not receive therapeutic benefit from other DMARDs or BRMs or developed antibodies to adequate trials of anti-TNF agents, specifically infliximab.[30]

Anti-CD20 Monoclonal Antibody

Rituximab is a genetically engineered chimeric anti-CD20 monoclonal antibody that causes B-lymphocyte depletion.[31] Although the exact role of B lymphocytes in the pathogenesis of RA is not clear, a small study in patients with RA demonstrated noticeable efficacy. Further clinical trials showed a sustained therapeutic effect lasting for at least 48 weeks after the initial treatment.[31–34] Adverse effects occurring during or up to 24 hours after the first infusion included changes in blood pressure (increases or decreases), cough, rash, and pruritus. The infusion-related reactions subsided with subsequent infusions. Serious infections occurred in a small number of rituximab-treated patients.

The exact role of rituximab in RA is not clearly defined, but it is indicated for patients with moderate to severe RA with a history of inadequate response to DMARDs and other BRMs. Rituximab carries a black-box warning of fatal infusion reactions and severe mucocutaneous reactions even though these events did not occur during the RA clinical trials. The benefits of rituximab must be tempered against the safety concerns reported with use of rituximab in the oncology setting.

Investigational Agents

Anti-IL-6 receptor monoclonal antibody (MRA) inhibits the binding of IL-6 and the IL-6 receptor.[35] IL-6 is produced in high amounts in patients with RA. High levels are indicative of joint damage and disease activity. Studies in patients not responding to methotrexate monotherapy have demonstrated safety and efficacy of MRA administration.[2] A trial designed to evaluate the safety and efficacy of MRA found that patients experienced dose-dependent improvements in disease activity with an acceptable side-effect profile. Because MRA may adversely affect the cholesterol profile, the United States Food and Drug Administration (FDA) may require additional aggressive control of cardiovascular risk factors so that the benefits outweigh the potential risks.[35]

Selecting a Biologic Response Modifier

The developments in the treatment of RA are tempered by the lack of evidence describing the long-term safety and efficacy of the BRMs. In addition, the cost associated with the medications can be a deterrent to use. Long-term data are needed to determine if patients receiving BRM therapy early in the course of disease have reduced disease activity, reduced joint deformities and disability, improved quality of life, and continued function as productive members of society. Cost analyses of long-term data may indicate that the increased expenses associated with BRMs are offset by the costs avoided for the treatment of advanced RA.

8 *The risk of infection in patients treated with BRMs must be considered when selecting and monitoring therapy.*[36] Influencing the immune response to reduce symptoms of RA may influence the body's response to pathogens. Of particular concern is the

use of TNF antagonists in patients with a history of tuberculosis exposure. TNF is important in the formation of granulomas that wall off tuberculosis infection. In theory, if TNF is inhibited, patients with latent tuberculosis may have a reactivated infection. Patients receiving BRM therapy should be screened for tuberculosis and other infections. Prophylaxis should be initiated in patients with previous tuberculosis exposure or in patients at high risk of developing tuberculosis.[22] BRMs should not be initiated during an acute, serious infection and should be discontinued temporarily during times of infection.[25]

Use of TNF antagonists is associated with an increased risk of malignancy, specifically lymphoma.[21] This relationship is still under investigation because the risk of lymphoma is already increased if a patient has the diagnosis of RA, and the risk increases with the severity of disease.[21] Patients should be monitored closely for signs and symptoms suggestive of malignancy. Therapy should be discontinued once the risks outweigh the potential benefits of treatment.



Patient Encounter, Part 2: The Medical History, Physical Examination, and Laboratory Tests

PMH
- Exercise-induced asthma
- Allergic rhinitis
- Carpal tunnel syndrome

FH
Father has hypertension, diabetes, dyslipidemia; mother has RA and a history of MI; two siblings (one brother, one sister) alive and well.

SH
She is a successful artist and works from home. She drinks alcohol occasionally and does not smoke or use illicit drugs.

Allergies: NKDA

Meds
- Albuterol 2 puffs 15 to 20 minutes before exercise
- Ortho Tri-Cyclen by mouth once daily
- Budesonide nasal spray one spray each nostril daily
- Calcium (with vitamin D) 600 mg by mouth twice daily
- Ibuprofen 400 mg by mouth every 4 hours daily PRN

ROS
(+) fatigue, (–) N/V/D, HA, SOB, chest pain, cough

PE
- **VS:** 126/74, P 70, RR 18, T 38°C (100.4°F)
- **Skin:** Warm, dry
- **HEENT:** NC/AT, PERRLA, TMs intact
- **CV:** RRR, normal S_1 and S_2, no m/r/g
- **Chest:** CTA
- **Abd:** Soft, NT/ND
- **Neuro:** A & O × 3; CN II–XII intact
- **Exts:** Bilateral tender and swollen PIPs, MCPs, and MTPs (symmetric)

Labs
ESR 66 mm/hour, RF (+), HLA-DR4, anti-CCP (+)

Synovial fluid analysis: Yellow, cloudy, decreased viscosity

Hand x-rays: Soft tissue swelling, joint space narrowing, no evidence of erosions

- Given this additional information, what is your assessment of the patient's condition?
- Identify your treatment goals for this patient.
- What nonpharmacologic and pharmacologic alternatives are available for this patient?



Patient Encounter, Part 3: Creating a Care Plan

Based on the information available, create a care plan for this patient's RA. The plan should include (1) a statement of the drug-related needs and/or problems, (2) the goals of therapy, (3) a patient-specific detailed therapeutic plan, and (4) monitoring parameters to assess safety and efficacy.
Six months later, the patient comes back and mentions that she would like to become pregnant. Does this change your treatment plan? If yes, devise a new treatment plan for AL.

Fertility, Pregnancy, and Fetal Development

Women of childbearing age should be counseled about the impact of antirheumatic drugs on fertility, pregnancy, fetal development, and lactation. Some women may experience a reduction in disease symptoms during pregnancy; however, many agents used to treat RA are known teratogens. Women desiring motherhood must consult with their physicians to carefully plan for the pregnancy and reduce risks to the developing fetus.[37] Low-dose corticosteroids generally are safe and effective. Certain NSAIDs, hydroxychloroquine, and azathioprine may be considered in severe disease. Methotrexate use (FDA pregnancy category X) is associated with spontaneous abortion, fetal myelosuppression, limb defects, and central nervous system abnormalities; therefore, pregnancy must be avoided.[37] Sulfasalazine, on the other hand, may be the drug of choice in women who are pregnant or planning to become pregnant owing to its safety profile.[37] There is limited evidence of safety and long-term effects of the use of BRMs in pregnant women. Case reports of pregnancy during BRM therapy show no increased risk of fetal toxicity, but long-term data still are needed.[25,37]

Male patients with RA must receive counseling about the effects of certain medications on their fertility and potential harm to the fetus. It is difficult to establish causality between use of a medication by a male and the effect on fertility or fetal development; therefore, a conservative approach must be taken. ❾ *Patients of childbearing potential and their partners must be counseled to (1) use proper birth control while undergoing treatment for RA and (2) discontinue medications at least 3 months before conception.*[37]

OUTCOME EVALUATION

- Rheumatologists rely on standardized criteria to assess treatment interventions through measurement of disease activity. The American College of Rheumatology (ACR) uses criteria for improvement based on percent improvement in tender and swollen joint count and the presence of at least three or more of the following measures: pain, patient global assessment, physician global assessment, self-assessed physical disability, and acute-phase reactants.[38] ACR20, ACR50, and ACR70 are common efficacy endpoints in clinical trials. The number corresponds with the percent improvement. As treatment continues to evolve, the acceptable criteria for 20% improvement may be too low. For example, if a patient has 10 tender and swollen joints, reducing that by 20% to 8 tender and swollen joints is, by definition, an improvement by ACR20 criteria. However, further reduction in symptoms or disease remission may have greater clinical significance and effect on the patient's quality of life.
- Physical disability from RA can be measured through the Stanford Health Assessment Questionnaire (HAQ).[39,40] This patient self-assessment tool was developed to evaluate patient outcomes in five dimensions of chronic conditions: (1) disability, (2) discomfort, (3) drug adverse effects, (4) dollar costs, and (5) death. Clinicians and clinical studies in rheumatology use HAQ to assess longitudinally changes that influence the patient's quality of life.[39,40]
- Before starting treatment for RA, assess the subjective and objective evidence of disease. For joint findings, this includes the number of tender and swollen joints, pain, limitations on use, duration of morning stiffness, and presence of joint erosions. Systemic findings may include fatigue and the presence of extraarticular manifestations. Obtain laboratory measurements of CRP and ESR. The impact of the disease on quality of life and functional status is also important.
- At follow-up visits, compare the patient's status to baseline or previous visits using the ACR criteria for improvement of disease activity and the HAQ to assess longitudinally the influence on quality of life.
- Assess the patient's response to initiation of DMARD therapy after allowing adequate time for the medication to achieve its therapeutic effect.
- Determine whether any adverse reactions associated with each antirheumatic medication are present.
- Monitor laboratory parameters to ensure patient safety and reduce the risk of adverse reactions.



Patient Care and Monitoring

1. Assess the patient's symptoms to determine if they are consistent with RA. Evaluate the duration of symptoms and their impact on daily living.
2. Review available diagnostic data to determine the severity of disease and whether the patient is at risk of experiencing poor outcomes.
3. Obtain a thorough medication history, including prescription drugs, over-the-counter drugs, and dietary supplement use.
4. Educate the patient on nonpharmacologic measures that will improve symptoms.
5. Formulate a therapeutic plan, taking into consideration patient-specific factors.
6. Evaluate the patient for the presence of adverse drug reactions, drug allergies, and drug interactions.
7. Develop a plan to assess safety and efficacy of the pharmacologic treatment plan. Determine if the appropriate doses of antirheumatic medications were used and if all medication were given a sufficient trial to achieve therapeutic benefit.
8. Stress importance of adherence with therapeutic regimen (including required laboratory monitoring, medication dosing and administration). Recommend a therapeutic regimen that is convenient and consistent with the patient's lifestyle.
9. Longitudinally evaluate the patient's clinical response to therapy and the impact on quality of life and mobility.
10. Evaluate the presence of comorbidities, and implement measures to control the increased risk.
    - *Cardiovascular:* Keep doses of NSAIDs and glucocorticoids low, consider initiation of folic acid to reduce homocysteine level elevations induced by methotrexate, consider initiation of low-dose aspirin and/or HMG-CoA reductase inhibitors (statins), and encourage smokers to discontinue tobacco use and assist with the development of a tobacco-cessation plan.[11,12]
    - *Infection:* Wash hands routinely, limit contact with individuals who are ill, and report signs and symptoms of infection immediately (e.g., fever, weight loss, and night sweats).
    - *Malignancy:* Report new onset of signs and symptoms (e.g., fever, chills, anorexia, and night sweats) immediately.[13]
    - Osteoporosis: Encourage patients to ingest adequate amounts of calcium and vitamin D, encourage smokers to discontinue tobacco use, and consider initiation of medications for osteoporosis (e.g., bisphosphonates, calcitonin, and parathyroid hormone) if the patient is taking glucocorticoids for an extended period of time or if the patient has evidence of low bone mineral density.[15,41]
11. Provide patient education in regard to RA, lifestyle modifications, and drug therapy:
    - What causes RA?
    - What are the comorbidities associated with RA?
    - How will lifestyle modifications affect RA?
    - What are the goals of therapy in the treatment of RA?
    - When and how should the medications be administered?
    - What potential adverse drug reactions may occur?
    - Which drugs may interact with therapy?
    - What are the warning signs to report to the physician?

ABBREVIATIONS

ACR:	American College of Rheumatology
BRM:	biologic response modifier
CBC:	complete blood count
CCP:	cyclic citrullinated peptide
CRP:	C-reactive protein
DMARD:	disease-modifying antirheumatic drug
ESR:	erythrocyte sedimentation rate
HAQ:	Health Assessment Questionnaire
MCP:	metacarpophalangeal joint
MTP:	metatarsophalangeal joint
PIP:	proximal interphalangeal joint
RA:	rheumatoid arthritis

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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55 Osteoarthritis

Benjamin J. Epstein, John G. Gums, and Karen Hall



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Identify risk factors associated with osteoarthritis (OA).
2. Recognize the signs and symptoms of OA.
3. Determine the goals of therapy for individual patients with OA.
4. Formulate a rational nonpharmacologic plan for patients with OA.
5. Recommend a pharmacologic plan for OA, taking into consideration individual patient factors.
6. Modify an unsuccessful treatment strategy for OA.
7. Develop monitoring parameters to assess effectiveness and adverse effects of pharmacotherapy for OA.
8. Deliver effective disease-state counseling, including lifestyle modifications and drug therapy, to facilitate effective and safe management of OA.

Key Concepts

❶ OA is the most common form of arthritis and is most prevalent in the middle to later years of life.
❷ The most common symptoms are joint pain, reduced range of motion, and brief joint stiffness after periods of inactivity.
❸ Treatment goals are to educate the patient and caregivers, relieve pain, maintain or restore mobility, minimize functional impairment, preserve joint integrity, and improve quality of life.
❹ Nonpharmacologic therapy is the cornerstone of treatment; education, exercise, weight loss, and cognitive behavioral intervention are integral components.
❺ Acetaminophen is the initial drug of choice; an adequate dose and duration of therapy should be used before resorting to other drug classes.
❻ Nonsteroidal anti-inflammatory drugs (NSAIDs) may be initiated if acetaminophen therapy fails. At equipotent doses, all NSAIDs elicit similar analgesic and anti-inflammatory responses. Selection is based on patient preference, dosing frequency, tolerability, and cost.
❼ Patients who do not respond adequately to one NSAID may respond to a different NSAID.
❽ NSAIDs are associated with gastrointestinal, renal, hepatic, and central nervous system toxicity and may increase blood pressure.
❾ NSAIDs that are selective for the cyclooxygenase-2 (COX-2) isozyme are less likely to cause gastrointestinal complications but may increase the risk of cardiovascular events. They are no more effective than nonselective NSAIDs. Selective agents should be reserved for patients at high risk of gastrointestinal complications and low risk for cardiovascular events.
❿ Glucosamine, tramadol, opioids, topical capsaicin, intraarticular corticosteroids, and surgery may be beneficial in certain situations.

❶ *Osteoarthritis (OA) is the most common form of arthritis.* Weight-bearing joints (e.g., hips and knees) are most susceptible, but non-weight-bearing joints, especially the hands, may also be involved. Because of its high prevalence and involvement of joints critical for daily functioning, the disease causes tremendous morbidity and financial burden. Recent estimates suggest that the total cost of caring for patients with OA equals or exceeds 2% of the gross national product.[1] OA ranks second only to cardiovascular disease as a cause of chronic disability; it is the most common reason for total-hip and total-knee replacement. ❶ *Osteoarthritis is strongly related to age; thus its incidence and the cost of care will*

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increase dramatically in the coming years owing to a burgeoning senior citizenry. The National Arthritis Data Workgroup predicts that by the year 2020, 54.9 million Americans will be affected by OA, a nearly 3.5-fold increase from current estimates.

EPIDEMIOLOGY

The National Center for Health Statistics estimates that 15.8 million Americans have signs and symptoms of OA. The true extent of the disease is much larger; nearly everyone has radiographic evidence of OA by the eighth decade of life, but individuals without symptoms often go undiagnosed. Approximately 6% of United States adults have daily symptomatic knee OA, and 3% report daily symptoms affecting the hip.[2] After age 60, 10% to 15% of persons report such symptoms.

The prevalence of OA is higher in women, and they have more generalized disease. Women are also more likely to have inflammation of the proximal and distal interphalangeal joints of the hands, which manifest as **Bouchard's** and **Heberden's** nodes, respectively. OA of the hip occurs more frequently in men.

The prevalence of OA in Caucasians approximates the rate in African Americans, but the latter may experience more severe and disabling disease. Persons of Chinese descent rarely have hip OA; they are also less likely to develop hand OA but more likely to develop knee OA.[3]

PATHOPHYSIOLOGY

OA is characterized by damage to **diarthrodial** joints and joint structures. In the past, OA was referred to as *degenerative joint disease* (DJD), *hypertrophic arthritis,* or *osteoarthrosis;* however, such nomenclature fails to appreciate the multiple metabolic and pathologic derangements that comprise OA (Fig. 55–1). OA is a multifactorial disease typified by progressive destruction of joint cartilage, erratic new bone formation, thickening of **subchondral** bone and the joint capsule, bony remodeling, development of **osteophytes,** variable degrees of mild **synovitis,** and other changes.[4]

The earliest stages of OA are characterized by increasing water content and softening of cartilage in weight-bearing joints. As the disease progresses, **proteoglycan** content of cartilage declines, and eventually, cartilage becomes hypocellular. Increasing levels of protease enzymes, such as matrix **metalloproteinases** (MMPs), occur before changes in cartilage, suggesting that these catabolic proteinases play an important role in the initiation and progression of OA.

Subchondral bone undergoes metabolic changes, including increased bone turnover, that appear to be precursors to tissue destruction. The normally contiguous bony surface becomes fissured**.** Persistent use of the joint eventually results in loss of cartilage, permitting bone-to-bone contact that ultimately promotes thickening and **eburnation** of exposed bone. Microfractures may appear in subchondral bone, and **osteonecrosis** may develop beneath the surface.

New bone is formed haphazardly, leading to the formation of osteophytes that extend into the joint capsule and ligament attachments and may encroach on the joint space. Progressive loss of joint cartilage, subchondral damage, narrowing of joint spaces, and changes in the underlying bone and soft tissues of the affected joints culminates in deformed, painful joints.

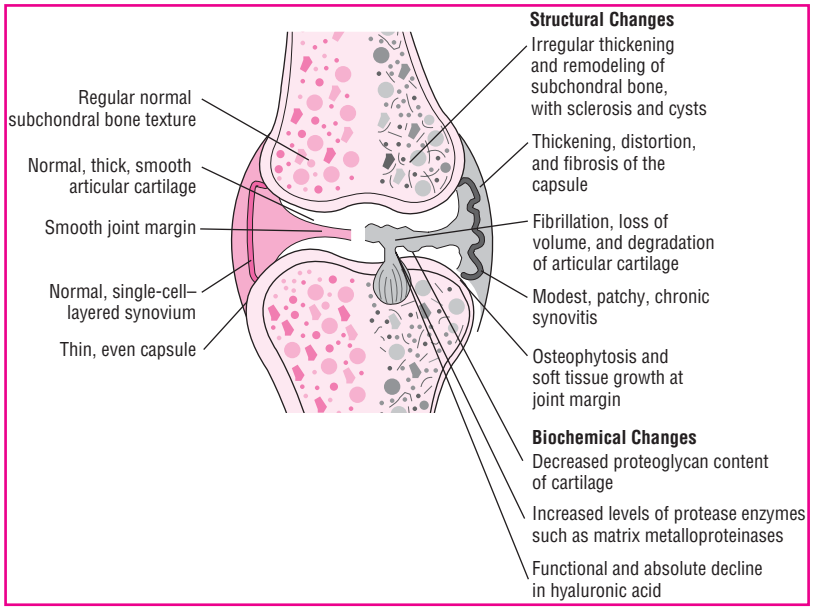


FIGURE 55–1. Characteristics of osteoarthritis in the diarthrodial joint. (Adapted from DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005, Figure 90-1, p.1687, with permission.)

Classification

OA is often divided into primary (idiopathic) and secondary disease (Table 55–1). Primary OA is the predominant form and occurs in the absence of a precipitating event. It may assume a localized, generalized, or erosive pattern. Localized OA is distinguished from generalized disease by the number of sites involved, whereas erosive disease is characterized by an erosive pattern of bone destruction and marked proliferation of interphalangeal joints of the hands. Secondary OA occurs when the disease is caused by congenital or developmental disorders or inflammatory, metabolic, or endocrine diseases.

Risk Factors

OA develops when systemic factors and biomechanical vulnerabilities combine. Systemic factors include age, gender, genetic predisposition, and nutritional status. Age is the strongest predictor of OA, although advanced age alone is insufficient to cause OA.

Joints exposed to biomechanical factors are at increased risk. Occupational and recreational activities involving repetitive motion or injury can provoke OA, although most daily activities do not produce enough joint trauma to cause OA, even after decades of repeated use. However, daily activities may lead to OA if a joint is susceptible because of previous injury, joint deformity, muscle weakness, or systemic factors. Heavy physical activity is a stronger predictor of subsequent OA than light to moderate activities.[5] This is especially true for older individuals, in whom the joint structure is less capable of coping with highly stressful activities. Obesity increases load-bearing stresses on hip and knee joints. The risk of OA increases by 10% for each kilogram of body weight above ideal body weight.[6]

TABLE 55–1. Classification of Osteoarthritis

Primary Osteoarthritis
Localized (involving one or two sites)
Generalized (involving three or more sites)
Erosive
Secondary Osteoarthritis
Mechanical incongruity of joint
Congenital or developmental defect
Posttraumatic
Prior inflammatory disease (rheumatoid arthritis, chronic gouty arthritis, pseudogout, infectious arthritis)
Metabolic disorder (hemochromatosis, ochronosis, Wilson's disease, chondrocalcinosis, Paget's disease)
Endocrinopathies (diabetes mellitus, obesity, acromegaly, iatrogenic hyperadrenocorticism, sex hormone abnormalities)
Neuropathic disorders
Intraarticular corticosteroid overuse
Avascular necrosis
Bone dysplasia

CLINICAL PRESENTATION AND DIAGNOSIS



Presentation of Osteoarthritis

General

- Patients are generally over the age of 50.
- Presentations encompass a spectrum ranging from asymptomatic to severe joint pain and stiffness with functional limitations.
- Joint involvement has an asymmetric local distribution without systemic manifestations.
- In contrast with some other forms of arthritis (e.g., rheumatoid arthritis and gout), inflammation usually is absent and is mild and localized when present.

Symptoms

- ❷ *The cardinal symptoms are use-related joint pain, typically described as deep and aching in character, and stiffness. In advanced cases, pain also may be present during rest.*
- Weight-bearing joints may be hindered by instability.
- ❷ *Joint stiffness ("gelling") abates with motion and recurs with rest.*
- ❷ *The stiffness generally lasts less than 30 minutes, limits range of joint motion, impairs daily activities, and may be related to weather.*

Signs

- One or more joints may be involved, usually in an asymmetric pattern.
- The following sites are most often involved in primary OA:
  - Distal interphalangeal finger joints (Heberden's nodes)
  - Proximal interphalangeal finger joints (Bouchard's nodes)
  - First carpometacarpal joint
  - Knees, hips, and cervicolumbar spine
  - Metatarsophalangeal joint of the great toe
- The following sites are involved most often in secondary OA:
  - Metacarpophalangeal joints
  - Wrists
  - Elbows
  - Glenohumeral joints
  - Ankles
- Joint examination may reveal local tenderness, bony proliferation, soft tissue swelling, crepitus, muscle atrophy, limited motion with passive/active movement, and effusion.

Laboratory Tests

- No specific laboratory test or value is diagnostic for OA.
- The erythrocyte sedimentation rate (ESR) and hematologic and chemistry panels are usually unremarkable.
- Aspirated synovial fluid (if obtained) often displays leukocytosis (less than 2000 WBCs/mm^3) and high viscosity.

Other Diagnostic Tests

- Radiologic evidence may be misleading because structural evidence of OA correlates poorly with symptoms.
- Radiographic changes are often absent in early OA.
- As the disease progresses, joint-space narrowing, subchondral bone sclerosis, and osteophytes may be detected.
- In late OA, there is gross deformity and possibly effusions.



Patient Encounter, Part 1

A 62-year-old obese woman presents to your clinic complaining of deep, aching pain in her right knee. The pain is provoked by walking and subsides with rest. She also notes that her knee is difficult to bend for 10 minutes after rising in the morning. The symptoms have worsened over the last several years. Your interview also reveals that she injured her knee several years ago getting out of a car.

- What information is suggestive of OA?
- What risk factors for OA does this patient have?
- What other information will you need before formulating a treatment plan for this patient?

TREATMENT

Desired Outcomes

Treatment is individualized and should consider medical history, physical examination, radiographic findings, distribution and severity of joint involvement, and response to previous treatment. Comorbid disease states, concomitant medications, and allergies are integrated into a holistic treatment approach. ❸ *Goals of therapy include (1) educating the patient and caregivers, (2) relieving pain, (3) maintaining or restoring mobility, (4) minimizing functional impairment, (5) preserving joint integrity, and (6) improving quality of life.*

General Approach to Treatment

A comprehensive treatment algorithm for OA is given in Fig. 55–2. Nonpharmacologic treatment is integral to achieving optimal outcomes in patients with OA. Pharmacologic therapy is used as an adjunctive measure to relieve pain; most treatments do not modify the disease course. Surgical intervention generally is reserved for patients with advanced disease complicated by unremitting pain or severely compromised function.

Nonpharmacologic Therapy

Nondrug therapy consists of a three-pronged approach consisting of education, lifestyle modification, and physical therapy. ❹ *Educational programs include a set of systematic educational activities designed to improve health behaviors and health status, thereby slowing OA progression.* The goal is to increase patient knowledge and self-confidence in adjusting daily activities in the face of evolving symptoms. Effective programs produce positive behavioral changes, decreased pain and disability, and improved functioning. In addition to physical outcomes, psychological outcomes such as depression, self-efficacy, and life satisfaction are positively influenced. Patients can be referred to the Arthritis Foundation (www.arthritis.org or 1-800-568-4045) for educational materials and information on support groups.

❹ *Lifestyle modification should be employed in all patients at risk for OA and in those with established disease.* Aerobic exercise and strength-training programs improve functional capacity in older adults with OA. Stretching and strengthening exercises should target affected and vulnerable joints. For example, inadequate quadriceps strength increases susceptibility of the knee joint to OA; thus quadriceps strengthening can be targeted to strengthen the knee joint and minimize risk. Isometric exercises performed three to four times weekly improve physical functioning and decrease disability, pain, and analgesic use. A major barrier to the widespread acceptance of exercise therapy in OA is the misconception that increased activity will exacerbate joint symptoms. Controlled clinical trials have invalidated this belief.[7] The American Geriatrics Society issued guidelines on the implementation of exercise in OA patients.[8] In general, it is advisable to recommend low-impact exercise be performed routinely.

Obesity's association with both the onset and progression of OA make weight loss a pivotal treatment strategy in overweight and obese patients. Women who lose an average of 5 kg lower their risk of knee OA by more than 50%. Symptomatic relief from knee OA and improved health-related quality of life occur in people with established knee OA who reduce their body weight. Weight loss should be pursued through dietary modification and increased physical activity (see Chap. 99). It is important to consider the patient's physical capabilities when implementing an exercise program.

❹ *Application of heat or cold treatments to involved joints improves range of motion, reduces pain, and decreases muscle spasms. Practical applications of heat therapy include warm baths or warm water soaks.* Heating pads should be used with caution, especially in the elderly, and patients must be warned of the potential for burns if used inappropriately.

Referral to a physical or occupational therapist may be helpful, particularly in patients with functional disabilities. Physical therapy is tailored to the patient and may include assessment of muscle strength, joint stability, and mobility; use of heat (especially prior to episodes of increased physical activity); structured exercise regimens; and implementation of assistive devices, such as canes, crutches, and walkers. The occupational therapist ensures optimal joint protection and function, energy conservation, and use of splints and other assistive devices.

Pharmacologic Therapy

Simple analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line agents for treating OA (Table 55–2).

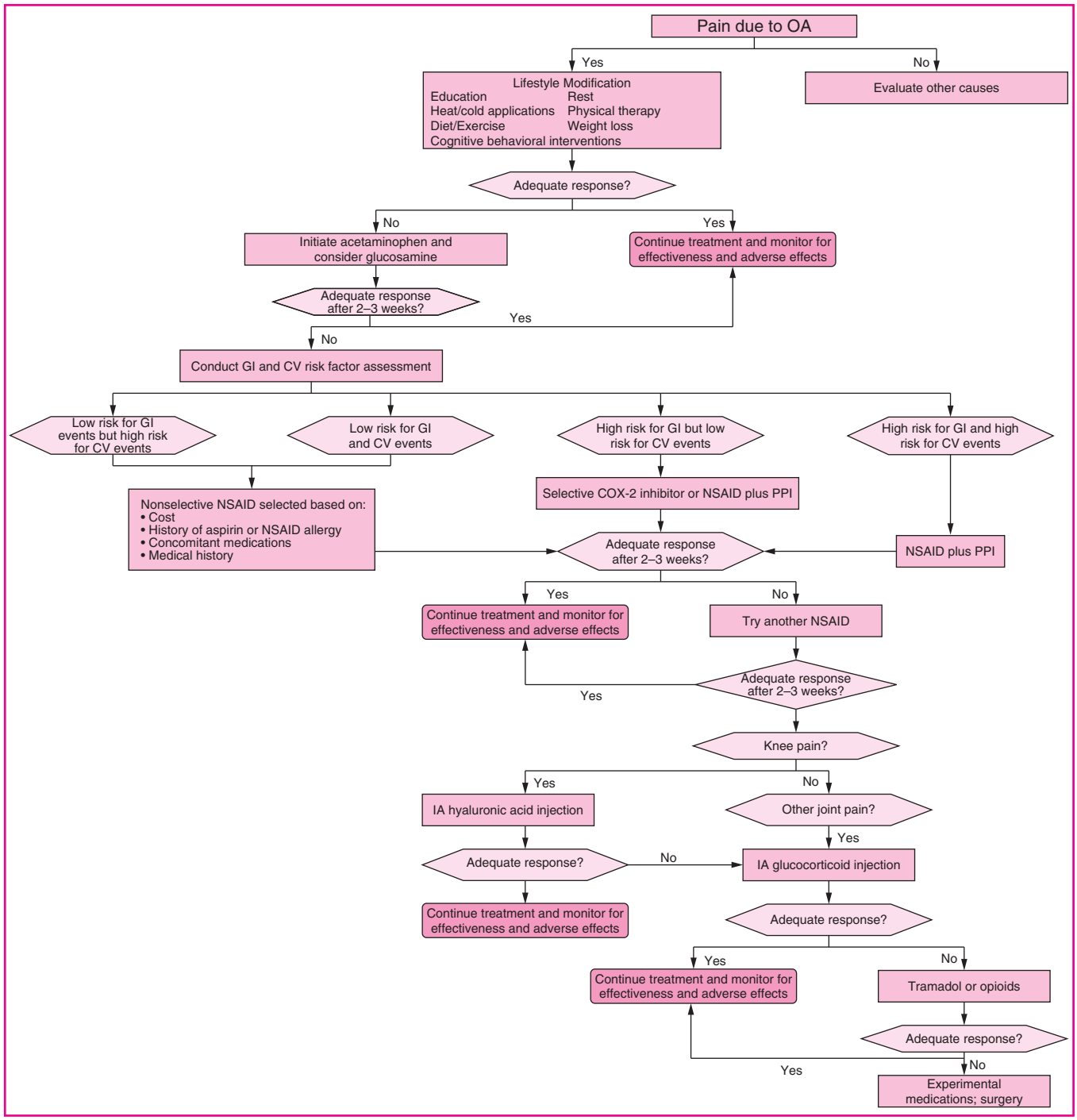


FIGURE 55–2. Treatment of osteoarthritis. OA, osteoarthritis; COX-2, cyclooxygenase-2; CV, cardiovascular; GI, gastrointestinal, IA, intraarticular; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

Acetaminophen

Acetaminophen is a centrally acting analgesic that produces analgesia by inhibiting prostaglandin production in the brain and spinal cord. ❺ *It is an effective and inexpensive analgesic with a favorable risk-benefit profile.*[9] It should be tried initially at an adequate dose and duration before considering an NSAID.[10] The American College of Rheumatology (ACR) and American Pain Society (APS) concur that acetaminophen is a first-line pharmacologic agent for treating mild pain that is unresponsive to nonpharmacologic measures.[11,12]

Acetaminophen should be administered in a scheduled manner (rather than on an as-needed basis) in doses up to

TABLE 55–2. Dosing Parameters of Agents Commonly Used to Treat OA

Medication	Dosage and Frequency	Maximum Dosage (mg/day)
Oral Analgesics		
Acetaminophen	325 mg every 4–6 hours or 1 g every 6–8 hours	4000
Tramadol	50–100 mg every 4–6 hours CrCl less than 30 mL/minute: 50–100 mg every 12 hours	400 (300 in elderly) 200
Nonselective NSAIDs by Chemical Class		
Carboxylic acid (salicylates)		
Aspirin	325–650 mg every 4–6 hours	3600[a]
Salsalate	500–1000 mg 2–3 times daily	3000[a]
Acetic acid		
Etodolac	300–600 mg twice daily 400–1000 mg once daily (extended-release)	1200
Diclofenac	50 mg 2–3 times daily 75 mg twice daily (delayed-release) 100 mg once daily (extended-release)	150
Indomethacin	25 mg 2–3 times daily 75 mg 1–2 times daily (sustained-release)	200
Nabumetone	500–1000 mg 1–2 times daily	2000
Propionic acid		
Ibuprofen	400–800 mg 3–4 times daily	3200
Naproxen	250–500 mg 2 times daily 750–1000 mg once daily (controlled-release) 275–550 mg 2 times daily (naproxen sodium)	1500 1650
COX-2-Selective Agents		
Meloxicam[b]	7.5–15 mg once daily	15
Celecoxib	100 mg twice daily or 200 mg once daily	200
Topical Analgesics		
Capsaicin		
Cream 0.025% or 0.075%	Apply to affected joint every 6–8 hours	
Nutritional Supplements		
Glucosamine sulfate	500 mg 3 times daily or 1500 mg once daily	
Chondroitin	400–800 mg 3 times daily with glucosamine	

[a]Serum salicylate levels should be monitored for doses greater than 3 g/day.
[b]Meloxicam is not considered to be a true COX-2-selective agent (see text).
CrCl, creatinine clearance; mL/minute, milliliters per minute.

4 g daily. This recommendation is based on its efficacy in placebo- and NSAID-controlled studies. Acetaminophen is as effective as NSAIDs for mild to moderate joint pain.[13] These data and a strong safety profile provide the rationale for using acetaminophen as first-line therapy in patients with OA.

A common reason for an inadequate response to acetaminophen is failure to use a sufficient dose for an adequate duration. A sufficient trial is defined as at least 2 to 3 g daily in divided doses for several weeks.

Despite being one of the safest analgesics, important adverse effects attributable to acetaminophen can occur, including hepatic and renal toxicity.[14] Total daily doses greater than 4 g are associated with an increased risk of hepatotoxicity. Concomitant use of alcohol may increase this risk; a maximum acetaminophen dose of 2.5 g daily is recommended in patients who consume more than two to three alcoholic beverages per day. Acetaminophen does not appear to exacerbate stable, chronic liver disease; it can be used with caution and vigilant monitoring of liver function in this population.[14]

Acetaminophen may worsen kidney function and increase blood pressure.[15-16] Nevertheless, acetaminophen remains the preferred analgesic for mild to moderate pain in patients with hypertension or kidney disease owing to the greater risks associated with NSAID use.[17] Monitoring specifically for these toxicities generally is unnecessary.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Prostaglandins play an important role in the function of several organ systems. These compounds are synthesized via the interaction of two isoforms of the **cyclooxygenase** enzyme (COX-1 and COX-2) with their substrate, arachidonic acid (Fig. 55–3).

The COX-1 enzyme is produced normally in various body tissues (e.g., gastric mucosa, kidney, and platelets). Prostaglandins produced by the actions of the COX-1 enzyme in the gastrointestinal tract preserve the integrity of the gastrointestinal mucosa by increasing mucus and bicarbonate secretion, maintaining mucosal blood flow, and decreasing gastric acid secretion. COX-1-associated prostaglandins also promote normal platelet activity and function. In the kidney, COX-1-mediated prostaglandins dilate the afferent arteriole, thereby maintaining intraglomerular pressure and glomerular filtration rate when renal blood flow is reduced.

In contrast, the COX-2 enzyme is not produced normally in most tissues, but its production is increased rapidly in the presence of inflammation and local tissue injury. This leads to the synthesis of prostaglandins involved in pain and inflammation. Consequently, blocking the COX-2 enzyme results in analgesic and anti-inflammatory effects. The beneficial effects of NSAIDs in reducing pain, decreasing joint stiffness, and improving function in patients with OA are thought to be due to inhibition of the COX-2 isoenzyme.

Most NSAIDs (e.g., ibuprofen, naproxen, and others) inhibit both COX-1 and COX-2 isoforms. That is, they are nonselective inhibitors of the COX enzyme system. Whereas inhibition of COX-2 is responsible for beneficial effects, inhibition of COX-1 is responsible for the most common and important adverse effects of NSAIDs. COX-2-selective inhibitors have been produced and marketed in attempts to preserve the beneficial effects of COX-2 inhibition while avoiding the deleterious effects associated with inhibition of the COX-1 enzyme. This approach has not been entirely successful, as discussed below.

❻ *NSAIDs are a reasonable alternative when acetaminophen fails to provide an acceptable analgesic response.* Some authorities recommend NSAIDs over acetaminophen for patients presenting with severe pain or signs and symptoms of inflammation, but this is a matter of much contention. The rationale for this recommendation is that acetaminophen's central mechanism of action renders it ineffective against peripheral joint inflammation, and therefore, less effective.[18] Consensus guidelines support the use of NSAIDs as an alternative to acetaminophen if clinical features of peripheral inflammation or severe pain are detected.[11,12] Unfortunately, there is no validated mechanism to identify patients who are more likely to respond to NSAIDs than acetaminophen.

❻ *At equipotent doses, the analgesic and anti-inflammatory activity of all NSAIDs and aspirin are similar. The selection of a specific NSAID should be based on tolerability, previous response, and cost.* ❼ *Some patients respond to one NSAID better than to another. If an insufficient response is achieved with one NSAID, another agent from the same or a different chemical class should be tried.* Pain relief occurs rapidly (within hours), but anti-inflammatory benefits are not realized until after 2 to 3 weeks of continuous therapy. This period is the minimal duration that should be considered an adequate NSAID trial.

Inhibition of the COX-1 isoenzyme is thought to be responsible primarily for the adverse effects of NSAIDs on the gastric mucosa, kidney, and platelets. Direct irritant effects also may contribute to adverse gastrointestinal events. ❽ *Minor gastrointestinal complaints, including nausea, dyspepsia, anorexia, abdominal pain, flatulence, and diarrhea, are reported by 10% to 60% of patients treated with NSAIDs. Gastric and duodenal mucosal ulceration can be detected in 7% to 13% of patients. Perforation, gastric outlet obstruction, and gastrointestinal bleeding are the most severe complications and occur in 1.5% to 4% of patients annually.*

Several risk factors predict a greater likelihood of gastrointestinal complications in NSAID-treated patients (see Chap. 15).

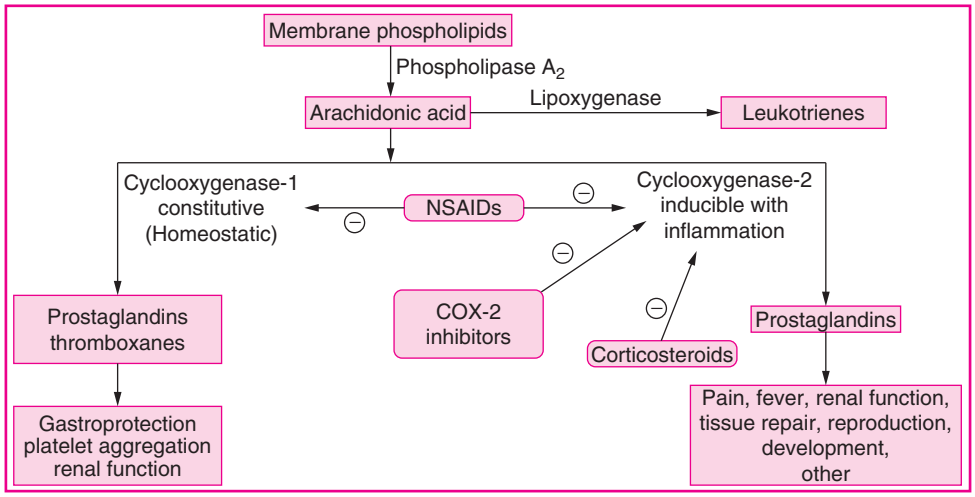


FIGURE 55–3. Synthesis pathway for prostaglandins and leukotrienes. COX-2, cyclooxygenase enzyme 2; NSAIDs, nonsteroidal anti-inflammatory drugs. (From DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005, Figure 90-3, p. 1694, with permission.)

It is not possible to detect high-risk patients based on symptoms alone because there is poor correlation between the presence of symptoms and actual gastroduodenal damage. Patients at high risk for gastrointestinal complications should be evaluated for the use of a COX-2-selective NSAID or concomitant treatment with a prophylactic gastroprotective agent such as a proton pump inhibitor or misoprostol. However, these strategies do not completely mitigate the risk of gastrointestinal complications.

❽ *NSAIDs can cause renal insufficiency when administered to patients whose renal function depends on prostaglandins. Patients with chronic renal insufficiency or left ventricular dysfunction, the elderly, and those receiving diuretics or drugs that interfere with the renin-angiotensin system are particularly susceptible.* Decreased glomerular filtration also may cause hyperkalemia. NSAIDs rarely cause **tubulointerstitial** nephropathy and renal papillary necrosis.

Caution is warranted in pregnant women and women of childbearing age because the risk of bleeding may be increased if the fetus is subjected to the antiplatelet activity of NSAIDs. Ibuprofen and naproxen are rated Food and Drug Administration (FDA) pregnancy category B in the first and second trimesters. Indomethacin and sulindac have not been rated, whereas celecoxib and etodolac are category C. NSAIDs are contraindicated during the third trimester because they may promote premature closure of the ductus arteriosus in the fetus.

NSAIDs are prone to drug interactions due to high protein binding, detrimental renal effects, and antiplatelet activity. Interactions are encountered frequently with aspirin, warfarin, oral hypoglycemics, antihypertensives, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), β-blockers, diuretics, and lithium. When an interaction with an NSAID is present, vigilant monitoring is warranted for therapeutic efficacy (e.g., NSAIDs blunt the antihypertensive efficacy of diuretics) and adverse effects (e.g., NSAIDs increase the risk of bleeding in anticoagulated patients).

Selective COX-2 Inhibitors

Elucidation of the activities of individual COX isoforms led to the development of drugs that selectively inhibit the inducible form of the enzyme, COX-2. Thus COX-2 inhibitors were expected to minimize NSAID gastrointestinal toxicity and antiplatelet effects (see Fig. 55–3).[19] ❾ *A common misconception is that COX-2 inhibitors are more effective than nonselective NSAIDs in relieving pain and inflammation. In clinical trials, patients experienced similar levels of pain relief with COX-2 inhibitors and nonselective NSAIDs.*

Celecoxib is the only agent currently on the market that is a true COX-2-selective inhibitor. However, meloxicam, sulindac, and diclofenac also display preferential affinity for the COX-2 isozyme. Celecoxib reduces endoscopically detected gastrointestinal lesions; however, the clinical importance of this observation has been challenged because many of these lesions are clinically silent and resolve spontaneously. Celecoxib did not reduce the incidence of significant upper gastrointestinal toxicity compared with NSAIDs in a large clinical trial.[20] The selective agents rofecoxib (removed from the United States market in 2004) and lumiracoxib (in Phase III clinical trials at the time of this writing) decrease clinically important events such as perforations, ulcers, and bleeding.[21,22]

The advent of COX-2-selective inhibitors has led to unexpected results. ❾ *By selectively inhibiting the COX-2 isoform, COX-2-selective NSAIDs increase the risk of cardiovascular events in certain patients.*[23] COX-2 is responsible for the production of prostacyclin, a vasodilatory and antiplatelet substance. On the other hand, COX-1 controls the production of thromboxane A_2, a vasoconstrictor and platelet aggregator. Selective inhibition of COX-2 results in decreased prostacyclin levels in the face of stable thromboxane A_2 levels. An imbalance in the thromboxane A_2:prostacyclin ratio ensues, which creates an environment that favors thrombosis.

As a consequence, more selective inhibitors of the COX-2 enzyme may offer enhanced gastrointestinal safety but compromised cardiovascular safety. As shown in Fig. 55–4, when the

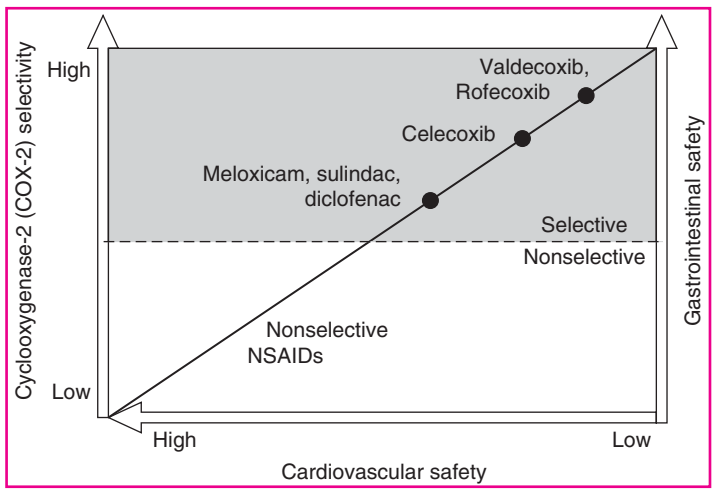


FIGURE 55–4. Relationship between COX-2 selectivity and cardiovascular and gastrointestinal safety. As NSAID selectivity for the COX-2 enzyme increases, cardiovascular safety decreases and gastrointestinal safety increases. Rofecoxib and valdecoxib are no longer available in the United States. Selectivities are approximations.

selectivity of NSAIDs increases, the risk of cardiovascular events appears to increase, whereas the risk of gastrointestinal toxicity declines. This relationship can be explained by the mechanism of theses drugs—greater selectivity results in a larger decrease in prostacyclin relative to thromboxane A_2 (favoring thrombosis) but also less gastrointestinal ulceration because of the greater preservation of mucosal protective factors.

Concomitant use of low-dose aspirin mitigates some of the increased cardiovascular risk but also obliterates the gastrointestinal safety of COX-2 selectivity.[21–23] Patients treated with a COX-2-selective agent plus aspirin experience gastrointestinal complications at a rate commensurate with that of patients given traditional nonselective agents. Use of less selective agents, such as meloxicam, to avoid cardiovascular concerns with COX-2 inhibitors may not be justified because neither gastrointestinal nor cardiovascular safety is optimized. In patients at risk for cardiovascular disease, a nonselective NSAID plus a proton pump inhibitor is a reasonable option.

The COX-2 enzyme is also produced normally in the kidney; thus COX-2 inhibitors exert renal effects similar to those of conventional NSAIDs. Both drug classes may increase sodium reabsorption and fluid retention and can provoke renal insufficiency and hyperkalemia. COX-2 inhibitors should be used with caution in patients with heart failure or hypertension.

COX-2 inhibitors are susceptible to the same drug interactions as nonselective agents. However, the interaction with warfarin is less pronounced because platelet function is affected to a lesser degree.

Glucosamine and Chondroitin

Glucosamine is believed to function as a "chondroprotective" agent, stimulating the cartilage matrix and protecting against oxidative chemical damage. Chondroitin is administered often in conjunction with glucosamine; it is thought to inhibit degradative enzymes and serve as a substrate for the production of proteoglycans. Numerous clinical trials have evaluated the efficacy of these substances for the treatment of OA; however, the quality of several of these studies has been questioned. ⓾ *In the context of such limitations, glucosamine and chondroitin reduce pain and improve mobility by 20% to 25%.*[24] *They also may slow disease progression by decreasing the rate of cartilage destruction, although the clinical impact of this effect is not clear.*[25] Glucosamine is not effective for treating acute pain; beneficial effects often mature over a period of weeks. Because these agents are loosely regulated in the United States as dietary supplements, product standards are inconsistent, and the constituents are not validated by any regulatory agency.

The landmark National Institutes of Health (NIH) study comparing glucosamine, chondroitin, glucosamine plus chondroitin, celecoxib, and placebo for OA was published recently.[26] Glucosamine, chondroitin, and their combination were no more effective than placebo in decreasing pain symptoms in 1583 patients with knee OA after 24 weeks. Celecoxib, however, was effective. In the subgroup of patients with moderate to severe OA pain, the combination of glucosamine and chondroitin appeared to have a moderate effect, although this subgroup analysis must be interpreted with caution. On the other hand, a European study (the GUIDE trial) that compared a prescription glucosamine product with acetaminophen and placebo in patients with knee OA reported that glucosamine performed better versus placebo than did acetaminophen.[27]

Interpretation of these results is challenging given the inconsistencies in study quality, differences in end points applied, preparations of glucosamine tested (glucosamine hydrochloride versus sulfate), and the comparator agents (celecoxib versus acetaminophen). Based on the available data, it appears that glucosamine and chondroitin may be effective for some patients with OA of the knee. Given the favorable safety profile of glucosamine and chondroitin, it is reasonable to present these agents as a treatment option to patients with symptomatic knee OA.

Intraarticular Therapy

⓾ *Intraarticular injection of corticosteroids or hyaluronan represents an alternative to oral agents for the treatment of joint pain.*[28] These modalities usually are reserved for patients unresponsive to other treatments because of the relative invasiveness of intraarticular injections compared with oral drugs, the small risk of infection, and the cost of the procedure.

Hyaluronan (or Hyaluronic Acid)

The mechanism of action of hyaluronan is not fully understood. Healthy cartilage is replete with hyaluronic acid, a viscous substance believed to facilitate lubrication and shock absorbency under varying conditions of load bearing. Patients with OA demonstrate an absolute and functional decline in hyaluronic acid; thus exogenous administration is referred to as *viscosupplementation.* In responders, the benefit of hyaluronan administration persists for periods that exceed its residence time in the synovium, suggesting that benefits beyond viscoelasticity are involved. Inhibition of inflammatory mediators and cartilage degradation, stimulation of the cartilage matrix, neuroprotective actions, and the ability of hyaluronan to induce its own synthesis may account in part for the benefit.

Pain and joint function have been evaluated frequently in clinical trials administering hyaluronan to patients with OA. Results are conflicting, with some suggesting dramatic improvements and others indicating no effect. In one controlled trial, hyaluronan injections relieved pain to a similar extent as oral NSAIDs.[29] Hyaluronan provides greater pain relief for a longer time than intraarticular corticosteroids, but corticosteroids work more rapidly.[29]

Several formulations of hyaluronan are available for the treatment of knee pain in patients with OA who are unresponsive to other measures. Administration typically consists of

weekly injections for 3 or 4 weeks and is well tolerated, although some patients may report local reactions. Rarely, postinjection flares and anaphylaxis have been reported. Intraarticular injection is associated with a low risk of infection (approximately 1 joint in 50,000 injections). Patients should be counseled to minimize activity and stress on the joint for several days after each injection.

Corticosteroids

Use of systemic corticosteroids is discouraged in patients with OA. 10 *However, in a subset of patients with an inflammatory component or knee effusion involving one or two joints, intraarticular corticosteroids can be useful as monotherapy or as an adjunct to analgesics.* The affected joint can be aspirated and subsequently injected with a corticosteroid. The aspirate should be examined for the presence of crystalline formation and infection. A single joint should not be injected more than three to five times per year.

The crystalline nature of corticosteroid suspensions can provoke a postinjection flare in some patients. The ensuing flare mimics the flare of arthritis and inflammation that accompanies infection; cold compresses and analgesics are recommended to treat symptoms in affected patients.

Tramadol

Use of opioid analgesics may be warranted when pain is unresponsive to other pharmacologic agents or when such agents are contraindicated. Tramadol is a centrally acting synthetic opioid oral analgesic that also weakly inhibits the reuptake of serotonin and norepinephrine. It is effective for the treatment of moderate pain but is devoid of anti-inflammatory activity. There is a low potential for abuse compared with conventional opioid analgesics. Surveillance of its abuse potential has failed to demonstrate a significant risk; therefore, tramadol is not scheduled as a controlled substance.

Tramadol is a reasonable option for patients with contraindications to NSAIDs or failure to respond to other oral therapies. 10 *For the treatment of hip or knee OA, tramadol is as effective as NSAIDs. The addition of tramadol to NSAIDs or acetaminophen may augment the analgesic effects of a failing regimen, thereby securing sufficient pain relief in some patients.* Moreover, concomitant tramadol may permit the use of lower NSAID doses.

Dizziness, vertigo, nausea, vomiting, constipation, and lethargy are all relatively common adverse events. These effects are more pronounced for several days after initiation and following upward dose titration. Seizures have been reported rarely; the risk is dose-related and appears to increase with concomitant use of antidepressants, such as tricyclic antidepressants or selective serotonin reuptake inhibitors. Tramadol should be avoided in patients receiving monoamine oxidase (MAO) inhibitors because tramadol inhibits the uptake of norepinephrine and serotonin.

Other Opioid Analgesics

Use of traditional opioid analgesics for nonmalignant pain is becoming more acceptable. Emerging evidence suggests that patients can achieve satisfactory analgesia by using nonescalating doses of opioids with a minimal risk of addiction.[30] Opioid analgesics should be reserved for patients who experience moderate to severe pain and do not respond to or are not candidates for other pharmacologic and nonpharmacologic strategies. These agents also may be useful in patients with conditions that preclude the use of NSAIDs, such as renal failure, heart failure, or anticoagulation. The APS and the American Academy of Pain Medicine (AAPM) support the use of opioids in the management of chronic nonmalignant pain when other management strategies fail.[31] Opioid analgesics should be initiated at low doses in combination with acetaminophen or an NSAID when possible. Combining opioids with other analgesics reduces the opioid requirement, thereby minimizing adverse events.

Few studies have explored the efficacy of opioids specifically for OA. The APS recommends against the use of codeine and propoxyphene for OA because of the high incidence of adverse effects and limited analgesic effectiveness. Oxycodone is the most extensively studied of the agents recommended for OA. However, other narcotic analgesics such as morphine, hydromorphone, methadone, and transdermal fentanyl are also effective.

Narcotic analgesics decrease pain, improve sleep patterns, and increase functioning in patients with OA who are unresponsive to nonpharmacologic therapy and nonnarcotic analgesics. Conservative initial doses are warranted, with the dose titrated to adequate response.

Such an approach should include an initial comprehensive medical history and physical examination, firm documentation that nonopioid therapy has failed, clearly defined treatment goals, an understanding between the provider and the patient of the true benefits and pitfalls of long-term opioids, use of a single provider and pharmacy whenever possible, and comprehensive follow-up.

Topical Analgesics

Topical analgesics sometimes are used for mild pain or as an adjunct to systemic therapy. There are limited data to support the use of salicylate-containing **rubefacients** (e.g., methyl salicylate and trolamine salicylate) or other **counterirritants** (e.g., menthol, camphor, and methyl nicotinate) in OA.[32] See Chap. 57 for more information on these products when used for musculoskeletal disorders.

Capsaicin achieves pain relief by depleting substance P from sensory neurons in the spine, thereby decreasing pain transmission. Capsaicin is not effective for acute pain; up to 2 weeks may be necessary before pain relief is appreciated. Most patients experience a local burning sensation at the site of application. The discomfort usually does not result in



Patient Encounter, Part 2: The Medical History, Physical Examination, and Diagnostic Tests

PMH
- Obesity (BMI = 34 kg/m^2)
- Hypertension for 7 years
- Type 2 diabetes mellitus
- Hyperlipidemia, currently at goal
- Gastroesophageal reflux disease (GERD)

FH
Father died of stroke at age 72; mother had OA of the hands.

SH
Works as a secretary. Denies alcohol, tobacco, and illicit drug use.

Meds
- Hydrochlorothiazide 12.5 mg once daily
- Enalapril 10 mg twice daily
- Metformin 1000 mg twice daily
- Atorvastatin 10 mg once daily
- Pantoprazole 40 mg every morning
- Enteric-coated aspirin 81 mg once daily
- Ibuprofen 200 mg prn for pain

Labs
Within normal limits.

Radiology: Radiography of the affected knee shows joint-space narrowing and subchondral bone sclerosis.

- Which parameters are consistent with a diagnosis of OA?
- What are the treatment goals for this patient?
- What pharmacologic and nonpharmacologic options are available to treat this patient?
- What factors are important to consider when selecting medications for this patient?

discontinuation and often abates within the first week. Patients should be cautioned not to allow capsaicin to come into contact with eyes or mucous membranes and to wash their hands after each application.

Topical NSAID preparations are used infrequently in North America. Theoretically, administration via a topical vehicle targets the joints involved and decreases systemic exposure. Randomized, controlled trials, typically of less than 4 weeks' duration, have suggested that topical NSAIDs are superior to placebo in relieving OA pain in the first 2 weeks of treatment, but the effect may decline over time.[33] Moreover, data are lacking to quantify the theoretical safety advantage of administering NSAIDs topically.

Surgery

⓾ *Surgery generally is reserved for patients who fail to respond to medical therapy and have progressive limitations in activities of daily living (ADL).* These patients should be referred to an orthopedic surgeon for evaluation. Most patients achieve substantial pain relief and functional restoration following total-joint arthroplasty.[34]



Patient Encounter, Part 3: Creating a Care Plan

Based on the information available, create a care plan for this patient's OA. The plan should include (1) the goals of therapy, (2) an individualized, detailed therapeutic plan, and (3) a plan for follow-up monitoring to document the patient's response and identify adverse reactions.

OUTCOME EVALUATION

- At baseline, quantify the patient's pain using a visual analogue scale, assess range of motion of affected joints, and identify activities of daily living that are impaired.
- In patients treated with acetaminophen or NSAIDs, assess pain control after 2 to 3 weeks. It may take longer for the full anti-inflammatory effect of NSAIDs to occur.
- Incorporate other measures to track disease progress. Use radiography to assess severity of joint destruction, determine 50-ft walking time and grip strength, and administer the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) and the Stanford Health Assessment Questionnaire, where appropriate, to assess activities of daily living.
- Ask patients if they are experiencing side effects or other problems with their medications and follow up with more specific questions.
- In patients taking NSAIDs, monitor for increases in blood pressure, weight gain, edema, skin rash, and central nervous system adverse effects such as headaches and drowsiness.
- Evaluate serum creatinine, complete blood count, and serum tranasaminases at baseline and every 6 to 12 months in patients treated with NSAIDs or acetaminophen.
- Perform stool guaiac in patients taking NSAIDs when clinically indicated.
- Monitor for drug interactions, including alcohol, at every visit.



Patient Care and Monitoring

1. Determine whether the patient's symptoms are consistent with OA. Review the patient's medical history to determine whether other rheumatologic diseases may be involved.
2. Assess symptoms to determine if pain warrants additional attention. Does the pain affect quality of life or interfere with activities of daily living?
3. Evaluate symptoms to determine what nonpharmacologic interventions can be recommended and whether pharmacologic treatment is warranted.
4. Obtain a thorough history of previous drug use, including prescription drugs, over-the-counter drugs, and dietary supplement products. Determine whether any of these treatments have been effective. Ask the patient about the dose and frequency of previous pharmacologic agents to determine if an adequate trial was given.
5. Educate the patient about appropriate use of nonpharmacologic treatments for OA.
6. Formulate a drug therapy plan, taking into consideration the patient's medical history, concomitant medications, and previous use of medications.
7. Develop a plan to monitor the patient's response to therapy.
8. Evaluate for the presence of adverse drug reactions, drug hypersensitivity, and drug interactions.
9. Document whether the patient has had improvements in quality-of-life measures, such as improved functioning, increased ability to perform activities of daily living, and improved well-being.
10. Emphasize the value of adherence to medication regimens and lifestyle modifications. Facilitate adherence by implementing medication regimens and lifestyle plans that are simple and consistent with the patient's lifestyle.
11. Educate the patient about OA, lifestyle modifications, and medications:
    - What causes OA?
    - How will lifestyle modifications affect the disease?
    - What are the expectations of treatment?
    - When and how should medications be taken?
    - What adverse effects are most common, do they decrease during therapy, and what are the warning signs of more severe complications?
    - What prescription and over-the-counter medications should be avoided to prevent drug-drug, drug-food, or drug-disease interactions?
    - What options are available if the current regimen fails?

ABBREVIATIONS

ACR:	American College of Rheumatology
APS:	American Pain Society
COX:	cyclooxygenase
DJD:	degenerative joint disease
MMP:	matrix metalloproteinases
NSAID:	nonsteroidal anti-inflammatory drugs
OA:	osteoarthritis
WOMAC:	Western Ontario and McMaster University Osteoarthritis Index

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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56 Gout and Hyperuricemia

Geoffrey C. Wall



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Recognize major risk factors for developing gout in a given person.
2. Develop a pharmacotherapeutic plan for a patient with acute gouty arthritis or uric acid nephropathy that includes individualized drug selection and monitoring for efficacy and safety.
3. Identify patients in whom maintenance therapy for gout and hyperuricemia is warranted.
4. Select an appropriate drug to reduce serum uric acid levels in patients with gout, and outline a plan for monitoring efficacy and toxicity.
5. Educate patients on appropriate lifestyle modifications to help prevent gouty arthritis attacks.

Key Concepts

❶ Gout results from deposition of uric acid crystals in joint spaces, leading to an inflammatory reaction that causes intense pain, erythema, and joint swelling.

❷ Some drugs can cause hyperuricemia and gout, such as thiazide diuretics, niacin, pyrazinamide, cyclosporine, and occasionally, low-dose aspirin.

❸ Long-term consequences of gout and hyperuricemia include joint destruction, tophi, and nephrolithiasis.

❹ Treatment of gout involves (1) acute relief of a gouty arthritis attack and (2) in some patients long-term maintenance treatment to prevent future attacks.

❺ Nonsteroidal anti-inflammatory drugs, colchicine, or corticosteroids are used for acute attacks. Selection depends on several patient factors, especially renal function.

❻ Asymptomatic hyperuricemia usually does not require treatment.

❼ Patients with recurrent attacks, evidence of tophi or joint destruction, or uric acid nephrolithiasis are candidates for maintenance therapy with allopurinol or probenecid to lower serum uric acid levels.

EPIDEMIOLOGY AND ETIOLOGY

Gout is the most common inflammatory arthritis in the United States and western Europe. The annual incidence is approximately 62 cases per 100,000 persons in the United States. The incidence increases with age and appears to be rising probably because of a larger number of patients with risk factors for gout.

PATHOPHYSIOLOGY

Gout is caused by an abnormality in uric acid metabolism. Uric acid is a waste product of the breakdown of purines contained in the DNA of degraded body cells and dietary protein. Uric acid is water soluble and excreted primarily by the kidneys, although some is broken down by colonic bacteria and excreted via the gastrointestinal tract.

The solubility of uric acid depends on concentration and temperature. At high serum concentrations, lower body temperature causes the precipitation of **monosodium urate** crystals. Collections of these crystals (called **microtophi**) can form in joint spaces in the distal extremities.

❶ *Gout results from deposition of uric acid crystals in joint spaces, leading to an inflammatory reaction that causes intense pain, erythema, and joint swelling.* Free urate crystals can activate several proinflammatory mediators, including tumor necrosis factor α (TNF-α), interleukin 1 (IL-1), and IL-8. Activation of these mediators signals chemotactic movement of neutrophils into the joint space that "ingest" monosodium urate crystals via phagocytosis. These neutrophils then are lysed and release proteolytic enzymes that trigger the clinical manifestations of an acute gout attack such as pain and swelling. These inflammatory mechanisms in gout, especially in untreated disease, can lead to cartilage and joint destruction (Fig. 56–1).

The increased serum uric acid involves either the underexcretion of uric acid (80% of patients) or its overproduction. The cause of overproduction or underexcretion of uric acid in

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FIGURE 56–1. Synovial fluid containing extracellular and intracellular monosodium urate crystals. (From Reginato AJ. Gout and other crystal arthropathies. In: Braunwald E, Fauci AS, Kasper DI, et al, (eds.) Harrison's Principles of Internal Medicine. 15th ed. New York: McGraw-Hill; 2001, Figure 322–1.)

most gout patients is unknown; this is referred to as *primary gout.*

The risk of gout increases as the serum uric acid concentration increases, and approximately 30% of patients with levels greater than 10 mg/dL (greater than 595 μmol/L) develop symptoms of gout within 5 years. However, most patients with hyperuricemia are asymptomatic. Other risk factors for gout include obesity, ethanol use, and dyslipidemia. Gout is seen frequently in patients with type 2 diabetes mellitus and coronary artery disease, but a causal relationship has not been established.

Uric acid excretion is reduced in patients with chronic kidney disease, putting them at risk for hyperuricemia. In patients with persistently acidic urine and hyperuricemia, uric acid **nephrolithiasis** can occur in up to 25% of patients; in severe cases, uric acid stones can cause nephropathy and renal failure. Extreme hyperuricemia can occur because of rapid tumor cell destruction in patients undergoing chemotherapy for certain types of cancer (see Chap. 85).

❷ *Some drugs can cause hyperuricemia and gout, such as thiazide diuretics, niacin, pyrazinamide, cyclosporine, and occasionally, low-dose aspirin.* In most cases, these drugs block uric acid secretion in the kidney. ❸ *Long-term consequences of gout and hyperuricemia include joint destruction, tophi, and nephrolithiasis.*

CLINICAL PRESENTATION AND DIAGNOSIS

Presentation of Acute Gouty Arthritis

General

Patients are usually in acute distress.

Symptoms

- Severe pain, swelling, and warmth in the affected joint(s)
- The attack is usually monarticular, and the most common sites are the metatarsophalangeal and knee joints.
- In elderly patients, gouty attacks may be atypical with insidious onset and polyarticular, often involving hand or wrist joints.

Signs

- Affected joint(s) are warm, erythematous, and swollen.
- Mild fever may be present.
- Tophi (usually on hands, wrists, elbows, or knees) may be present in chronic, severe disease.

Laboratory Tests

- The white blood cell (WBC) count in peripheral blood may be only mildly elevated.
- The serum uric acid level often is elevated but may be normal during an acute attack.
- Other laboratory markers of inflammation [e.g., increased erythrocyte sedimentation rate (ESR)] are often present.

Diagnosis

Aspiration of affected joint fluid is essential for a definitive diagnosis. Joint fluid containing negatively birefringent monosodium urate crystals confirms the diagnosis. Joint fluid has an elevated WBC count with neutrophils predominating.

Although rarely performed, a 24-hour urine collection can be obtained to determine if the patient is an overproducer or an underexcretor of uric acid. Individuals who excrete more than 800 mg of uric acid in this collection are considered overproducers. Patients with hyperuricemia who excrete less than 600 mg/day are classified as underexcretors of uric acid.

Radiographs of affected joints may have characteristic appearances of gout, including cystic changes, punched-out lytic lesions with overhanging bony edges, and soft-tissue calcified masses. These signs may appear in other arthropathies as well.

TREATMENT

❹ *Treatment of gout involves (1) acute relief of a gouty arthritis attack and (2) in some patients long-term maintenance treatment to prevent future attacks.*

Desired Outcomes

The goals of therapy of an acute attack are (1) achieving rapid and effective pain relief, (2) maintaining joint function, (3) preventing disease complications, (4) avoiding treatment-related adverse effects, (5) providing cost-effective therapy, and (6) improving quality of life. Infrequent gouty arthritis is a self-limited disease, and treatment usually focuses on symptom relief.

Nonpharmacologic Therapy

Nondrug modalities play an adjunctive role and usually are not effective when used alone. Immobilization of the affected extremity speeds resolution of the attack. Applying ice packs to the joint also decreases pain and swelling, but heat application may be detrimental.

Pharmacologic Therapy

❺ *Nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids are used for acute attacks. Selection depends on several patient factors, especially renal function* (Fig. 56–2). Each drug class has a unique safety and efficacy profile in gout that should be considered carefully before choosing a specific agent (Table 56–1). Generally, the earlier in the course of the arthritic attack these agents are employed, the better the outcome.

Nonsteroidal Anti-Inflammatory Drugs

The NSAIDs largely have supplanted colchicine as the treatment of choice, and many NSAIDs have been used successfully. These agents are most effective when given within the first 24 hours of the onset of pain. Most studies have shown similar results among agents, and all NSAIDs are considered to be effective. Doses at the higher end of the therapeutic range are often needed.

Indomethacin was used traditionally, but its relative cyclooxygenase-1 (COX-1) selectivity theoretically increases its gastropathy risk. Thus other generic NSAIDs may be preferred. Adverse effects of NSAIDs include gastropathy (primarily peptic ulcers), renal dysfunction, and fluid retention. NSAIDs generally should be avoided in patients at risk for peptic ulcers, those taking warfarin, and those with renal insufficiency or uncontrolled hypertension or heart failure.

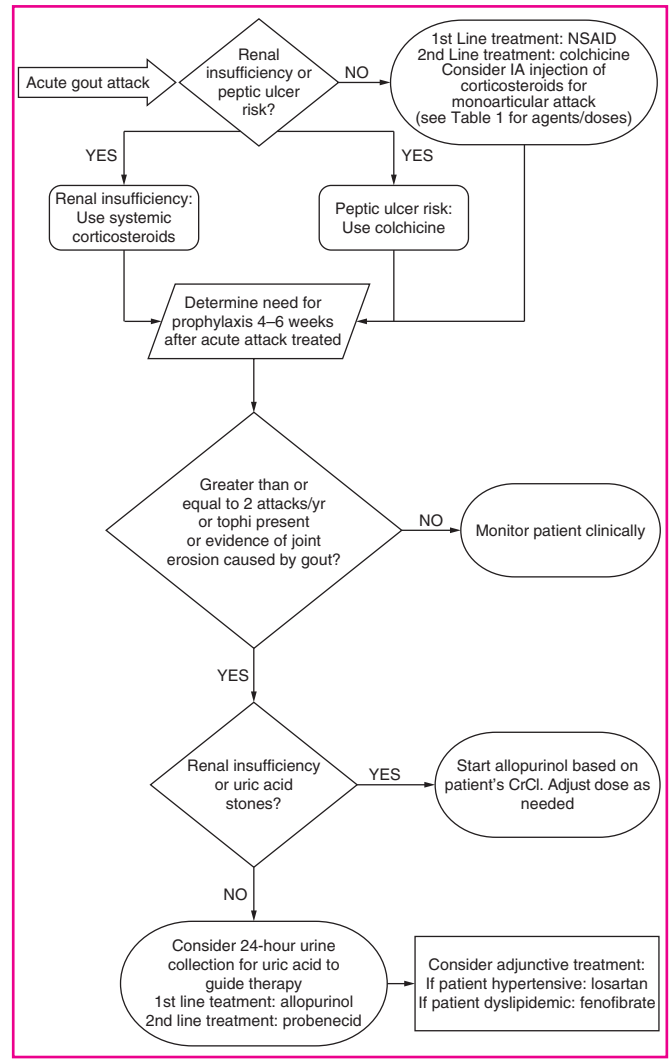


FIGURE 56–2. Treatment algorithm for gout and hyperuricemia. Renal insufficiency is defined as an estimated creatinine clearance (CrCl) of less than 30 mL/minute. IA, Intraarticular; NSAID, nonsteroidal anti-inflammatory drug.

Cyclooxygenase-2 (COX-2)–selective inhibitors produce results comparable with those of traditional NSAIDs. However, cardiovascular safety concerns and the high cost of COX-2 inhibitors argue against their use for this disorder.

Colchicine

Colchicine has a long history of successful use and was the treatment of choice for many years. It is used infrequently today because of its low therapeutic index. Colchicine is thought to exert its anti-inflammatory effects by interfering with the function of mitotic spindles in neutrophils by binding of tubulin dimers; this inhibits phagocytic activity.

Oral colchicine is absorbed rapidly from the gastrointestinal tract and metabolized extensively in the liver.

TABLE 56–1. Dosage Regimens for Acute Gout and Antihyperuricemic Treatment

Drug	Dose
Drugs for Treatment of Acute Gout	
NSAIDs[a]	
Fenoprofen	800 mg PO q 6 hour
Flurbiprofen	100 mg PO qid for 1 day, then 50 mg PO qid
Ibuprofen	600 to 800 mg PO qid
Indomethacin*	150–200 mg PO daily (in 3 divided doses) for three days, then 100 mg PO daily (in 2 divided doses) for 4 to 7 days
Indomethacin*	50 mg PO tid
Ketoprofen	50 mg PO qid or 75 mg PO tid
Meclofenamate	100 mg PO tid to qid
Naproxen*	1000 mg daily × 3 days, then 500 mg daily × 7 days *or* 750 mg PO initially, then 250 mg PO q8h
Piroxicam	40 mg PO once daily
Sulindac*	200 mg bid × 7 to 10 days
Tolmetin	400 mg PO tid to qid
Celecoxib	200 mg PO bid
Meloxicam	7.5–15 mg PO once daily
Colchicine	0.6 mg PO every hour for up to 3 doses, then 0.6 mg 1–2 times daily if desired before antihyperuricemic therapy is started; may occasionally use in low doses for prophylaxis; avoid the intravenous formulation
Local corticosteroids	
Methylprednisolone	10–40 mg × 1 dose by intraarticular injection
Systemic corticosteroids	
Prednisone (example)	40–60 mg PO once daily × 3 days, then decrease by 10 mg every 3 days
Triamcinolone acetonide	60 mg × 1 dose by intramuscular injection
Antihyperuricemic Treatment	
Allopurinol	Starting dose: CrCl greater than 90 mL/minute = 300 mg/day CrCl 60–90 mL/minute = 200 mg/day CrCl 30–60 mL/minute = 100 mg/day CrCl less than 30 mL/minute = 50 mg/day Adjust dosage based on follow-up uric acid levels; maximum 800 mg/day
Probenecid	Starting dose 250 mg PO bid; may increase to 1000 mg PO bid

[a]Drugs that are FDA approved for treatment of gout are indicated with an asterisk.
NSAIDs, nonsteroidal anti-inflammatory drugs; CrCl, creatinine clearance.
Adapted with permission from Terkeltaub RA. Gout. New Engl J Med. 2003; 349:1647–1655. Copyright ©2003 Massachusetts Medical Society. All rights reserved. Drug regimens derived from various sources.

About two-thirds of patients with acute gout respond favorably if it is given within the first 24 hours of symptom onset. Unfortunately, more than 80% of patients experience adverse effects. Gastrointestinal effects (e.g., nausea, vomiting, diarrhea, and abdominal pain) are most common and are considered a forerunner of more serious systemic toxicity, including myopathy and bone marrow suppression (usually neutropenia). Some clinicians still use the strategy of continuous dosing until either pain relief or gastrointestinal side effects occur. However, systemic toxicity can occur with oral colchicine without prior gastrointestinal effects, especially in patients with renal insufficiency. Because of these problems, oral colchicine should be reserved for patients who are at risk for NSAID-induced gastropathy or who have failed NSAID therapy.

Use of intravenous colchicine to circumvent adverse gastrointestinal effects is discouraged due to the increased risk of serious and potentially fatal systemic effects with this route. The intravenous form should not be used in patients with moderate or more severe renal impairment (creatinine clearance less than or equal to 50 mL/minute), and total doses should not exceed 4 mg in a 7-day period. The potential extravasation of intravenous colchicine is also a concern.

Corticosteroids

When only one or two joints are affected, **intraarticular** corticosteroid injection can provide rapid relief with a relatively



Patient Encounter, Part 1

A 48-year-old man with a history of hypertension, peptic ulcer disease (gastric ulcer 1 year ago), and morbid obesity presents to the emergency department complaining of excruciating pain in his left big toe and both ankles. This is similar to a painful episode he had with his left toe and ankle 6 months ago. On examination, his left great toe and both ankles are red, swollen, and warm to the touch. He describes the pain as throbbing and rates it as a 10 of 10 (where 10 is the worse pain he has ever experienced). He admits to drinking a six-pack of beer on weekends. He weighs 150 kg (330 lbs) and is 5 ft, 9 in (175 cm) tall. Medications include chlorthalidone 25 mg/day and pantoprazole 40 mg/day. Serum creatinine is 1.0 mg/dL (88.4 µmol/L).

- What information suggests gout as the cause of his symptoms?
- What risk factors for gout does he have?
- If the diagnosis is an acute attack of gouty arthritis, what treatment plan would you outline for this patient?

low incidence of side effects. Joint fluid obtained by **arthrocentesis** should be examined for evidence of joint-space infection and crystal identification. If no infection is present, intraarticular injection can proceed.

Systemic corticosteroids are a useful option in patients with contraindications to NSAIDs or colchicine (primarily renal impairment) or polyarticular attacks, especially in elderly patients. A single intramuscular injection of a long-acting corticosteroid such as triamcinolone hexacetonide may be used. Oral agents may be needed, especially for severe attacks. Prednisone 40 to 60 mg (or an equivalent dose of another agent) is given daily, with a gradual taper over 2 weeks.

Too rapid tapering of corticosteroids can cause a rebound gouty flare. To prevent this flare, low-dose colchicine (0.6 mg PO daily) sometimes is added to systemic corticosteroid regimens. This is probably unnecessary if an adequate taper is prescribed.

Short-term adverse effects from corticosteroids include fluid retention, hyperglycemia, central nervous system stimulation, weight gain, and increased risk of infection. Patients with diabetes should have blood glucose levels monitored carefully during the corticosteroid course.

Corticotropin [adrenocorticotropic hormone (ACTH)] has been used for acute gouty flares. Worldwide supply problems and the possible superiority of traditional corticosteroids have resulted in decreased use.

ANTIHYPERURICEMIC GOUT PROPHYLAXIS

Gout is an episodic disease, and the number of attacks varies widely from patient to patient. Thus the benefit of long-term prophylaxis against acute gout flares must be weighed against the cost and potential toxicity of therapy that may not be necessary in all patients. ❻ *Asymptomatic hyperuricemia usually does not require treatment.*

Nonpharmacologic Therapy

Lifestyle modifications alone usually are insufficient for lowering serum uric acid levels in gout patients. Patients should be advised to lose weight if obese and to discontinue ethanol consumption. Low-purine diets are not well tolerated; instead, dietary recommendations should focus on general nutrition principles. Drugs that may cause or aggravate hyperuricemia should be discontinued if possible. Few patients adhere to lifestyle modifications long term, and pharmacologic therapy usually is needed to treat hyperuricemia adequately.

Pharmacologic Therapy

❼ *Patients with recurrent attacks, evidence of tophi or joint destruction, or uric acid nephrolithiasis are candidates for maintenance therapy with allopurinol or probenecid to lower serum uric acid level*s. Because hyperuricemia is the strongest modifiable risk factor for acute gout, prophylactic therapy involves either decreasing uric acid production or increasing its excretion (see Table 56–1). The goal of therapy is to decrease serum uric acid levels significantly, leaving less uric acid available for conversion to monosodium urate crystals.

Ideally, the selection of long-term prophylactic therapy involves determining the cause of hyperuricemia (primarily by analyzing a 24-hour urine collection for uric acid) and tailoring therapy appropriately. If less than 600 mg of uric acid is found in the 24-hour sample, the patient is considered an underexcretor. However, this approach is not used commonly for several reasons. The urine collection is inconvenient for patients and clinicians and does not identify patients who may be both overproducers and underexcretors of uric acid. Also, drugs used to increase uric acid excretion (**uricosurics**) generally are not as well tolerated as drugs that decrease production, and uricosurics increase the risk of uric acid nephrolithiasis.

Because allopurinol (which reduces uric acid production) is effective in both overproducers and underexcretors and is generally well tolerated, many clinicians forgo the 24-hour urine collection and treat patients empirically with it.

Allopurinol

Most patients in the United States are treated with allopurinol, which usually is effective if the dosage is titrated appropriately. The drug and its primary active metabolite, oxypurinol, reduce serum uric acid concentrations by inhibiting the enzyme xanthine oxidase, thereby blocking the oxidation of hypoxanthine and xanthine to uric acid.

Allopurinol is well absorbed with a short half-life of 2 to 3 hours. The half-life of oxypurinol approaches 24 hours, allowing allopurinol to be dosed once daily. Oxypurinol is cleared primarily renally and can accumulate in patients with reduced kidney function. Allopurinol should not be started during an acute gout attack because sudden shifts in serum uric acid levels may precipitate or exacerbate gouty arthritis. Rapid shifts in serum uric acid can change the concentration of monosodium urate crystals in synovial fluid, causing more crystals to precipitate. Thus some clinicians advocate a prophylactic dose of colchicine (0.6 mg/day) during initiation of antihyperuricemic therapy. Acute episodes should be treated appropriately before maintenance treatment is started.

The initial dose of allopurinol is based on the patient's renal function. Patients with creatinine clearances of 50 mL/minute or less should receive a starting dose of less than 300 mg/day to minimize adverse effects. The relationship between dose of allopurinol and its most severe side effects is controversial. However, the dose can be adjusted upward as needed and tolerated. It is reasonable to reduce the dose temporarily in patients who develop reversible acute renal failure.

Serum uric acid levels must be monitored periodically, with the first follow-up level obtained 6 months (or sooner) after starting therapy. The target serum uric acid level is less than 6 mg/dL (less than 357 µmol/L). The dose should be titrated upward (to a maximum of 800 mg/day) or downward as these levels dictate.

Allopurinol generally is well tolerated; nausea and diarrhea occur in a small percentage of patients. A generalized, maculopapular rash occurs in about 2% of patients. Although usually mild, this can progress to severe skin reactions such as Stevens-Johnson syndrome. Perhaps the most feared side effect is the so-called allopurinol hypersensitivity syndrome. This constellation of signs and symptoms includes severe desquamating skin lesions, high fever (usually greater than 39°C or 102.2°F), hepatic dysfunction, leukocytosis with predominant eosinophilia, and renal failure. Although rare, this severe reaction has a 20% mortality rate. Patients with a history of the syndrome should never again receive allopurinol (including desensitization) or oxypurinol (which is available outside the United States). Patients with a mild skin rash who require allopurinol can be desensitized to it using published protocols.

There are several important drug-drug interactions with allopurinol. The effects of both theophylline and warfarin may be potentiated by allopurinol. Azathioprine and 6-mercaptopurine are purines whose metabolism is inhibited by concomitant allopurinol therapy; the dose of these drugs must be reduced by 75% with allopurinol cotherapy. Patients taking allopurinol who receive ampicillin are at increased risk of skin rashes.

Probenecid

Probenecid is a uricosuric agent that blocks the tubular reabsorption of uric acid, increasing its excretion. Because of its mechanism of action, probenecid is contraindicated in patients with a history of uric acid stones or nephropathy. Probenecid loses its effectiveness as renal function declines and should be avoided when the creatinine clearance is 50 mL/minute or less. Its uricosuric effect is counteracted by low aspirin doses, which many patients receive for prophylaxis of coronary heart disease.

Although generally well tolerated, probenecid can cause gastrointestinal side effects such as nausea and other adverse reactions, including fever, rash, and rarely, hepatic toxicity. Patients should be instructed to maintain an adequate fluid intake and urine output to decrease the risk of uric acid stone formation. Some experts advocate alkalinizing the urine to decrease this risk.

Other Uricosuric Agents

Sulfinpyrazone was used in the past but is no longer available in the United States. Several other medications have



Patient Encounter, Part 2

The patient returns for a follow-up visit at your clinic 6 weeks later. He reports no pain or swelling in the joints affected previously. The emergency room doctor had instructed him to stop the chlorthalidone, so he is currently taking only pantoprazole.

PE

- **VS:** 164/84, P 72, RR 15, T 37.2°C (99°F)
- **Exts:** Trace edema in both ankles.

Labs

- Serum uric acid 11.5 mg/dL (684 µmol/L)
- Serum creatinine 0.9 mg/dL (79.6 µmol/L).
- Uric acid crystals were identified on arthrocentesis of the ankle 6 weeks ago.

- Given this additional information, what is your assessment of the patient's condition?
- Is the patient a candidate for antihyperuricemic therapy? If so, which agent would you choose?
- What nonpharmacologic recommendations do you have for the patient?
- What do you suggest for treating the patient's hypertension?

mild uricosuric effects and may be appropriate adjunctive therapy in some patients. Losartan increases both uric acid excretion and urine pH and may be an option in hypertensive patients with gout. Fenofibrate is also a uricosuric and may be appropriate in selected dyslipidemic patients with gout. New agents undergoing investigation for hyperuricemia include febuxostat and polyethylene glycol–bonded uricase.

OUTCOME EVALUATION

Acute Gout

- Monitor the patient for pain relief and decreased swelling of the affected joints. Both parameters should be improved significantly within 48 hours of starting acute gout therapy.
- Assess the patient's subjective complaints and objective information for adverse effects. For NSAID therapy, be alert for new-onset epigastric pain, dark or tarry stools, blood in vomitus, dizziness or light-headedness, development of edema, decreased urine output by more than 50% over a 24-hour period, or shortness of breath. For colchicine, monitor for nausea or vomiting, diarrhea, easy bruising, cold or flulike symptoms, light-headedness, muscle weakness, or pain. Counsel the patient to inform you of any new medications started or stopped while taking colchicine.
- Monitor patients receiving intraarticular corticosteroid injections for increased swelling or pain at the injection site.
- Assess patients receiving systemic corticosteroids for mental status changes, fluid retention, increased blood glucose, muscle weakness, or development of new infections.

Antihyperuricemic Therapy

- Assess for new gouty arthritis attacks or the development of tophi. If neither one develops, continue antihyperuricemic therapy as prescribed.
- Obtain the first follow-up serum uric acid level within 6 months of starting therapy. Then monitor levels at least every 6 to 12 months, and adjust the dose to achieve a target serum uric acid level of less than 6 mg/dL (less than 357 μmol/L).
- Evaluate patients taking allopurinol for development of rash, nausea, or new fever. These symptoms usually appear within the first 3 months of therapy but can occur anytime.
- Assess patients receiving probenecid for fever, nausea, or skin rash. Reevaluate therapy if a significant decrease in urine output occurs (greater than 50% in a 24-hour period).



Patient Care and Monitoring

1. Assess the patient's symptoms to determine the time of attack onset, which joints are affected, the level of pain, and other symptoms.
2. Review the patient history for contributing lifestyle factors and other disease states that may help guide therapy.
3. Obtain a thorough medication history for prescription drug, nonprescription drug, and dietary supplement use. Determine if any of these products may be contributing to hyperuricemia.
4. Educate the patient on lifestyle modifications that will improve symptoms, including weight loss, if appropriate, and avoidance of ethanol.
5. If the diagnosis of gout has not been confirmed previously, consider aspiration of an affected joint to identify uric acid crystals.
6. Initiate therapy to treat the acute gout attack without delay. Develop a plan to assess this therapy after 24 and 48 hours.
7. Select therapy based on comorbidities and potential for adverse effects. In patients with no other disease states, NSAIDs are the preferred drug class.
8. Assess the need for continuous antihyperuricemic therapy. Use patient factors such as comorbidities to select an agent. Allopurinol is the standard prophylactic agent used in the United States.
9. Do not start antihyperuricemic therapy within 4 weeks of an acute attack.
10. Evaluate the patient for the presence of adverse drug reactions, drug allergies, and drug interactions.
11. Stress the importance of adherence with the therapeutic regimen, including lifestyle modifications, to prevent future gout attacks and long-term complications.
12. Provide patient education about the disease state, lifestyle modifications, and drug therapy.

ABBREVIATIONS

NSAID:	nonsteroidal anti-inflammatory drug
SUA:	serum uric acid
MSU:	monosodium urate
WBC:	white blood cell
CrCl:	creatinine clearance
IA:	intraarticular

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

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57 Musculoskeletal Disorders

Jill S. Burkiewicz



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Describe the pathophysiologic principles associated with tissue injury and inflammation.
2. Identify the desired therapeutic goals and outcomes for a patient with musculoskeletal injury or pain.
3. Identify the factors that guide selection of an analgesic or counterirritant for a particular patient.
4. Recommend appropriate nonpharmacologic and pharmacologic therapy for a patient with musculoskeletal injury or pain.
5. Design a patient education plan including nonpharmacologic therapy and preventative strategies.
6. Develop a monitoring plan to assess treatment of a patient with musculoskeletal disorders.

Key Concepts

❶ The two primary goals of treatment of musculoskeletal disorders are to (1) relieve pain and (2) maintain functionality.
❷ The cornerstone of nonpharmacologic therapy for acute injury in the first 48 to 72 hours is known by the acronym *RICE: r*est, *i*ce, *c*ompression, and *e*levation.
❸ Heat should not be applied during the acute injury phase (the first 48 hours) because it promotes swelling and inflammation.
❹ There are two main approaches to pharmacologic intervention for pain relief: oral (systemic) and topical agents.
❺ Localized pain may be treated effectively with local topical therapy, whereas generalized pain may be treated best with systemic agents.
❻ Acetaminophen is the drug of choice for mild to moderate regional musculoskeletal pain without inflammation.
❼ Aspirin has not been demonstrated to be more effective than acetaminophen, and because its safety profile may be inferior it is not recommended for treatment of acute musculoskeletal pain.
❼ NSAIDs are a preferred choice over acetaminophen in musculoskeletal disorders where inflammation is evident.
❽ Patient education on proper use of counterirritants is essential to therapeutic success.
❿ Patients using capsaicin should be advised to apply it regularly and consistently three to four times daily and that full effect may take 2 to 3 weeks or longer.

The musculoskeletal system consists of the muscles, bones, joints, tendons, and ligaments. Disorders related to the musculoskeletal system often are classified by etiology. Acute soft-tissue injuries include strains and sprains of muscles and ligaments. Repeated movements in sports, exercise, work, or activities of daily living may lead to repetitive strain injury, where cumulative damage occurs to the muscles, ligaments, or tendons.[1–3] While tendonitis and bursitis can arise from acute injury, more commonly these conditions occur as a result of chronic stress.[3,4] Other forms of chronic musculoskeletal pain, such as pain from rheumatoid arthritis (see Chap. 54) or osteoarthritis (see Chap. 55), are discussed elsewhere in this text.

EPIDEMIOLOGY

Musculoskeletal disorders are commonly self-treated, so true estimates of the incidence of both acute and chronic injury are difficult to obtain. Musculoskeletal disorders, including arthritis, are among the most frequently reported health problems in the United States.[5] These disorders account for a large portion of the utilization of health care resources and are the leading cause of work-related disability in all ages, including Americans aged 65 and over.

In addition to chronic conditions such as arthritis and low-back pain, some musculoskeletal disorders are induced by

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trauma at the workplace either via repetition and cumulative trauma or owing to a single strain.[6,7] For each reported disorder, it is likely that there are at least 10 unreported work-related musculoskeletal disorders related to repetitive stress to the bones and joints.[8] In the elderly, these injuries may not be related to work but to daily life. Instability combined with activities of daily living such as stair climbing and lifting objects may lead to strains and sprains.[2]

Muscle injuries comprise the majority of sports-related injuries, and roughly half are related to overuse.[3,9,10] The ankle and the knee are common sites of sports injuries.[11,12] Soccer, football, basketball, track and field, and other sports that require rapid acceleration or higher speeds pose a greater risk of muscle strain.[13] *Overuse musculoskeletal injury* is the phrase used to describe disorders arising from repetitive motion. This injury is common in activities such as running, particularly during periods of increased intensity or duration of training.[3] It also can occur in the workplace with repeated, unvaried motion.[14]

PATHOPHYSIOLOGY

Skeletal muscle consists of muscle fibers linked together by connective tissue. Tendons and ligaments are composed of collagenous fibers that have a restricted capability to stretch. Tendons connect the muscle to the bone, whereas ligaments connect bone to bone (Fig. 57–1).

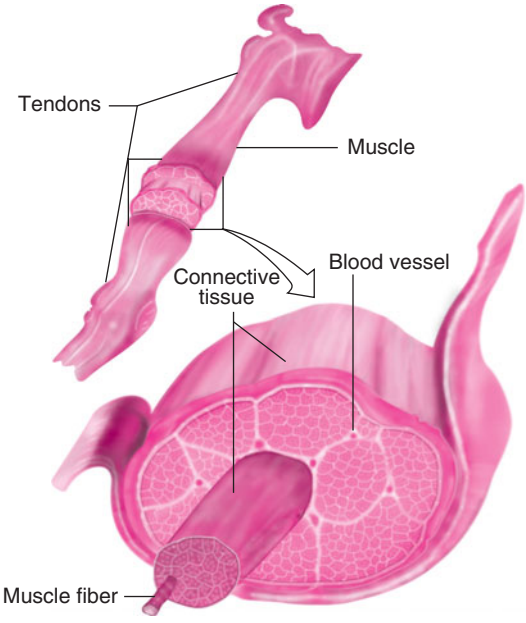


FIGURE 57–1. Skeletal muscle fiber organization. Tendons attach muscle to bone. (From Widmaier EP, Raff H, Strang KT, et al, (eds.) Vander, Sherman, & Luciano's Human Physiology: The Mechanisms of Body Function. 9th ed. New York: McGraw-Hill; 2004, Figure 9-1.)

Muscle Strains and Sprains

A **sprain** is an overstretching of supporting ligaments that results in a partial or complete tear of the ligament.[12] While a **strain** also arises from an overstretching of the muscle-tendon unit, it is marked by damage to the muscle fibers or muscle sheath without tearing of the ligament.[10] The key difference between a sprain and a strain is that a sprain involves damage to ligaments, whereas a strain involves damage primarily to muscle. One common example of muscle strain and sprain is low-back pain.[7]

Overloading the muscle and connective tissue results in complete or partial tears of the skeletal muscle, tendons, or ligaments.[9,10] This usually occurs when the muscle is activated in an *eccentric contraction,* defined as a contraction in which the muscle is being lengthened.[13] Examples of this type of contraction include setting down a large, heavy laundry basket or lowering oneself from a chin-up bar. Small tears can occur in the muscle because it is lengthening while also trying to contract to support the load. This leads to rupture of blood vessels at the site of the injury, resulting in the formation of a hematoma. Within 24 to 48 hours, an inflammatory response develops. In the inflammatory stage, macrophages remove necrotic fibers.[9,10] However, there is some evidence that activated neutrophils also release free radicals and proteases that cause further damage to the area.[15] Finally, capillaries grow into the area, and muscle fibers regenerate during the repair and remodeling phases of healing.[10]

Bursitis and Tendonitis

Bursitis is an inflammation of the bursa, the fluid-filled sac near the joint where the tendons and muscles pass over the bone. The bursa assists with movement by reducing friction between joints. **Tendonitis** (also known as *tendinitis*) is an inflammation of the tendon or, more specifically, the fibrous sheath that attaches muscle to bone.[3] **Tenosynovitis** is an inflammation of the tendon sheath.

Repetitive overuse of a tendon can cause cellular changes in the tissues. Specifically, collagenous tendon tissue is replaced with tissue that lacks the longitudinal structure of a normal tendon.[16] As a result, the tendon progressively loses elasticity and its ability to handle stress or weight. This makes the tendon vulnerable to rupture or inflammation (tendonitis and tenosynovitis).

Repeated use also may cause degradation of collagen.[17] In fact, many patients diagnosed with chronic tendonitis may not have inflammation but instead have tendinosis, a condition marked by these collagen changes. Overuse of a joint also can result in an inflamed bursa. Since the bursa serves to reduce friction within the joint space, bursitis causes stiffness and pain.

Inflammation and Peripheral Pain Sensation

Inflammation is a common pathway in soft-tissue injury of musculoskeletal disorders. Inflammatory processes lead to two outcomes: swelling and pain. Inflammatory processes

traditionally are considered to be a necessary part of the remodeling process because inflammatory cells remove damaged tissue.[18,19] However, inflammation also contributes to continued pain and swelling that limits range of motion.

The initial injury exposes membrane phospholipids to phospholipase A_2, leading to the formation of arachidonic acid (Fig. 57–2).[18,19] Next, arachidonic acid is transformed by cyclooxygenase (COX) to thromboxanes and prostaglandins, including prostaglandin E_2 (PGE_2). PGE_2 is the most potent inflammatory mediator; it increases vascular permeability, leading to redness, warmth, and swelling of the affected area. The increased permeability also increases **proteolysis**, or the breakdown of proteins in the damaged tissue.

Neutrophils, lymphocytes, and monocytes are attracted to the area, and monocytes are converted to macrophages.[18,19] The macrophages then stimulate additional prostaglandin production. Phagocytic cells and other players in the immune system release cytokines, including interleukins, interferon, and tumor necrosis factor.

In addition to increasing vascular permeability, prostaglandins also induce pain by sensitizing pain receptors to other substances such as bradykinin. Bradykinin, prostaglandins, and other inflammatory mediators lower the pain threshold through peripheral pain sensitization. These substances make nerve endings more excitable, and the nerve fibers are more reactive to serotonin, heat, and mechanical stimuli.[19] The process also facilitates production of additional prostaglandins. In a cyclic fashion, the prostaglandins then sensitize the nerves to bradykinin action. Leukotrienes produce a similar peripheral sensitization to painful stimuli.

Without interruption, the neurochemicals ultimately lead to a firing of the unmyelinated or thinly myelinated afferent neurons. This sends messages along the pain pathway in the periphery and transfers the pain message to the central nervous system. Interruption of this cycle via anti-inflammatory agents such as aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) is an important step in treating pain.

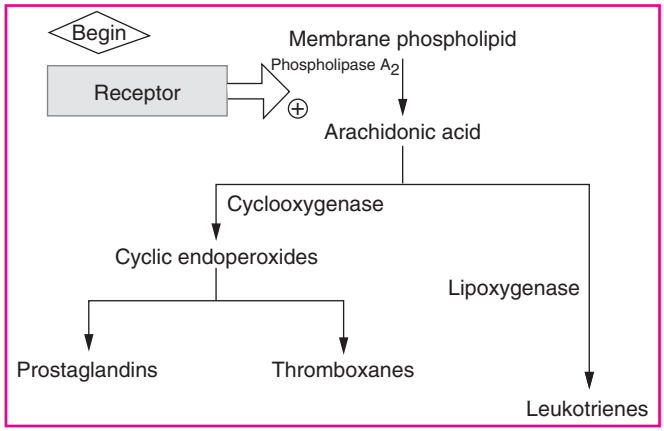


FIGURE 57–2. Eicosanoid synthesis pathway. Cyclooxygenase is inhibited by nonsteroidal anti-inflammatory drugs and aspirin. (From Widmaier EP, Raff H, Strang KT, et al, (eds.) Vander, Sherman, & Luciano's Human Physiology: The Mechanisms of Body Function. 9th ed. New York: McGraw-Hill; 2004, Figure 5-11.)

Nerve receptors, or **nociceptors,** may release substance P, a peptide that causes vasodilation when released.[20] This dilation occurs mainly through substance P–induced production of the vasodilator nitric oxide. Substance P also generates the release of histamine, leading to bradykinin release and activation of an inflammatory process. Capsaicin relieves pain by stimulating the release of substance P from sensory nerve fibers, which ultimately depletes stores of substance P.

CLINICAL PRESENTATION AND DIAGNOSIS



Presentation of Musculoskeletal Disorders[12]

General

- Clinical presentation varies based on the etiology of the disorder.
- Repetitive strain or overuse injuries may have a gradual onset.
- Musculoskeletal disorders owing to acute injury may be associated with other signs of the injury such as abrasion.
- Low-back pain may be more chronic in nature.

Signs and Symptoms of Acute Soft-Tissue Injury (Strains, Sprains)[12]

- Discomfort ranging from tenderness to pain; it may occur at rest or with motion.
- Swelling and inflammation of the affected area
- Bruising or abrasion
- Loss of motion
- Mechanical instability

Signs and Symptoms of Repetitive Strain or Overuse Injury (Tendonitis, Bursitis)[3,21,22]

- Pain and stiffness that may occur at rest or with motion.
- Localized tenderness on palpation
- Mild swelling of the affected area
- Decreased range of motion
- Muscle atrophy

Other Diagnostic Tests and Assessments[23]

- *Radiograph (x-ray):* Evaluate bony structures to rule out fracture, malalignment, or joint erosion as the primary cause of pain.
- *Magnetic resonance imaging (MRI):* Soft-tissue imaging to evaluate for tendon or ligament tears.
- *Ultrasound:* Superficial soft-tissue imaging to evaluate for tears in tendons or ligaments. Does not penetrate bone, so it is of limited usefulness for assessing tendons or ligaments deep within joints.
- *Pain scale:* Patient self-rating of pain on a scale of 0 (no pain) to 10 (worst possible pain). Used to assess pain both at rest and with movement. Determined at baseline and to assess response to therapy.



Patient Encounter 1, Part 1

A 32-year-old man presents with left ankle pain. He was playing football with friends earlier today and twisted his ankle. The pain occurs at rest and is worsened by movement and weight-bearing activities. There is moderate swelling and mild bruising of the left ankle.

- What information is suggestive of a musculoskeletal disorder?
- What is your assessment of the patient's ankle pain?
- What additional information do you need to formulate a treatment plan?

TREATMENT

Desired Outcomes

❶ *The primary goals of treatment of musculoskeletal disorders are to (1) relieve pain and (2) maintain functionality.* This is accomplished by decreasing the severity and duration of pain, shortening the recovery period, and preventing acute pain from an acute injury from becoming chronic pain. Prevention of swelling and inflammation are initial goals in acute injury because the degree of swelling is directly related to range of motion.[12] If these goals are achieved, functional limitations are decreased. Ideally, a patient should be able to continue to perform activities of daily living (e.g., eating, dressing, cooking, and doing laundry) and maintain normal functions in the workplace. Children ideally should be able to maintain usual play activities and sports schedules.

Further goals include a return to usual activity and prevention of future injury. It is also important to minimize the potential for adverse drug events during treatment.

General Approach to Treatment

Treatment of musculoskeletal disorders involves three phases: (1) therapy of an acute injury using the RICE principle, (2) pain relief using oral or topical agents, and (3) lifestyle and behavioral modifications for rehabilitation and to prevent recurrent injury or chronic pain (Fig. 57–3).

In many cases, musculoskeletal disorders may be self-treated with over-the-counter oral or topical agents. However, further evaluation may be warranted if acute pain persists longer than 7 to 10 days, symptoms worsen or subside and then return, or there are signs of a more serious condition.[12,22,24–25] Warning signs of more serious conditions include joint deformity or dislocation or lack of movement in a joint. Low-back pain accompanied by burning, radiating pain or difficulty urinating requires further evaluation.

In children and adolescents, treatment practices are similar to the approach in adults with a focus on nonpharmacologic therapy and oral analgesics. Children younger than age 2, elderly persons, and pregnant women also may need special care.

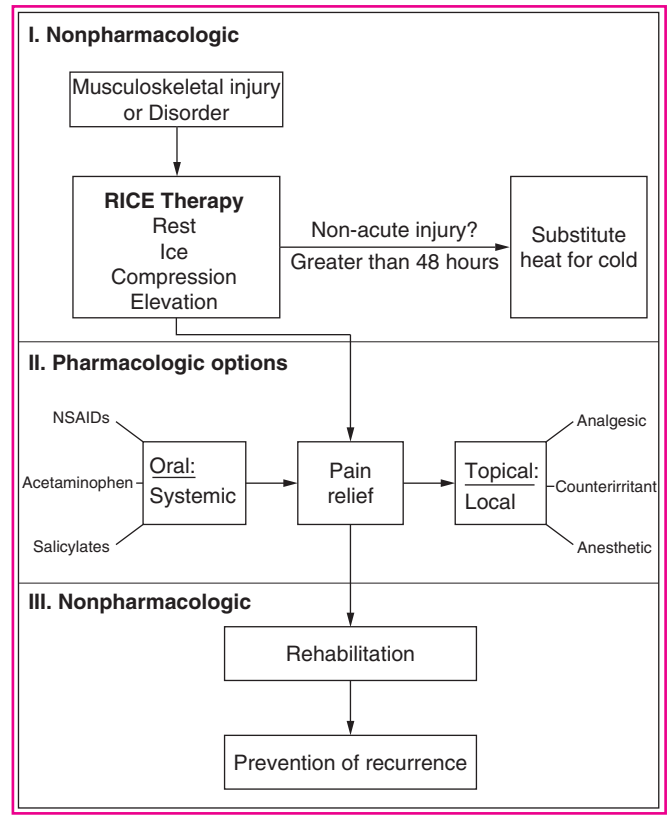


FIGURE 57–3. Treatment plan for musculoskeletal injury or disorder.

Nonpharmacologic Therapy: RICE

❷ *The cornerstone of nonpharmacologic therapy for acute injury in the first 48 to 72 hours is known by the acronym RICE: rest, ice, compression, and elevation*[10,13] (Table 57–1). Rest eases pressure on the affected area and promotes pain control during the acute inflammatory phase (the first 1 to 5 days after injury). Ice, compression, and elevation initially minimize bleeding from broken blood vessels. Cold causes vasoconstriction, assisting in prevention of a large hematoma and providing analgesia by slowing nerve impulses. Compression, achieved by wrapping the area with an elastic bandage, also reduces the size of the developing hematoma. Preventing formation of a hematoma is important because a large hematoma may limit mobility and range of motion. Both cold and compression also decrease interstitial edema and swelling that accompany the injury. Elevation decreases blood flow and increases venous return from the affected area.

In addition to minimizing the acute inflammatory response, rest prevents additional injury to the affected area.[13] The properties of the muscle-tendon unit are altered during the acute injury, with limitations on the ability of the muscles and tendons to stretch. Early activity predisposes a patient to further injury, but prolonged inactivity can lengthen recovery times.

TABLE 57–1. RICE Therapy

Therapy	General Guidelines	Therapeutic Benefit
Rest	Rest the affected area. Use supports such as slings and crutches as necessary. Employ during the acute inflammatory phase, 1–5 days after injury.	Analgesia Anti-inflammatory Prevent further injury
Ice	Cool the affected area by application of crushed ice in a plastic bag covered with a thin cloth or by cool water (55°F or 13°C). Cool the affected area for 15–20 minutes; repeat every 2 hours for the first 48 hours.	Analgesia Anti-inflammatory
Compression	Compress the affected area with an elastic bandage or support. Begin wrapping the bandage at the point most distal to the injury (e.g., at the toes for an ankle injury); apply firmly but not tightly. If the area distal to the injury (e.g., fingers, toes) throbs or turns cold or blue, the bandage is too tight and should be loosened.	Anti-inflammatory Adjunctive analgesia
Elevation	Elevate the area (especially the extremities) above heart level.	Anti-inflammatory

Clinicians should instruct patients to use crushed ice or ice chips because the area will cool more evenly than with large pieces of ice. Patients should not apply ice directly to the affected area or leave it on for longer than the recommended 20 minutes because frostbite may occur.[12] A thin sheet or napkin will protect the skin and also allow for better cold transfer than thicker material such as a towel. Alternatively, soaking the area for 20 minutes in a cool bath (55°F or 13°C) provides effective cooling.

For small areas, an ice massage for 5 to 10 minutes can cool the area and add relief.[21] This is accomplished by freezing water in a paper cup and removing the top part of the cup to expose the ice. The exposed ice is rubbed on the affected area. Any ice application should be stopped if the area becomes white or blue.

❸ *Heat should not be applied during the acute injury phase (the first 48 hours) because it promotes swelling and inflammation.*[12] After the first 48 hours, many patients find that heat decreases pain and eases muscle stiffness associated with immobility. A heating pad, heat wrap, or warm bath may be used on day 3 or later as long as no swelling develops after heat is applied. Heat should be discontinued if increased swelling occurs. Clinicians should educate patients to avoid sleeping with heating pads or sitting or lying on them because this may result in burns.

Pharmacologic Therapy

❹ *There are two main approaches to pharmacologic intervention for pain relief: oral (systemic) and topical agents.* The choice between systemic or topical options is often guided by patient preference. For example, many topical products have a medicinal odor and require frequent applications. The extent of musculoskeletal pain also guides treatment choice. ❺ *Localized pain may be treated effectively with local topical therapy, whereas generalized pain may be treated best with systemic agents.* Factors such as alcohol use, liver function, renal function, allergies, age, and comorbid conditions should be considered when choosing among therapeutic options.

Oral Analgesics

Nonopioid analgesics, including acetaminophen, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs), are used commonly for musculoskeletal disorders. All these agents provide analgesia, but aspirin and NSAIDs also work peripherally to decrease production of the principal mediator of acute inflammation, PGE_2.[18] NSAIDs and aspirin inhibit the enzyme cyclooxygenase (COX). While the mechanism of action of acetaminophen is less clear, it appears that acetaminophen acts as a weak inhibitor of prostaglandin (PG) production. In contrast to aspirin and NSAIDs that inhibit PG production peripherally, acetaminophen exerts its effect centrally with little or no anti-inflammatory effect.[26]

Acetaminophen

❻ *Acetaminophen is the drug of choice for mild to moderate regional musculoskeletal pain without inflammation.*[27,28] Comparative trials between acetaminophen and oral NSAIDs demonstrate equivalent analgesia in some situations, but NSAIDs may be preferred in others.[28] Therefore, if adequate analgesia is not achieved with acetaminophen, switching to an NSAID is a reasonable approach. Acetaminophen offers the advantage of less gastrointestinal (GI) toxicity than NSAIDs. While tolerability of acetaminophen is high at therapeutic doses, hepatotoxicity has been reported after overdose and at therapeutic doses, especially in combination with other factors.[29] Acetaminophen should be used with caution in patients who have liver disease or consume alcohol because of the risk of hepatotoxicity.[23]

Salicylates

❼ *Aspirin has not been demonstrated to be more effective than acetaminophen, and because its safety profile may be inferior, it is not recommended for treatment of acute musculoskeletal*

pain.[28] Gastric irritation is more common with aspirin, and bleeding risk may be increased because aspirin irreversibly inhibits platelet aggregation.[28] Patients with aspirin-induced asthma should avoid aspirin and other salicylates.[29] Aspirin should be avoided in children due to a risk of Reye's syndrome.

Some salicylates are specifically marketed for musculoskeletal back pain, such as magnesium salicylate. However, no studies specifically support use of these salicylates over other systemic analgesics. Magnesium salicylate should be used with caution in renal impairment because hypermagnesemia may occur.[31]

NSAIDs

NSAIDs are used commonly for musculoskeletal pain because of their availability without a prescription and anti-inflammatory effects.[30,31] ❽ *NSAIDs are a preferred choice over acetaminophen in musculoskeletal disorders where inflammation is evident.*[27] However, there is some controversy because the inflammatory response may be necessary for healing.[13] Nevertheless, most experts recommend the use of NSAIDs early after acute injury to control inflammation and the range-of-motion limitations that may accompany swelling.[27]

NSAIDs are particularly beneficial for chronic overuse injury, where inflammation is central to the pain and loss of motion. While NSAIDs may be helpful in relieving pain and inflammation in tendonitis, many tendonopathies may not be due to inflammation. Therefore, use of a simple analgesic such as acetaminophen may relieve pain adequately.[22]

The analgesic effects of NSAIDs are attributed to inhibition of the COX-2 enzyme, whereas the negative GI effects are due to inhibition of COX-1.[28] Patients taking oral anticoagulants, those with a history of peptic ulcer disease, or others at high risk for GI complications may be considered candidates for a COX-2 inhibitor or a combination of a nonselective NSAID with a gastroprotective agent such as a proton pump inhibitor (PPI). Because most PPIs are available by prescription only, such patients should be referred to a physician.

COX-2 inhibitors such as celecoxib are associated with adverse effects such as nephrotoxicity and a potential increased risk of myocardial infarction (see Chaps. 55 and 15 for additional information). Combination of COX-2 inhibitors with alcohol may increase GI adverse effects. All NSAIDs should be used with caution in patients with aspirin-induced asthma.[31]

Opioids

Opioid analgesics can be used for patients not responding adequately to nonopioid analgesics or for moderate to severe pain.[28] These agents generally are given alone or in combination with simple analgesics such as acetaminophen. Tolerance and physical dependence are considerations but less of a concern when treating acute pain. When used in equivalent doses, opioids produce similar pain relief and adverse effects such as sedation, nausea, constipation, and respiratory depression.

Topical (External) Analgesics

Topically (or externally) applied drugs that exert an analgesic, anesthetic, or antipruritic effect locally by suppressing cutaneous sensory receptors are termed *external analgesics.*[24] These medications are applied directly to the affected area to create high local concentrations of the drug.[32,33] Formulations include gel, cream, lotion, liquid, liniment, or aerosol spray. Negligible systemic concentrations are achieved with intact skin, minimizing systemic adverse effects. Topical application should not be confused with transdermal delivery, where drug absorption into the bloodstream produces a systemic effect. Musculoskeletal disorders often are treated with topical (but not transdermal) medications.

After application, the topical medication penetrates the skin to the soft tissue and peripheral nerves.[24] Here, the drug suppresses the sensitization of pain receptors, thus reducing pain and burning. External analgesics also include counterirritant products that, in contrast, stimulate cutaneous sensory receptors, producing a burning, warming, or cooling sensation that masks the underlying pain. In effect, the irritation or inflammation caused by the counterirritant distracts from the underlying pain.

Some patients prefer external analgesics to systemic analgesics because the rubbing during application can be comforting. External analgesics are useful adjuvants to nonpharmacologic therapy and systemic analgesic therapy to provide additional relief.[34] The agents also offer a therapeutic option in patients who cannot tolerate systemic analgesics.

Topical NSAIDs

Topical NSAIDs are available commercially in Canada and Europe. In the United States, these agents may be compounded in specialty pharmacies.[35] These agents exert a local anti-inflammatory and analgesic effect.[36–38] In soft-tissue injury such as strains and sprains, topical NSAIDs are superior in efficacy to placebo and similar to oral NSAIDs.[36,37] Tissue concentrations of topical NSAIDs are high enough to produce anti-inflammatory effects, but systemic concentrations after application remain low.[36–38]

Theoretically, the risk of serious GI adverse events should be less than with oral NSAIDs, but long-term studies evaluating these events are lacking.[38] Studies comparing topical NSAIDs with other topical products, including counterirritants, are also needed.[35] Local cutaneous adverse reactions (e.g., erythema, pruritus, and irritation) occur in 1% to 2% of patients and may be due in part to the vehicle used.[38]

Local Anesthetics

Nonprescription topical anesthetics such as lidocaine and benzocaine are available in many types of products. Local anesthetics decrease discharges in superficial somatic nerves and cause numbness on the skin surface but do not penetrate deeper structures such as muscle where the pain often lies.

However, local anesthetics may be helpful when abrasion accompanies the injury.[39] Application of an over-the-counter antibiotic ointment containing an anesthetic may provide soothing relief, promote healing of abrasions, and prevent soft-tissue infection. Minor abrasions should be cleansed thoroughly with mild soap and water before application. More severe abrasions may require removal of debris or foreign bodies by a clinician followed by irrigation with normal saline.

Counterirritants

Counterirritants are categorized by the Food and Drug Administration (FDA) into four groups (groups A–D) based on their primary actions (Table 57–2). They produce a feeling of warmth, cooling, or irritation that diverts sensation from the primary source of pain. Because these irritant effects are central to the beneficial actions, counterirritants should not be combined with topical anesthetics or topical analgesics.

Counterirritants are approved for the temporary relief of minor aches and pains related to muscles and joints.[24] These symptoms may be associated with simple backache, arthritis, strains, sprains, or bruises. Many are available commercially as combination products with ingredients from different counterirritant groups. Active ingredients in marketed products sometimes change; clinicians should be aware of the current ingredients before providing a product recommendation.

TABLE 57–3. Patient Education for Counterirritants[24]

Apply up to 3 to 5 times daily to affected area.
Only use externally on the skin; do not ingest.
Do not apply to broken or damaged skin or cover large areas.
Wash hands immediately after application.
Avoid contact with the eyes and mouth.
Do not use with heating pads or other methods of heat application because burning or blistering may occur.
Do not wrap or bandage the area tightly after application.
Consult a physician if
- Symptoms worsen.
- Symptoms persist for more than 7 days.[a]
- Symptoms resolve but then recur.
- Intended for use in a child younger than age 2.

[a]Capsaicin may be used for chronic pain and must be applied consistently for efficacy.

❾ *Patient education on proper use of counterirritants is essential to therapeutic success* (Table 57–3).

Rubefacients (group A) are counterirritants that produce redness on application. Topical rubefacients containing salicylates (e.g., methyl salicylate and trolamine salicylate) are used most commonly. Turpentine oil is no longer judged as either safe or effective but remains in few products.[24] Clinical trial data evaluating the effect of rubefacients on acute pain from

TABLE 57–2. Nonprescription Counterirritant External Analgesics

Group and Effect	Agents and Concentration	Example Products	Comments
Group A			
Rubefacients: Produce redness	Allyl isothiocyanate 0.5–5%	Musterole Extra	Mustard derivative Pungent odor Avoid inhalation
	Ammonia water 1–2.5%	Made by dilution of concentrated solution with water	More concentrated solutions are highly caustic Avoid inhalation
	Methyl salicylate 10–60%	Analgesic Balm[a] BenGay Ultra Strength[a] Icy Hot Chill Stick[a]	Caution in aspirin sensitivity May produce systemic concentrations
	Trolamine salicylate 10–20%	Aspercreme	May increase INR with warfarin
		SportsCreme	Little odor unless in combination product
Group B			
Produce cooling	Camphor 3–11% Menthol 1.25–16%	JointFlex BenGay Patch Icy Hot Patch Mineral Ice	Medicinal odor Sensation of heat follows cooling Mild anesthetic effects at low concentrations
Group C			
Produce vasodilation	Methyl nicotinate 0.25–1%	ArthriCare Multiaction[b]	May produce systemic vasodilation
Group D			
Irritate without redness	Capsaicin 0.025–0.25%	Capzasin-P Zostrix	Must use regularly Burning effect subsides with regular use
	Capsicum oleoresin 0.025–0.25%	ArthriCare Multiaction[b]	

[a]Included in combination products that also contain menthol and/or camphor.
[b]Combination product with capsicum oleoresin, menthol, and methyl nicotinate.
INR, international normalized ratio.

strains, sprains, sports injuries, and chronic musculoskeletal pain are lacking.[40] A systematic review of available evidence concluded that topical salicylates may be effective for acute pain but have limited effectiveness in chronic pain.[40]

Application of topical salicylates can lead to systemic effects, especially if the product is applied liberally. Repeated application and occlusion with a wrap or bandage also can increase systemic concentrations.[41] Salicylate-containing counterirritants should be used with caution in patients in whom systemic salicylates are contraindicated, such as patients with severe asthma or aspirin allergy.[42] Topical salicylates have been reported to increase prothrombin time in patients on warfarin and should be used with caution in patients on oral anticoagulants.[43]

The group B counterirritants menthol and camphor exert a sensation of cooling through direct action on sensory nerve endings.[42,44] A sensation of warmth follows the cooling effect. The agents also have mild anesthetic activity at low concentrations.[44] In higher concentrations, they act as counterirritants and cause a burning sensation by stimulating cutaneous nociceptors. Menthol and camphor are used often in combination with rubefacients.

Menthol, also known as peppermint oil, is used widely in toothpastes, mouthwashes, gum, sore-throat lozenges, lip balms, and nasal decongestants. For topical analgesic use, it is available in creams, lotions, ointment, and patches. The patches can be trimmed to fit the affected area.

Menthol and camphor have caused respiratory distress in infants and should not be used in children under 2 years of age. Despite limits on the concentration of available products, camphor can be toxic to children even in small amounts.[45] Patients should be advised to keep the products out of the reach of children.

The group C counterirritants methyl nicotinate and histamine dihydrochloride produce vasodilation.[24] Methyl nicotinate is a nicotinic acid derivative that produces prostaglandin-mediated vasodilation.[46] NSAIDs and aspirin block the production of prostaglandins and decrease methyl nicotinate–induced vasodilation. Application over a large area has been reported to cause systemic symptoms and syncope, possibly due to vasodilation and a decrease in blood pressure.[47] Patients should be educated to apply only scant amounts to the affected area to avoid this effect.

The primary counterirritant in group D is capsaicin, a natural substance found in red chili peppers and responsible for the hot, spicy characteristic when used in foods.[32,33,48] Capsaicin stimulates the release of substance P from local sensory nerve fibers, depleting substance P stores over time. A period of reduced sensitivity to painful stimuli follows, and transmission of pain impulses to the central nervous system is reduced.[42]

As with other counterirritants, capsaicin and its derivatives (i.e., capsicum and capsicum oleoresin) exert a warming or burning sensation. With repeated application, desensitization occurs, and the burning sensation subsides. This typically occurs within the first 1 to 2 weeks. After discontinuation, resensitization occurs gradually and returns completely within a few weeks.[48]

Owing to the lag time between initiation and effect, capsaicin is not used for treatment of acute pain from injury. Instead, topical capsaicin is used for chronic pain from musculoskeletal and neuropathic disorders. Capsaicin preparations have been studied in the treatment of pain from diabetic neuropathy, osteoarthritis, rheumatoid arthritis, postherpetic neuralgia, and other disorders.[48] It is often used as an adjuvant to systemic analgesics in these chronic pain conditions.

While systemic adverse effects to capsaicin are rare, local adverse effects are expected and common.[48] Patient education regarding consistent use of capsaicin products is essential to achieving therapeutic outcomes. Product should be applied in a thin layer and rubbed into the skin thoroughly until little remains on the surface.[42] ⓫ *Patients using capsaicin should be advised to apply it regularly and consistently three to four times daily and that full effect may take 1 to 2 weeks or longer.* Patients should be assured that the burning effects will diminish with repeated application. Adherence to therapy is essential because the burning sensation may persist if applications are less frequent than recommended. Because the burning sensation may be enhanced with heat, patients should avoid hot showers or baths immediately before or after application. Wearing gloves during application can decrease the potential for unintended contact with eyes or mucous membranes.[41] Dried product residue has been reported to cause respiratory effects on inhalation,[48] and caution should be used in patients with asthma or other respiratory illnesses.

Muscle Relaxants

Where pain is worsened by muscle spasm, oral muscle relaxants may serve as a useful adjunct to therapy.[25] These agents include baclofen, metaxalone, methocarbamol, carisoprodol, and cyclobenzaprine. Muscle relaxants may decrease spasm and stiffness associated with either acute or chronic musculoskeletal disorders. These agents should be used with caution because they all may cause sedation, especially in combination with alcohol or narcotic analgesics.

Lifestyle and Behavioral Modifications

After treatment of the acute injury with RICE and pharmacologic therapy, the final phase of therapy is rehabilitation and prevention of future injury. For most injuries, prolonged immobilization can lengthen the recovery time by causing wasting of the healthy muscle fibers.[10,49] Rehabilitation starts with the development of range of motion via stretching exercises. Patient should warm the muscle first with light activity or moderate heat.[10] Warmth produces relaxation and increases elasticity. Next, the patient should start general strengthening exercises.[12,50] Resistance exercises using resistance bands available at sporting goods stores are an effective method of strengthening.[12] Strengthening exercises should be continued beyond the healing phase to prevent future injury.



Patient Encounter 1, Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH
- Asthma, well controlled with current medication regimen
- Allergic rhinitis

SH
Denies smoking. Drinks alcoholic beverages on most days.

Meds
- Fluticasone 220 mcg 1 puff twice daily
- Albuterol (salbutamol) 2 to 4 puffs four times daily as needed

Allergies: Aspirin (difficulty breathing)

Diagnostic Tests: Radiographs of left ankle show no evidence of fracture

- What are your treatment goals?
- What nonpharmacologic and pharmacologic treatments options are available?
- Are there treatment options that should be avoided? If so, which options and why?

After rehabilitation, the patient should be educated about behavior changes to prevent reinjury or the development of chronic pain.[3,23] The warm-up and strengthening routines learned in the rehabilitation phase should be continued. For overuse injury, correction of biomechanical abnormalities with proper footwear and changes in technique may correct misalignments and imbalances.[3] Repetitive trauma can be decreased with proper training (e.g., by implementing a gradual increase in mileage in a running plan).

Proper lifting techniques can decrease low-back pain.[7] Lifting methods include standing with legs shoulder-width apart, lifting with the legs and not the back, and keeping the object close to the body. In the workplace, repetitive motion can be decreased through proper ergonomic design and diversification of job tasks.[14] In pain of the lower extremity, weight loss in overweight or obese patients can assist in reduction of further inflammation and help to prevent reinjury or repetitive strain injuries.[21] Nonweight-bearing activities, such as swimming or bicycling, can be recommended for initial return to activity.[23]



Patient Encounter 1, Part 3: Creating a Care Plan

Based on the information presented, create a care plan to treat this patient's ankle injury. Your plan should include (1) the goals of therapy and desired outcomes, (2) a patient-specific therapeutic plan, including nonpharmacologic therapy, and (3) a plan to monitor the outcome of therapy to determine if goals of therapy have been met and adverse effects avoided.



Patient Encounter 2

A 40-year-old woman presents with right elbow pain. On questioning, you determine that she works in a factory performing repetitive tasks with her right arm. She reports the onset of pain as gradual over the last few months. When she wakes in the morning, she has minimal pain after rest, but the pain intensifies after a few hours at work. She tends to have less pain on the weekends. She reports decreased range of motion compared with the left side. She is a nonsmoker and does not drink. She has no significant past medical history or allergies. She takes no medications.

- Given this information, what is your assessment of the patient's elbow pain?
- What is the likely etiology of the pain?
- What nonpharmacologic and pharmacologic treatments options would be feasible?
- Based on the information presented, create a care plan for this patient's elbow injury. Your plan should include (1) the goals of therapy and desired outcomes, (2) a patient-specific therapeutic plan, including nonpharmacologic therapy, and (3) a monitoring plan to determine if goals of therapy have been met and adverse effects avoided.

OUTCOME EVALUATION

- Use a pain scale to monitor treatment interventions to ensure that pain relief is achieved. Ask the patient to rate pain on a scale of 0 (no pain) to 10 (worst possible pain) both at rest and with movement. Compare the results with baseline pain assessment to monitor the response to therapy. In pediatric patients, use a visual pain scale with facial expressions depicting various degrees of pain.
- Assess range of motion at baseline and after treatment by comparing movement with unaffected limb and functionality before the injury. Assess functionality by asking patients if they are able to perform activities of daily living or participate in exercise as desired.
- If pain from acute injury does not decrease greatly within 7 to 10 days, further diagnostic evaluation is warranted.
- For patients using capsaicin products, assess adherence to regular application for therapeutic benefit. Assess chronic pain control in 2 weeks.
- Assess medication adverse effects on a regular basis. When NSAIDs and aspirin are used, ask about GI tolerability. Inquire about local adverse effects, such as burning, when topical counterirritants are used for treatment.
- Evaluate adherence to preventative rehabilitation measures such as proper footwear, warm-up before activity, strength training, and proper lifting technique.



Patient Care and Monitoring

1. Assess the patient's symptoms to determine if empirical care is appropriate or whether diagnostic evaluation is warranted. Determine the timing of injury (if applicable), duration of pain, type and degree of pain, and exacerbating factors. Determine if the musculoskeletal disorder interferes with usual activities or range of motion.
2. Assess exacerbating or alleviating factors. Ask if the patient has tried any nonpharmacologic or pharmacologic treatments.
3. Obtain a complete medication history, including history of prescription drug, nonprescription drug, and dietary supplement use. Determine if the patient has used any successful or unsuccessful treatments for this condition in the past.
4. Gather patient history. Assess factors involved in drug selection. Inquire about social history and alcohol use. Ask the patient about drug allergies and chronic health problems such as asthma.
5. Educate the patient on nonpharmacologic therapy, including each of the steps in RICE (rest, ice, compression, and elevation). If injury is the source of the pain and it occurred more than 48 hours ago, consider heat instead of ice.
6. Assess patient preference for systemic (oral) or local (topical) therapy. Would frequent application of topical medications be possible? Would the patient accept topical medications with a medicinal odor?
7. Recommend appropriate pharmacologic therapy and educate on proper use. If a counterirritant is recommended, counsel patients on the irritant effect of the product and recommend washing hands immediately after use and to avoid heating pads. For patients using a capsaicin product, emphasize that adherence to regular application is required for effectiveness.
8. Develop a plan to assess effectiveness of pharmacologic therapy. If pain is from an acute injury, assess effectiveness within 7 to 10 days. For chronic pain treated with capsaicin, begin to assess pain control in 2 weeks.
9. Evaluate for adverse effects and drug interactions. For patients on topical therapy, evaluate for local adverse effects. For patients on acetaminophen or NSAIDs, inquire about alcohol use.
10. Stress lifestyle modifications for rehabilitation and prevention. Recommend strength training, range-of-motion exercises, and a warm-up period before exercise. In repetitive-motion injury, recommend methods to correct biomechanical abnormalities and vary work tasks as applicable. Refer to a physical therapist or sports trainer as needed.

ABBREVIATIONS

COX:	cyclooxygenase
PG:	prostaglandin
NSAIDs:	nonsteroidal anti-inflammatory drugs
GI:	gastrointestinal
INR:	international normalized ratio

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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58 Glaucoma

Mikael D. Jones



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Identify risk factors for the development of chronic open-angle glaucoma and acute angle-closure glaucoma.
2. Recommend a frequency for glaucoma screening based on patient-specific risk factors.
3. Compare and contrast the pathophysiologic mechanisms responsible for open-angle glaucoma and acute angle-closure glaucoma.
4. Compare and contrast the clinical presentation of chronic open-angle glaucoma and acute angle-closure glaucoma.
5. List the goals of treatment for patients with primary open-angle glaucoma suspect, primary open-angle glaucoma, and acute angle-closure glaucoma.
6. Choose the most appropriate therapy based on patient-specific data for open-angle glaucoma, glaucoma suspect, and acute angle-closure glaucoma.
7. Develop a monitoring plan for patients on specific pharmacologic regimens.
8. Counsel patients about glaucoma, drug therapy options, ophthalmic administration techniques, and the importance of adherence to the prescribed regimen.

Key Concepts

❶ Practitioners can play an important role in eye care by assessing patients for risk factors and referring to an ophthalmologist for appropriate screening and evaluation.

❷ Acute primary angle-closure glaucoma is a medical emergency and requires laser or surgical intervention.

❸ Patients with ocular hypertension or primary open-angle glaucoma typically have a slow, insidious loss of vision. This is contrasted by the course of acute primary angle-closure glaucoma which can lead to rapid vision loss that develops over hours to days.

❹ The goals of therapy are to prevent further loss of visual function; minimize adverse effects of therapy and its impact on the patient's vision, general health, and quality of life; control intraocular pressure in order to reduce or prevent further optic nerve damage; and educate and involve the patient in the management of their disease.

❺ Current therapy is directed at altering the flow of aqueous humor, which is the major determinant of intraocular pressure.

❻ Since primary open-angle glaucoma is a chronic, often asymptomatic condition, the decision of when and how to treat patients is difficult since the treatment modalities are often expensive and have potential adverse effects or complications; therefore the clinician should evaluate the potential effectiveness, toxicity, and the likelihood of patient adherence for each therapeutic modality.

❼ An initial target intraocular pressure should be set at 20% lower than the patient's baseline intraocular pressure. The target intraocular pressure can be set lower (30% to 50% of baseline intraocular pressure) for patients that already have severe disease or have normal-tension glaucoma.

❽ It is important to review the patient's medication history for potential drug-drug and drug-glaucoma interactions, adherence, presence of systemic and ocular adverse drug reactions, and ability to use ophthalmic preparations.

Glaucoma refers to a spectrum of ophthalmic disorders characterized by neuropathy of the optic nerve and loss of retinal ganglion cells which leads to permanent deterioration of the visual field and potentially total vision loss. Glaucoma can be classified as primary and secondary. Primary glaucoma refers to glaucoma that cannot be attributed to a preexisting ocular or systemic disease, while secondary glaucoma refers to glaucoma

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that can be attributed to preexisting ocular or systemic disease. Examples of primary glaucoma include open-angle, closed-angle, and congenital. Examples of secondary glaucoma include pigmentary glaucoma, neovascular glaucoma, traumatic glaucoma, and pseudoexfoliative glaucoma.

Primary open-angle glaucoma (POAG) is characterized by normal anterior chamber angles, glaucomatous changes of the optic disc, and peripheral visual field loss. Patients with elevated intraocular pressure (IOP) without glaucomatous changes are considered to have ocular hypertension. Patients with ocular hypertension that have normal-appearing anterior chamber angles and an eye exam suspicious of early glaucomatous damage are classified as primary open-angle glaucoma suspects**.** Primary angle-closure glaucoma (PACG) is the obstruction of the anterior angle by the iris, causing moderate to high elevations in IOP. POAG and PACG represent the most common types of glaucoma and therefore will be the focus of this chapter.

EPIDEMIOLOGY

Over 66.8 million people worldwide have glaucoma, making it the second leading cause of blindness worldwide.[1] In the United States it is estimated that 2.22 million people are affected by POAG, and by 2020 this number will increase to 3.36 million. The prevalence varies with race and ethnicity and it is 3 to 5 times more prevalent in African-Americans than Caucasians. The prevalence of POAG increases with age and is rarely seen in patients less than 40 years of age.[2–4]

The prevalence of PACG is lower than that of POAG and varies significantly by race and ethnicity. It is low in patients of European descent (0.09% to 0.16%) but higher in patients of Chinese (1.3%), Eskimo (2.9% to 5%), and Asian Indian (4.33%) descent. PACG is also more prevalent with increasing age and female gender.[5,6]

Risk Factors

Primary Open-Angle Glaucoma

❶ *Practitioners can play an important role in eye care by assessing patients for risk factors and referring to an eye care specialist for appropriate screening and evaluation.* Risk factor evaluation is essential in determining the frequency of comprehensive eye exams for patients (Table 58–1). It is also useful in making decisions regarding when to initiate therapy and determining the sequence of pharmacotherapeutic or surgical treatment modalities.[2]

The five primary risk factors associated with POAG are family history, age, race, central corneal thickness (CCT), and elevated IOP (Table 58–2). Patients who have first-degree relatives with POAG are at higher risk of developing glaucoma than patients with no family history of POAG. Even though IOP is no longer a diagnostic criterion, it is associated with an increased prevalence and progression of the disease.[2,4,5] Central corneal thickness has recently been recognized as a risk factor for POAG. For instance, in the Ocular Hypertension Study, patients with ocular hypertension and thinner CCT (less than 555 microns) had a greater risk of progressing to POAG.[2,7,8]

TABLE 58–1. Recommended Frequency of Comprehensive Adult Medical Eye Evaluation[34]

Age (years)	With Risk Factors for Glaucoma	No Known Risk Factors
Greater than or equal to 65	6–12 months	1–2 years
55–65	1–2 years	1–3 years
40–54	1–3 years	2–4 years
Under 40	2–4 years	5–10 years

Reproduced with permission from Ref. 34.

The five major risk factors identified for PACG are **hyperopia**, family history of PACG, age (greater than 30 years), gender, and Eskimo or Asian ethnicity. Patients that are hyperopic, female, or of Eskimo or Asian ethnicity tend to have more shallow anterior angles which predispose the eye to angle closure. Advancing age is associated with a decrease in the depth of the anterior angles, because the lens becomes thickened and is displaced towards the anterior portion of the eye. Patients who have first-degree relatives with glaucoma are at greater risk for developing PACG, with a prevalence of 1% to 12% for Caucasians.[5,6,9]

PATHOPHYSIOLOGY

The pathophysiologic alterations seen with POAG optic neuropathy are not fully understood. Elevated IOP is clearly associated with damage and eventual death of optic nerves; however, optic neuropathy can still occur in patients with normal IOP. Optic nerve degeneration in the absence of elevated IOP indicates the presence of independent factors that contribute to the death of the optic nerve. The key to understanding the pathophysiology and treatment of POAG relies on an understanding of aqueous humor dynamics and optic nerve anatomy and physiology.[4,5,10,11]

TABLE 58–2. Risk Factors for Glaucoma[2,9,34]

Primary Open-Angle Glaucoma	Primary Angle-Closure Glaucoma
Main Risk Factors • Elevated intraocular pressure • African or Hispanic descent • Family history of glaucoma • Older age • Thinner central corneal thickness	**Risk Factors** • Advancing age • Asian or Eskimo ethnicity • Female gender • Hyperopia • Shallow anterior chamber • Family history of angle-closure glaucoma
Possible Risk Factors • Systemic hypertension • Diabetes • Myopia • Low diastolic perfusion pressures	

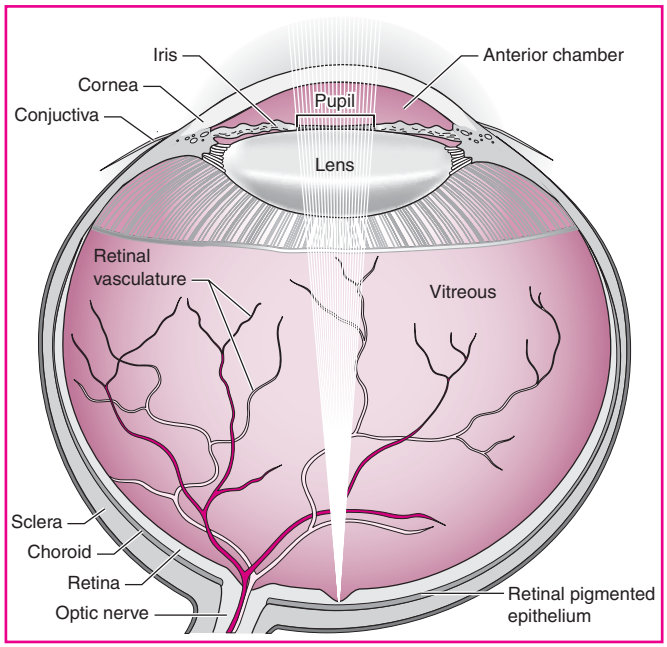


FIGURE 58–1. Anatomy of the eye. (From Lesar TS, Fiscella RG, Edward D. Glaucoma. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1714, with permission.)

Aqueous Humor

The eye is separated into two segments by the lens: the anterior segment and the posterior segment (Figs. 58–1 and 58–2) The anterior segment of the eye is separated by the iris into the posterior and anterior chambers. The ciliary body, a ring-like structure that surrounds and supports the lens, produces and secretes an optically neutral fluid called aqueous humor through the diffusion and ultrafiltration of plasma. The nonpigmented epithelium of the ciliary body secretes the aqueous humor into the posterior chamber. Aqueous humor formation can be modified pharmacologically through the α- and β-adrenoceptors, carbonic anhydrase, and sodium and potassium activated adenosine triphosphatase of the nonpigmented ciliary epithelium.

After the transport of aqueous humor into the posterior chamber, it flows through the pupil into the anterior chamber where it provides oxygen and nutrition to the avascular lens and cornea. Aqueous humor then exits the anterior chamber through the trabecular meshwork and drains into Schlemm's canal which drains aqueous humor into the episcleral venous system.

Eighty percent of aqueous humor drains through the trabecular meshwork, which is a lattice of connective tissue that surrounds the anterior chamber. The size of the trabecular meshwork can be altered by the contraction or the relaxation of the ciliary muscle. Stimulation of muscarinic receptors on the ciliary muscle causes contraction, which in turn causes the pores of the trabecular meshwork to open, increasing aqueous humor outflow.

A second pathway, uveoscleral outflow, comprises the other 20% of aqueous humor drainage. In the uveoscleral pathway, aqueous humor exits the anterior chamber through the iris root and through spaces in the ciliary muscles, which then drains into suprachoroidal space. Uveoscleral outflow can be pharmacologically modulated by adrenoceptors, prostanoid receptors, and prostamide receptors.[4,10,12–15]

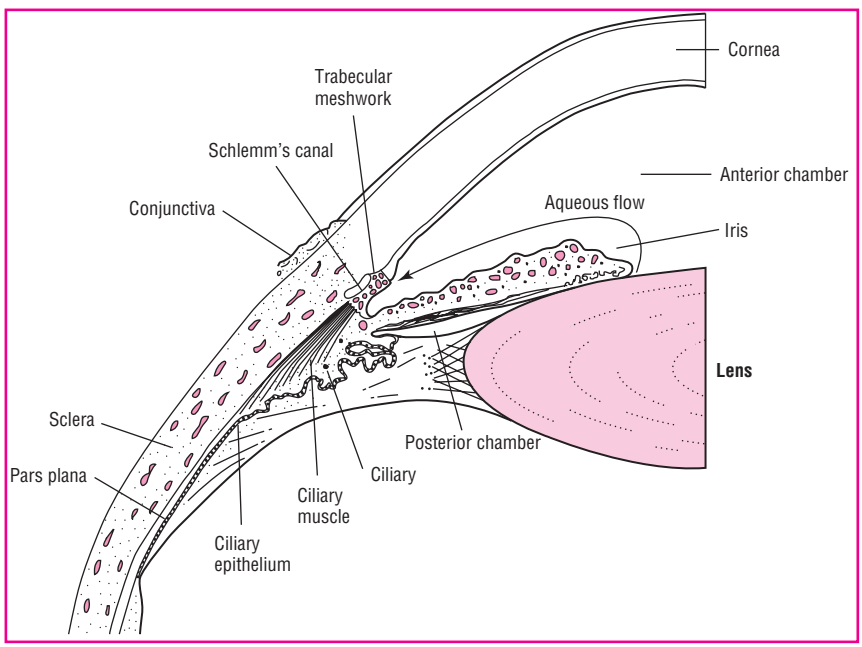


FIGURE 58–2. Anterior chamber of the eye and aqueous humor flow. (From Lesar TS, Fiscella RG, Edward D. Glaucoma. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1715, with permission.)

Intraocular Pressure

IOP is dependent upon the balance between aqueous humor production and outflow, and is important because the refractive properties of the eye depend on IOP to maintain the curvature of the cornea.[16] The distribution of IOP in the population is 10 to 21 mm Hg and is slightly skewed towards higher values; however, caution should be used in assigning this range as being "normal" for IOP since optic neuropathy can be present in the normal range and can be absent at higher IOPs. Elevated IOP is generally considered to be greater than 21 mm Hg. Optic nerve damage generally is slow and takes several years for noticeable progression between 20 and 30 mm Hg, while an IOP of 40 to 50 mm Hg may lead to rapid optic nerve damage. IOP varies in a cyclic fashion over the 24-hour day. IOP was thought to be lowest at night and at its maximum in the morning; however, more recent evidence suggests that not all individuals follow this pattern. Patients with and without glaucoma may exhibit a rhythm that consists of a peak in IOP right after falling asleep. Nighttime peaks in IOP are detrimental to patients with glaucoma, because systemic blood pressure decreases during the night, leading to a low ocular perfusion pressure. Decreased ocular perfusion pressure can lead to further optic nerve damage, therefore highlighting the importance of IOP control throughout the day.[11,17,18]

IOP is clinically measured by tonometry and can be performed via applanation, indentation, and indirect tonometry.[19] CCT affects the accuracy of IOP measurements. Thin corneas (less than 540 microns) can produce falsely low IOP readings, whereas thick corneas (greater than 555 microns) may produce falsely high readings. The potential consequences of this error in measurement may lead to overtreatment of patients with falsely high IOP and undertreatment of patients with falsely low IOP. The Ocular Hypertension Study demonstrated that CCT is a strong predictive factor for the development of POAG. Patients with corneas less than 555 microns and IOP greater than 25.75 mm Hg had a 36% risk of progressing from ocular hypertension to glaucoma. The CCT should be taken into account when evaluating a patient's IOP.[7] IOP is no longer used as a diagnostic criterion for glaucoma, since the presence of glaucomatous changes can be absent at high IOPs and can be present at lower IOPs. Ocular hypertension is present in about 3 to 6 million people in the United States population; however, less than 10% will have progression to POAG within 5 years.[7] Patients who have a baseline IOP of less than 21 mm Hg with no single measurement greater than 24 mm Hg and meet the criteria for POAG are considered to have normal-tension glaucoma (NTG). Fifteen to forty percent of patients diagnosed with POAG actually meet the criteria for NTG.[2,20]

Optic Nerve

The posterior segment of the eye contains vitreous humor (a clear jelly-like substance), the retina, the retinal vasculature, and the optic nerve head. The retina transforms light energy into neural signals, which are transmitted out of the eye by the retinal ganglion cells. The axons of the retinal ganglion cells converge and exit at the optic nerve head (optic disc) to form the optic nerve (Fig. 58–3). The optic nerve contains one million nerve fibers and synapses at the lateral **geniculate nucleus** of the brain. The optic nerve head is the portion of the optic nerve that is susceptible to elevations in IOP and is visible on funduscopic examination. The optic nerve head is vertically oval and pale yellow with a depression in the center of the optic nerve, called a physiologic cup, which is formed by convergence of the axons. The area surrounding the optic nerve head is the nerve fiber layer, which consists of converging retinal ganglion cell axons. The nutrition of the retina is dependent upon the transport of trophic factors from the retinal cell ganglion axons to their cell bodies.

Glaucomatous changes to the optic nerve head precede visual field loss, making optic nerve head evaluation a useful screening and prognostic tool. The optic nerve head should be assessed for cupping, nerve fiber layer changes, and the presence of splinter hemorrhages using a **slitlamp biomicroscope**. Cupping refers to an increase in the size of the physiologic cup. The cup increases with the loss of retinal ganglion cell axons and the collapse the **lamina cribrosa**. The cup size is expressed as the ratio of the size of the cup to the size of the optic nerve head. A cup-to-disc ratio greater than 0.55 is associated with an increased risk of developing visual field loss. Other findings include atrophy and notching of the nerve fiber layer.[4,5,21,22] The pathophysiology of glaucomatous neurodegeneration has not been completely elucidated. It is unclear whether the optic neuropathy is caused by increased IOP, decreased retinal blood flow, or a combination of these factors.[4,5] Several theories, including autoimmune reactions, excess nitric oxide, and glutamate toxicity have been proposed as to what ultimately causes the retinal ganglion cells to undergo apoptosis.[4,5,23]

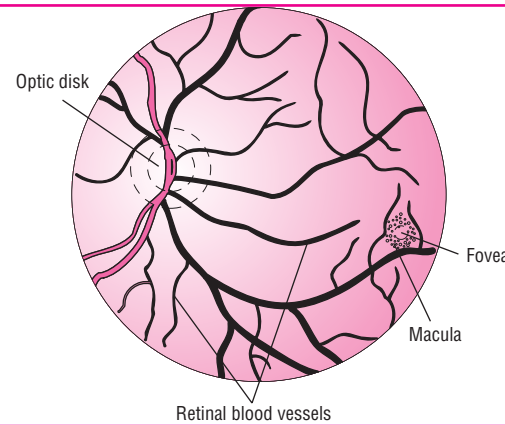


FIGURE 58–3. Normal fundus of the eye and optic disk and cup. (From Lesar TS, Fiscella RG, Edward D. Glaucoma. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1715, with permission.)

The level of IOP is related to the death of retinal ganglion cell and optic nerve fibers. As optic neurodegeneration progresses over time, the optic nerve becomes more susceptible to high IOP. Increased IOP causes the retinal ganglion cell axons to undergo mechanical stress, alters axonal protein transport, and decreases blood supply to the retina and the optic nerve, leading to tissue ischemia.[4,22,24] Glaucomatous optic neuropathy may also occur independent of increased IOP as illustrated by the fact that 15% to 40% of patients with POAG meet criteria for NTG and 25% to 38% of patients will have progression of their POAG despite control of IOP. Pressure-independent causes of optic neuropathy include abnormal blood flow, systemic hypotension, and abnormal blood coagulability.[11,19] Current glaucoma therapies fail to target IOP-independent glaucoma pathophysiologic factors. However, IOP reduction may still be beneficial, as the rate of visual field progression is decreased in some patients that receive IOP reduction via medical or surgical modalities.[25,26]

Pathophysiology of Angle-Closure Glaucoma

PACG involves a mechanical obstruction of aqueous humor outflow through the trabecular meshwork by the peripheral iris. Two major mechanisms of trabecular meshwork obstruction by the peripheral iris include pupillary block and an abnormality of the iris called iris plateau. Pupillary block is the more common mechanism of obstruction and results from a complete or functional apposition of the central iris to the anterior lens and is associated with mid-dilation. The trapped aqueous humor increases pressure behind the iris causing the peripheral iris to bow forward and obstruct the trabecular meshwork. Plateau iris refers to an anterior displacement of the peripheral iris caused by anteriorly positioned ciliary processes. In this configuration the peripheral iris bunches as the eye dilates. Both of these mechanisms result in the occlusion of aqueous humor outflow, causing IOP elevation at extreme levels that can lead to vision loss in hours to days.[5,9,21,27,28] The degree of obstruction or angle closure can be determined by **gonioscopy**.

The development of PACG is associated with several anatomic risk factors that lead to shallow anterior chambers. PACG patients may have a thick, anteriorly displaced lens that results from myopia or old age. The axial length of the eye is smaller in individuals with PACG, which leads to a lens that is situated more anteriorly than those without PACG.[27,28]

Medications with anticholinergic properties induce mydriasis, which can lead to angle closure in pupillary block and plateau iris. Pupillary block may also be induced by drugs that cause miosis.[12]

PACG can be separated into three categories: acute primary angle closure, subacute primary angle closure, and chronic primary angle closure. Acute PACG is the sudden obstruction of the trabecular meshwork which leads to rapid increases in IOP resulting in pressure-induced optic neuropathy if left untreated. ❷ *Acute PACG is a medical emergency and requires laser or surgical intervention.* Subacute PACG is characterized by self-limiting angle closure that resolves spontaneously. Recurrent attacks or a prolonged acute attack can lead to the development of peripheral anterior **synechia**. Chronic PACG is characterized by the presence of peripheral anterior synechia that partially obstruct the flow of aqueous humor through the trabecular meshwork resulting in an elevated IOP that is similar to what it is seen in POAG.[9,27,28]

Clinical Course

❸ *Patients with ocular hypertension or POAG typically have a slow, insidious loss of vision. This is contrasted by the course of acute PACG which can lead to rapid vision loss that develops over hours to days.* For POAG, only 4% to 8% of patients may progress to legal blindness. It may take 13 to 16 years for a patient to go blind from glaucoma. A patient's quality of life may not be affected until significant visual field loss is present and the



Clinical Presentation of Primary Open-Angle Glaucoma

General
- Adult onset (usually greater than 40 years of age).
- Patients may be unaware they have glaucoma and may be diagnosed during routine eye evaluation.
- POAG is usually bilateral with asymmetric disease progression.

Symptoms
- Patients with severe disease progression may report loss of peripheral vision and may describe the presence of scotomata (blind spots) in their field of vision.

Signs

Ophthalmoscopic examination may reveal:

- Optic nerve head (optic disc) cupping.
- Large cup-to-disc ratio.
- Diffuse thinning, focal narrowing, or notching of the optic nerve head rim.
- Splinter hemorrhages.
- Optic nerve head and nerve fiber layer changes occur before visual field changes can be detected.

Diagnostic Tests
- Gonioscopy: anterior chamber angles are open.
- Applanation tonometry: elevated IOP (greater than 21 mm Hg) may be present; however, a patient can have signs of optic neuropathy without elevated IOP.
- Pachymetry: measures central corneal thickness; thin corneas (less than 540 microns) are considered a glaucoma risk factor.
- Automated static threshold perimetry: evaluates visual fields; useful in diagnosis and determining if there is disease progression.
- Other diagnostic tests: scanning laser polarimetry, confocal scanning laser ophthalmoscopy, and optical coherence tomography.



Clinical Presentation of Acute Angle-Closure Glaucoma

General
- Medical emergency due to high risk of vision loss.
- Unilateral in presentation, but the fellow eye is at risk.

Symptoms
- Ocular pain.
- Red eye.
- Blurry vision.
- Halos around lights.
- Systemic symptoms may develop:
  1. Nausea and vomiting.
  2. Abdominal pain.
  3. Headache.
  4. Diaphoresis.

Signs
- Cloudy cornea caused by corneal edema.
- Conjunctival hyperemia.
- Pupil semi-dilated and fixed to light.
- Eye will be harder on palpation through closed eyelid.

Diagnostic Tests
- Gonioscopy: anterior chamber angles will be closed; peripheral anterior synechiae may be present.
- Applanation tonometry: elevated IOP (greater than 21 mm Hg, but when symptoms are present IOP may be greater than 30 mm Hg).
- Slitlamp biomicroscopy: reveals shallow anterior chamber depth; signs of previous attacks include peripheral anterior synechiae, iris atrophy, glaukomflecken, and pupillary dysfunction.

patient can no longer perform the activities of daily living.[29] Vision loss does not occur until there has been significant loss of the retinal ganglion cells. Peripheral vision is the most susceptible to glaucomatous damage, with central vision being preserved until advanced disease progression has occurred. Visual field abnormalities include **paracentral scotoma**, **nasal scotoma**, and **arcuate scotoma**. Patients may also have problems with depth perception and contrast sensitivity. Peripheral vision may worsen until the patient has tunnel vision and ultimately total field loss. Visual fields can be measured by **perimetry** and can detect defects in the visual field before a patient may notice.[4,5,12]

TREATMENT

Primary Open-Angle Glaucoma

Desired Outcomes and Goals

❹ *The goals of therapy are to prevent further loss of visual function; minimize adverse effects of therapy and its impact on the patient's vision, general health, and quality of life; maintain IOP at or below a pressure at which further optic nerve damage is unlikely to occur; and educate and involve the patient in the management of their disease.* ❺ *Current therapy is directed at altering the flow of aqueous humor, which is the major determinant of IOP.*

General Approach

❻ *Since POAG is a chronic, often asymptomatic condition, the decision of when and how to treat patients is difficult since the treatment modalities are often expensive and have potential adverse effects or complications. The clinician should evaluate the potential effectiveness, toxicity, and the likelihood of patient adherence for each therapeutic modality. The ideal therapeutic regimen should have maximal effectiveness and patient tolerance to achieve the desired therapeutic response.* The American Academy of Ophthalmology (AAO) publishes Preferred Practice Patterns for POAG and POAG Suspect.[2]

Prior to the selection of a therapeutic modality, the target IOP should be determined for each patient. The target IOP ideally represents an IOP range that will slow the progression of optic neuropathy, not simply obtaining an IOP in the range of 10 to 21 mm Hg. Currently, the initial target IOP is an estimate, but it should be modified based on the progression of the disease at each follow-up visit. ❼ *The AAO recommends an initial target IOP to be set at 20% lower than the patient's baseline IOP. The target IOP can be set lower (30% to 50% of baseline IOP) for patients that already have severe disease or have normal-tension glaucoma.*[2,25,26]

Initial IOP control can be achieved by medical, laser, surgical, or a combination of these therapies. The AAO guidelines do not provide a specific recommendation on which therapeutic modality should be selected first, but patients in the early stages of glaucoma should receive treatment. The Early Manifest Glaucoma Trial evaluated the effectiveness of reducing IOP in early untreated POAG. The trial demonstrated that patients who received a topical medication combined with laser therapy had slower progression of glaucoma by an average of 18 months.[30] Initial therapy with laser trabeculoplasty is at least as effective as treatment with a topical β-adrenergic antagonist in preserving visual function and optic nerve head status and can be considered as initial treatment.[2] Even though initial treatment of POAG with surgical trabeculectomy compared to medical therapy has similar visual field outcomes at 5 years, surgical intervention is associated with more eye discomfort and increased risk of cataract development.[20,25,26] Surgical therapy is typically not considered as a first-line therapy.[4] Medical treatment is the most commonly selected therapeutic modality. A well-tolerated ocular antihypertensive at the lowest concentration should be selected as the initial mediation (Table 58–3). If monotherapy alone lowers IOP but does not reach target pressure, then combination therapy or switching to another agent is appropriate. Increasing the concentration or dose frequency can also be tried when possible (Figure 58–4). A uniocular trial can be used to assess the safety and effectiveness of a topical medication prior

TABLE 58–3. Topical Drugs Used in the Treatment of Open-Angle Glaucoma

Drug	Pharmacologic Properties	Common Brand Names	Dose Form	Strength (%)	Usual Dose[a]	Mechanism of Action
β-Adrenergic Blocking Agents						
Betaxolol	Relative β_1-selective	Generic	Solution	0.5	1 drop twice a day	All reduce aqueous production of ciliary body
		Betoptic-S	Suspension	0.25	1 drop twice a day	
Carteolol	Nonselective, ISA	Generic	Solution	1	1 drop twice a day	
Levobunolol	Nonselective	Betagan	Solution	0.25, 0.5	1 drop twice a day	
Metipranolol	Nonselective	OptiPranolol	Solution	0.3	1 drop twice a day	
Timolol	Nonselective	Timoptic, Betimol	Solution	0.25, 0.5	1 drop every day—one to two times a day	
		Timoptic-XE	Gelling solution	0.25, 0.5	1 drop every day[a]	
Nonspecific Adrenergic Agonists						
Dipivefrin	Prodrug	Propine	Solution	0.1	1 drop twice a day	Increased aqueous humor outflow
α_2-Adrenergic Agonists						
Apraclonidine	Specific α_2-agonists	Iopidine	Solution	0.5, 1	1 drop two to three times a day	Both reduce aqueous humor production; brimonidine known to also increase uveoscleral outflow
Brimonidine		Alphagan P	Solution	0.15, 0.1	1 drop two to three times a day	
Cholinergic Agonists Direct-Acting						
Carbachol	Irreversible	Carboptic, Isopto Carbachol	Solution	0.75, 1.5, 2.25, 3	1 drop two to three times a day	All increase aqueous humor outflow through trabecular meshwork
Pilocarpine	Irreversible	Isopto Carpine, Pilocar	Solution	0.25, 0.5, 1, 2, 4, 6, 8, 10	1 drop two to three times a day 1 drop four times a day	
		Pilopine HS	Gel	4	Every 24 hours at bedtime	
Cholinesterase Inhibitors						
Echothiophate		Phospholine iodide	Solution	0.125	Once or twice a day	
Carbonic Anhydrase Inhibitors						
Topical						
Brinzolamide	Carbonic anhydrase type II inhibition	Azopt	Suspension	1	Two to three times a day	All reduce aqueous humor production of ciliary body
Dorzolamide		Trusopt	Solution	2	Two to three times a day	
Systemic						
Acetazolamide		Generic	Tablet	125 mg, 250 mg	125–250 mg two to four times a day	
			Injection	500 mg/vial	250–500 mg	
		Diamox Sequels	Capsule	500 mg	500 mg twice a day	
Dichlorphenamide		Daranide	Tablet	50 mg	25–50 mg one to three times a day	
Methazolamide		Generic	Tablet	25 mg, 50 mg	25–50 mg two to three times a day	

(*Continued*)

TABLE 58–3. Topical Drugs Used in the Treatment of Open-Angle Glaucoma (*Continued*)

Drug	Pharmacologic Properties	Common Brand Names	Dose Form	Strength (%)	Usual Dose[a]	Mechanism of Action
Prostaglandin Analogs						
Latanoprost	Prostaglandin $F_{2\alpha}$ analog	Xalatan	Solution	0.005	1 drop every night	Increases aqueous uveoscleral outflow and to a lesser extent trabecular outflow
Bimatoprost	Prostamide analog	Lumigan	Solution	0.03	1 drop every night	
Travoprost		Travatan	Solution	0.004	1 drop every night	
Combinations						
Timolol-dorzolamide		Cosopt	Solution	Timolol 0.5% Dorzolamide 2%	1 drop twice daily	

[a]Use of nasolacrimal occlusion will increase the number of patients successfully treated with longer dosage intervals.
ISA, intrinsic sympathomimetic activity.
From Lesar TS, Fiscella RG, Edward D. Glaucoma. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1722, with permission.

to initiation in both eyes; however, uniocular drug trials do not predict the IOP response of the second eye, and the effect of a medication must be assessed independently using baseline IOP measurements. The lack of correlation between IOP of fellow eyes may be explained by asymmetric IOP in each eye or the potential for contralateral IOP lowering of a uniocularly applied medication.[31,32]

Treatment Considerations for the Treatment of Ocular Hypertension

POAG suspects should be considered for topical medication therapy if they can be expected to develop optic nerve damage or they may already have early glaucomatous nerve damage that cannot be reliably diagnosed because of inconclusive exam findings. The Ocular Hypertension Treatment Study demonstrated that a 20% decrease in IOP can reduce the progression from ocular hypertension to POAG over a 5-year period. The incidence of progression to POAG in the treatment (4.4%) and control (9.5%) groups was small, which underscores the importance of selecting patients at high-risk of progressing to POAG.[33] When medical therapy is indicated, a well-tolerated agent should be selected and optimized following the POAG algorithm (Fig. 58–4). The risk-to-benefit ratio of therapy should be reassessed in patients that may require third- or fourth-line agents to control IOP. Surgical or laser intervention are rarely indicated in the treatment of glaucoma suspects.[34]

Nonpharmacologic Therapy

Laser trabeculoplasty uses laser energy aimed at the trabecular meshwork to improve the outflow of aqueous humor and can be used as first-line therapy, especially in patients unable or unwilling to adhere to medical therapy. Laser trabeculoplasty may be used as bridge therapy between medical and surgical intervention, and approximately 50% of laser trabeculoplasty procedures will fail at 10 years. Trabeculectomy is the removal of a portion of the trabecular meshwork to improve aqueous humor outflow. Failure rates of trabeculectomy are less compared to laser trabeculoplasty (20% to 30% failure at 10 years). The most common reason for trabeculectomy failure is scarring of the channel created by the partial removal of the trabecular meshwork. Mitomycin C and fluorouracil are used as antifibrotic agents to decrease scarring at the site of trabeculectomy; however, patients undergoing trabeculectomy are also at increased risk of developing cataracts.[2,4,35]

Ethnicity should be considered with respect to the sequence of surgical or laser therapy in patients that fail maximal medical therapy. The Advanced Glaucoma Intervention Study found that African-Americans who have failed medical therapy had better long-term visual function outcomes if they received argon laser trabeculoplasty, while Caucasians had better long-term visual function outcomes if they received surgical trabeculectomy.[35] Other surgical procedures include cyclodestructive and non-penetrating glaucoma surgery. Patients should be educated about the risks and benefits of laser and surgical intervention. Patients should understand that they may require additional procedures or medical therapy to main long-term IOP control.[2,4]

Primary Angle-Closure Glaucoma

Desired Outcomes and Goals

Therapeutic modalities for PACG are targeted at decreasing IOP. The goals of therapy are to preserve visual function by controlling the elevation in IOP, manage an acute attack of angle closure, reverse or prevent angle closure using a laser and/or surgical intervention, and educate and involve the patient in the management of the disease.[9]

General Approach

The treatment of choice for PACG is laser iridotomy. Medical therapy is used to lower IOP, reduce pain, and reverse corneal edema prior to the iridotomy. IOP should first be lowered

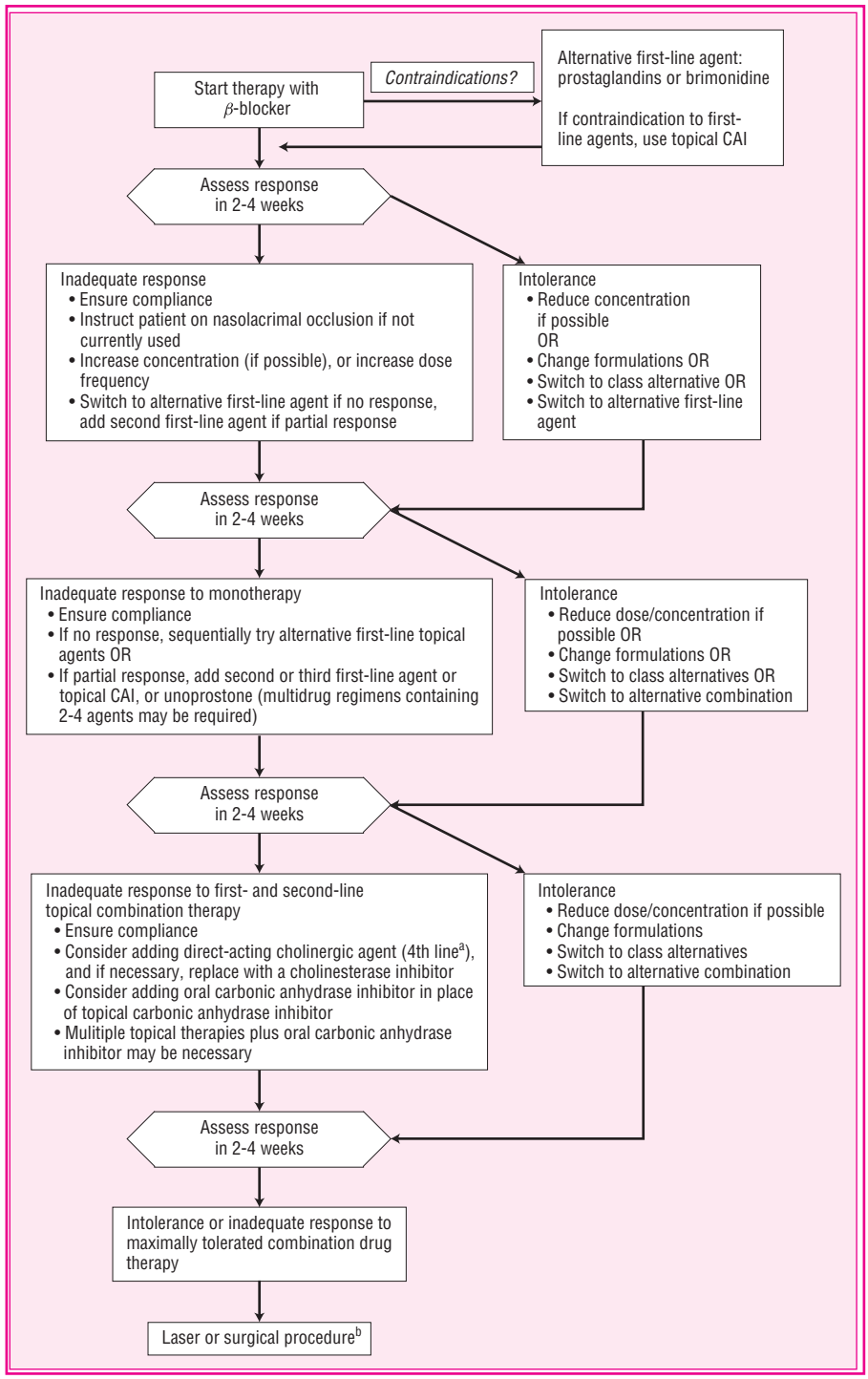


FIGURE 58–4. Algorithm for the pharmacotherapy of open-angle glaucoma.
[a]Fourth-line agents not commonly used any longer.
[b]Most clinicians believe laser procedure should be performed earlier (e.g., after three-drug maximum, poorly adherent patient).
CAI, carbonic anhydrase inhibitor. (From Lesar TS, Fiscella RG, Edward D. Glaucoma. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1720, with permission.)

with topical β-blockers, topical α-agonists, prostaglandin $F_{2\alpha}$ analogs, systemic carbonic anhydrase inhibitors, or hyperosmotic agents. Once the IOP has been controlled, miotics (i.e., pilocarpine) can be used to break the pupillary block. A topical IOP-lowering agent should be continued to control IOP until laser iridotomy can be performed. Corneal indentation with a cotton-tipped applicator or gonioscopic lens may break pupillary block. If laser iridotomy cannot be performed, incisional iridectomy is used. A topical corticosteroid may be employed to decrease inflammation. The fellow eye is at high risk of having an acute attack and should receive prophylactic iridotomy. Patients with chronic angle closure should also receive laser iridotomy. Acute and chronic angle-closure patients may require chronic medical therapy if the patient has PACG superimposed on preexisting POAG, or synechia formation causes continued increases in IOP.[5,36]

Nonpharmacologic Therapy

Laser iridotomy uses laser energy to cut a hole in the iris to alleviate the aqueous humor build-up behind the iris, resulting in reversal of appositional angle closure. Incisional iridectomy is the surgical removal of a small portion of the iris to allow drainage of aqueous humor trapped in the posterior chamber. Surgical iridectomy is reserved for when laser iridotomy is not possible or indicated.[5,9,36]

Pharmacologic Therapy

Beta-Adrenergic Antagonists

Topical β-adrenergic antagonists (β-blockers) are generally considered first-line agents for the treatment of POAG unless contraindications are present.[10,13] Topical β-blockers decrease IOP by reducing the formation of aqueous humor made by the ciliary body, which results in a 20% to 35% reduction in IOP.[10,13,37] Timolol, levobunolol, metipranolol, and carteolol are non-selective for β_1- and β_2-adrenergic receptors, while betaxolol has β_1-selective properties. All of the topical β-blockers have similar efficacy and adverse-effect profiles. Betaxolol reduces IOP to a lesser extent than the non-selective β-blockers, but may cause less exacerbation of pulmonary disease. Despite the intrinsic sympathomimetic activity demonstrated by carteolol, this does not translate into a clinically significant decrease in pulmonary or cardiovascular adverse effects.

Topical β-blockers are typically administered twice daily. A gel-forming solution of timolol (Timoptic-XE) can be administered once daily. Tachyphylaxis may occur in 20% to 50% of patients on monotherapy with a β-blocker, resulting in the need for a different agent or combination therapy. Patients on concurrent systemic β-blockers may experience less IOP reduction than patients only on topical β-blockers.[10,38]

Ocular medication requires the use of concentrated drug solutions to penetrate the eye. Excess drug drains into the nose via the nasolacrimal duct where it is absorbed into the systemic circulation. β-Blockers can cause significant systemic adverse effects through this pathway, since first-pass hepatic metabolism is bypassed, resulting in pharmacologically significant serum drug concentrations.[39] Bronchospasm is the most common pulmonary effect of topical β-blockers. Pulmonary edema, status asthmaticus, and respiratory arrest have been reported with β-blockers as well. Cardiovascular effects include bradycardia, hypotension, and congestive heart failure exacerbation. As with systemic β-blockers, topical β-blockers have also been reported to cause depression, hyperlipidemia, and mask symptoms of hypoglycemia. Topical β-blockers are generally contraindicated in patients with asthma, chronic obstructive pulmonary disease, sinus bradycardia, second- or third-degree heart block, cardiac failure, and hypersensitivity to the product.[10,23,39–41]

Local side effects are usually tolerable and may be caused by preservatives, therefore switching from one product to another may alleviate the local side effects. Stinging of the eyes upon instillation is the most common adverse effect. Other local adverse effects include conjunctivitis, keratitis, dry eyes, and **uveitis**.[10,13]

Patients prescribed topical β-blockers should be counseled on the nasolacrimal occlusion technique to decrease systemic absorption.

Ocular Hypotensive Lipids

The ocular hypotensive lipids in typical ophthalmology practice are considered first-line alternatives to topical β-blockers because of their superior efficacy and safety profiles. Many clinicians may choose to use the ocular hypotensive lipids as first-line agents, especially in patients that have an initial requirement to lower IOP by more than 25%, or in patients that have relative or absolute contraindications to topical β-blockers. However, latanoprost is currently the only ocular hypotensive lipid drug that has a Food and Drug Administration (FDA) indication for first-line therapy. Bimatoprost and travoprost are indicated by the FDA for patients who are intolerant of other IOP-lowering therapy or insufficiently responsive to another IOP-lowering medication.[10,38]

Latanoprost and travoprost are analogs of prostaglandin $F_{2\alpha}$ and are agonists of the prostanoid FP receptor, which appears to lower IOP by increasing aqueous humor outflow through the uveoscleral pathway. Bimatoprost is a prostamide analog and appears to lower IOP by activating prostamide receptors in the uveoscleral pathway and possibly through increasing outflow through the trabecular meshwork. The exact mechanism is still unclear of how uveoscleral outflow is increased, but stimulation of prostanoid FP receptors and prostamide receptors in the ciliary body cause remodeling of the extracelluar matrix, making it more permeable to aqueous humor, thus increasing aqueous humor outflow through the ciliary muscles.[14,15,42]

Latanoprost, travoprost, and bimatoprost are administered once daily at bedtime and should not be increased to twice daily, as this may decrease effectiveness. These agents lower IOP by 25% to 35% and unlike topical β-blockers, can effectively lower nocturnal IOP, providing IOP control throughout the day and night. The prostaglandin analogs can be used as monotherapy or combination therapy.[10,38] For patients who are non-responsive to latanoprost, switching to brimatoprost may allow some patients to reach their IOP goal, presumably because of the proposed difference in the site of action of each drug.[43,44]

The ocular hypotensive lipids are well tolerated and rarely cause systemic side effects (though headache has been reported). Local effects include conjunctival hyperemia, stinging on instillation, an increase in iris pigmentation, **hypertrichosis**, and darkening of the eyelashes. Increases in iris pigmentation occur most commonly in patients with multi-colored irides on long-term prostaglandin analog therapy. The mechanism of this effect is by its action on melanocytes of the iris, in which the irides become darker because of increased production of melanin in the iris.[45,46] The 12-month incidence of iris pigmentation varies between the agents. Latanoprost appears have the highest incidence of iris pigmentation after 12 months of therapy (5.2% to 25%) compared to travoprost (3.1%) and bimatoprost (1% to 5.5%).[47–52] The increase in pigmentation may be irreversible or may reverse at a very slow rate. Increased iris pigmentation

appears to be only a cosmetic effect, but may affect product selection, especially when choosing monocular therapy. Conjunctival hyperemia or engorgement of conjunctival blood vessels is a common adverse effect caused by a vasodilatory effect on scleral blood vessels. It is most prominent early in therapy and usually subsides over time. While generally a benign adverse effect, patients may have a concern if it affects their cosmetic appearance. Latanoprost has the lowest incidence of hyperemia (14% to 27.6%) compared to bimatoprost (9% to 46%) and travoprost (49.5%).[47–52] The ocular hypotensive lipids should be used with caution in some patients, since they may worsen anterior uveitis and herpetic keratitis. Cystoid macular edema has been reported during treatment with the ocular hypotensive lipids, therefore use caution in patients with intraocular inflammation, **aphakic** patients, **pseudophakic** patients with a torn posterior lens capsule, or in patients with risk factors for macular edema.[10,38]

Patients prescribed ocular hypotensive lipids should be counseled on potential adverse effects and appropriate administration. Patients receiving latanopost therapy should be instructed to refrigerate the dropper bottle until opened. After the bottle has been opened it can be stored at room temperature for 6 weeks.

Alpha$_2$-Adrenergic Agonists

Brimonidine and apraclonidine are α_2-adrenergic agonists that decrease IOP by reducing aqueous humor production. Brimonidine has a higher selectivity to the α_2 receptor than apraclonidine and has a dual mechanism of action by increasing uveosceral outflow.[10,14] Brimonidine may have neuroprotective effects that are being studied in the Low-Pressure Glaucoma Treatment Study.[53] Apraclonidine is often used for the prevention and treatment of post-surgical IOP elevations and no longer commonly used for long-term treatment of POAG because of tachyphylaxis and a high rate of blepharoconjunctivitis. Brimonidine lowers IOP by 14% to 28%. Peak IOP-lowering effect is similar to that of timolol, but the trough IOP-lowering effect is less than with timolol. Brimonidine is usually administered every 8 hours. A 12-hour dosing schedule may be employed by using nasolacrimal occlusion when instilling the drops. Brimonidine-purite 0.1% and 0.15% solution (Alphagan P®) has similar efficacy compared to the brimondine 0.2% solution, because the purite solution's higher pH allows for more drug to penetrate the cornea.[10,13,14]

Apraclonidine and brimonidine cause both local and systemic effects. Local effects of apraclonidine include blepharoconjunctivitis, foreign body sensation, pupillary mydrasis, and eyelid retraction. Brimonidine does not cause the α_1-mediated mydrasis and eyelid retraction, but does cause blepharoconjunctivitis, though at a lesser rate than apraclonidine. The brimonidine-purite solution has a lower incidence of ocular allergy. Systemic effects of both agents include headache, dry mouth, and fatigue.

Brimonidine is typically used as an adjunctive agent in combination with other agents but could be used as a first-line agent as well. The frequency of dosing and local adverse effects may lead to non-adherence in some patients. Patients prescribed brimonidine should be counseled on the nasolacrimal occlusion technique to reduce systemic adverse effects and to improve efficacy.[10,13]

Carbonic Anhydrase Inhibitors

Carbonic anhydrase inhibitors decrease aqueous humor production by inhibition of the carbonic anhydrase isoenzyme II located in the ciliary body. In the eye, carbonic anhydrase catalyzes the conversion of water and carbon dioxide to bicarbonate and hydrogen ion, which is a significant step in aqueous humor production. Carbonic anhydrase inhibitors are available in systemic and topical preparations.[10,13,14]

Topical Carbonic Anhydrase Inhibitors

Dorzolamide and brinzolamide are the only topical carbonic anhydrase inhibitors available and lower IOP by 15% to 24%. Both medications are administered every 8 hours and are used as adjunctive therapy or as monotherapy for patients that cannot tolerate first-line agents. Nasolacrimal occlusion may allow for dosing every 12 hours.[10,13] Recently the European Glaucoma Prevention study found that dorzolamide did not prevent the progression of patients with ocular hypertension to POAG despite a 15% to 22% reduction of IOP over 5 years. Unlike the Ocular Hypertension Treatment Study, a goal IOP reduction of at least 20% was not required for treatment, and surprisingly, the placebo treatment had a clinically significant effect on IOP.[54]

Local side effects include burning, stinging, itching, foreign body sensation, dry eyes, and conjunctivitis. Brinzolamide may have a lower incidence of these side effects since the drug is in a neutral pH solution. Dorzolamide has been reported to cause irreversible corneal decompensation. Taste abnormalities have been reported with each agent. Both topical carbonic anhydrase inhibitors are sulfonamides and are contraindicated in patients with history of sulfonamide hypersensitivity.[10,13]

A combination product of timolol (0.5%) and dorzolamide (2%) (Cosopt™) is available and can be administered twice daily and provides an additive reduction in IOP.

Systemic Carbonic Anhydrase Inhibitors

There are three systemic carbonic anhydrase inhibitors: acetazolamide, dichlorphenamide, and methazolamide. These agents effectively lower IOP by 20% to 30% but are reserved as third-line agents because of their significant adverse effects. They are typically used as bridge therapy from maximal medical therapy to laser or surgical intervention. The systemic carbonic anhydrase inhibitors can also be used to lower IOP in acute angle-closure glaucoma. Acetazolamide has an intravenous formulation that can be utilized in patients having nausea due to the angle-closure attack. Acetazolamide and methazolamide are the best tolerated of the three agents.

The systemic carbonic anhydrase inhibitors are associated with significant adverse effects which include paresthesias of the hands and feet, nausea, vomiting, and weight loss. Patients

can develop systemic acidosis, hypokalemia, hyponatremia, and nephrolithiasis due to the inhibition of renal carbonic anhydrase. Sulfonamide allergy, renal failure, hepatic insufficiency, chronic obstructive pulmonary disease, and decreased serum potassium and sodium levels are all contraindications of systemic carbonic anhydrase inhibitor therapy. Blood dyscrasias from bone marrow suppression have been reported and include agranulocytosis, aplastic anemia, neutropenia, and thrombocytopenia.[10,13]

Cholinergic Agents

Cholinergic agents (also called parasympathomimetics or miotics) were the first class of agents used to treat glaucoma. The class can be divided into direct-acting cholinergic agents and indirect-acting cholinergic agents

Direct-Acting Cholinergic Agents

Pilocarpine directly stimulates the muscarinic (M_3) receptors of the ciliary body which causes contraction of the ciliary muscle. This results in widening of the spaces in the trabecular meshwork, which causes an increase in aqueous humor outflow and reduces IOP by 20% to 30%.

Pilocarpine requires administration four times daily, since the IOP-lowering effect lasts only 6 hours. Pilocarpine is available in 1%, 2%, 4%, 6%, and 8% concentrations. Higher concentrations may be needed for patients with dark irides to obtain adequate IOP reduction. A pilocarpine 4% gel is available and allows for once-daily dosing at bedtime.[10,13,23] In the treatment of acute angle-closure glaucoma, it is important to delay use until IOP has been controlled, because pilocarpine could worsen angle closure by causing anterior displacement of the lens. Once IOP is controlled pilocarpine can be given to break pupillary block by instilling one drop twice in an hour.

The adverse effects of pilocarpine are caused by the induction of miosis. The contraction of the ciliary muscle causes the lens to displace forward, which can lead to accommodation spasm, myopia, and brow ache. Pupillary constriction can also affect night vision. Pilocarpine should be avoided in patients with severe myopia, as it increases the risk of developing retinal detachment. Systemic effects may occur at higher concentrations and include, nausea, vomiting, diarrhea, and bradycardia.

Carbachol stimulates the same muscarinic receptor as pilocarpine and also inhibits acetylcholinesterase, the enzyme that metabolizes acetylcholine. Carbachol is more potent than pilocarpine, but it causes more accommodation spasm and brow ache and may also cause anterior uveitis. Carbachol is rarely used today because of the side-effect profile.

Indirect-Acting Cholinergic Agents

Ecothiophate iodide and denecarium bromide inhibit acetylcholinesterase. Inhibition of this enzyme increases the availability of acetylcholine at the nerve junction, thus increasing the stimulation of the muscarinic (M_3) receptors of the ciliary body. These products are given twice daily and have similar efficacy to pilocarpine in the degree of IOP reduction. The side-effect profile is similar to that of pilocarpine; however, they can deplete systemic cholinesterases and pseudocholinesterases and may cause the formation of cataracts. These agents should be discontinued at least 1 week prior to general surgical procedures. Succinylcholine and some local anesthetics are metabolized by pseudocholinesterases, therefore depletion of this enzyme by ecothiophate or denecarium may lead to toxic effects. These agents are typically used when other topical agents have failed and are limited to use in patients who have had their lenses removed or who have artificial lenses.[10,13]

Hyperosmotics

Glycerin, isosorbide, and mannitol are hyperosmotic agents which increase the osmolality of blood. These agents create an osmotic gradient that draws water from the vitreous humor, thus decreasing IOP. The resulting dehydration of the vitreous humor may cause posterior movement of the lens, which then causes the anterior chamber to deepen, thus opening the anterior angle. If the patient is not vomiting, glycerin (1 to 1.5 g/kg of a 50%) solution and isosorbide (1.5 to 2 g/kg) can be given orally. Isosorbide is preferred in patients with diabetes since it is not metabolized into glucose. If the patient has nausea or vomiting, mannitol (20%) can be given intravenously at a dose of 1 to 2 g/kg over 45 minutes. The hyperosmotic agents are rapid acting, reaching peak effect in 30 to 60 minutes. Headache and thirst are common complaints. Patients that are already dehydrated are at risk of developing central nervous system dehydration which can lead to coma. These agents should be used with caution in patients with renal or cardiovascular disease, as extracellular water is increased.[36]

Non-selective Adrenergic Agonists

Epinephrine and its prodrug, dipivefrine, are rarely used for the treatment of glaucoma and are considered last-line agents because of their systemic side-effect profile. Dipivefrine enhances the corneal penetration. Once it absorbs through the cornea it is enzymatically cleaved to epinephrine. Epinephrine has α- and β-agonist activity and is thought to increase the outflow of aqueous humor through the trabecular meshwork and the uveoscleral pathway. Both products are instilled twice daily and reduce IOP by 15% to 25%. Local adverse effects include mydriasis, conjunctival hyperemia, and ocular irritation. Aphakic patients should not use these medications because they cause a reversible cystoid macular edema. Epinephrine and dipivefrine should not be used in patients with narrow angles since these agents can cause acute angle closure. Systemic side effects include palpitations, increased blood pressure, and arrhythmia, and therefore they should be used with caution in patients with cardiovascular

disease, cerebrovascular disease, and hyperthyroidism. Using the nasolacrimal occlusion technique may decrease systemic effects.[10,13]

SPECIAL CONSIDERATIONS: DRUG-INDUCED GLAUCOMA

Medications have the potential to cause or exacerbate both POAG and PACG; however, PACG is more likely to be exacerbated by medications than POAG. The use of medications with anticholinergic or sympathomimetics properties can precipitate angle closure. Sulfa-based drugs cause swelling of the ciliary body which causes an anterior displacement of the lens resulting in a decrease in anterior chamber depth. Controlled POAG is rarely exacerbated by anticholinergics, sympathomimetics, and sulfa-based drugs unless the patient is concomitantly at risk for angle closure. For uncontrolled or untreated POAG the risks and benefits should be considered before employing these agents. POAG can be exacerbated by corticosteroids. Corticosteroids increase IOP by causing obstruction of the trabecular meshwork with extracellular material. The increase in IOP appears to increase with potency and intraocular penetration. Ophthalmic corticosteroid preparations carry the highest risk of increasing IOP.[12]

OUTCOME EVALUATION

Primary Open-Angle Glaucoma

Evaluate patients 2 to 4 weeks after the initiation or alteration of medical therapy. The clinician should elicit the status of ocular health since the last visit, systemic medical history, medication history, and presence of local and ocular adverse effects of medications. IOP measurement, visual acuity assessment, and slitlamp biomicroscopy should be performed at every POAG follow-up visit. The frequency of visual field and optic nerve evaluation depends on whether IOP is controlled, the length of time IOP has been controlled, and whether there is progression of the disease. Patients who are at target IOP and have no disease progression should have optic nerve head evaluation and visual field testing every 6 to 18 months. Patients with disease progression or who are not at target IOP should receive optic nerve head evaluation every 2 to 12 months and visual field testing every 1 to 6 months.[1] Assess the patient's ability to use topical eye drops.[2,34] Finally, evaluate the patient's adherence to their medical regimen. Non-adherence among patients on topical medical therapy ranges from 5% to 80%. Suspect non-adherence in patients that have visual field and optic nerve progression despite a low IOP measurement, since patients may be more adherent to their medical regimen immediately prior to their visit. Specific patient factors related to the risk of non-adherence have yet to be established, therefore there are few objective measures of adherence. Pharmacy refill histories may be useful in assessing adherence, but do not confirm that the patient is actually taking the regimen as prescribed. Using adherence aids, prescribing the least complex regimen, and educating patients about their glaucoma are ways to reduce non-adherence.[55]

Adjust therapy if patients fail to reach their target IOP. Patients who have achieved target IOP yet have progressive damage of the optic nerve or who have worsening of their visual fields should have further adjustment of their therapy. Evaluate these patients further for possible reasons of continued disease progression. Consider determining the diurnal pattern of IOP and looking for signs of poor ocular perfusion pressure. Establish a lower target IOP. Adjust therapy in patients that are intolerant, non-adherent, or develop contraindications to their drug therapy regimen. Consider increasing the target IOP and reducing drug therapy for patients who have stable disease and who have maintained a low IOP, and closely follow these patients to assess their response.[2,34]

Primary Angle-Closure Glaucoma

Follow-up of angle-closure glaucoma occurs in the postoperative period. Evaluate the patency of the iridotomy and IOP in the postoperative period. Perform gonioscopy and optic nerve head evaluation if not already performed. Treat patients according to POAG guidelines if they have underlying POAG or areas of peripheral anterior synechia with the presence of optic neuropathy.[9]



Application of Ophthalmic Solutions or Suspension

1. Clean hands with soap and water.
2. Avoid touching the dropper tip with your fingers or against your eye to maintain sterility of the product; shake the dropper bottle if the product is a suspension.
3. Tilt head back; pull down the lower eyelid with the index finger.
4. Hold the dropper bottle with the other hand as close as possible without touching the eye. The dropper should be pointing towards the eye with the remaining fingers bracing against the face.
5. Gently squeeze the bottle so that one drop is placed into the pocket.
6. Close your eye for 2 to 3 minutes to allow for the maximum corneal penetration of drug.
7. Use a tissue to wipe away any excess liquid.
8. Replace and retighten the cap to the dropper bottle.
9. Wait at least 5 minutes before instilling another ophthalmic drug preparation.
10. Application of some ophthalmic preparations (suspension and gels) may cause blurring of vision.



Patient Monitoring and Care

1. In undiagnosed patients assess their risk factors for glaucoma and their recommended interval of glaucoma screening.
2. Obtain a thorough history of the patient's prescription, nonprescription, and natural product use. Review for potential drug-drug and drug-glaucoma interactions.
3. Evaluate diagnostic tests (e.g., IOP, visual fields, and optic nerve evaluations) to determine if the patient's current glaucoma therapy is effective.
4. Assess the patient's ability to use ophthalmic preparations.
5. Determine the patient's adherence level to the prescribed medication regimen and factors contributing to poor adherence.
6. Evaluate the patient for systemic and ocular adverse drug reactions and drug allergies.
7. Provide patient education with regard to disease state, drug therapy, and surgical or laser therapy:
   - What causes glaucoma or puts people at risk for glaucoma.
   - Possible complications of glaucoma.
   - How to use ophthalmic preparations appropriately.
   - When to take their medications.
   - Potential adverse drug reactions of medical therapy.
   - Potential benefits and complications of laser or surgical procedures.



Patient Encounter, Part 1

Risk Factor Evaluation and Recommended Frequency of Eye Care

A 65-year-old African-American female with a history of diabetes, mild intermittent asthma, and hypertension presents to your clinic for her yearly check-up. She states that she is concerned about losing her eyesight because her sister has started losing her vision from glaucoma. She states that she has not noticed any changes in her vision.

Meds

Metformin 1,000 mg orally twice a day
Albuterol 2 puffs every 6 hours as needed for wheezing
Lisinopril 10 mg orally daily

- What risk factors does this patient have for glaucoma?
- Based on the available information how often would you recommend that this patient receive a comprehensive eye evaluation?



Patient Encounter, Part 2

The patient was referred to an ophthalmologist for a comprehensive eye evaluation. The ophthalmology report reveals that the patient has an IOP (as assessed by applanation tonometry) of 26 mm Hg. Gonioscopic examination reveals open anterior angles in both eyes. Pachymetry reveals a corneal thickness of 510 microns. Ophthalmoscopy reveals physiologic cupping of the optic discs in both eyes and visual field examination reveals a nerve fiber bundle defect consistent with glaucoma.

- Given this additional information, what additional risk factors does this patient have for glaucoma?
- What is your assessment of the patient's condition?
- Identify the goals of therapy for this patient.
- What pharmacologic and nonpharmacologic treatment modalities are available for this patient?



Patient Encounter, Part 3

Develop a patient-specific care plan for this patient. Be sure to address the patient's drug-related needs, goals of therapy, risks and benefits of potential therapies, and plan for follow-up of therapy. List the monitoring parameters for effectiveness and safety for the chosen therapy. Explain how you would counsel the patient on the chosen therapy, including the administration of an ophthalmic preparation.

ABBREVIATIONS

AAO:	American Academy of Ophthalmology
CAI:	carbonic anhydrase inhibitor
CCT:	central corneal thickness
FDA:	Food and Drug Administration
IOP:	intraocular pressure
M_3:	muscarinic receptor
NTG:	normal-tension glaucoma
PACG:	primary angle-closure glaucoma
POAG:	primary open-angle glaucoma

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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59 Allergic Rhinitis

Kristi N. Hofer and Michelle W. McCarthy



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Differentiate between seasonal and perennial allergic rhinitis.
2. Describe the immune-mediated mechanism of allergic rhinitis.
3. List the symptoms of allergic rhinitis.
4. Identify the desired therapeutic outcomes in the management of allergic rhinitis.
5. Recommend appropriate treatment for patients with allergic rhinitis.
6. Educate patients regarding potential adverse effects of the medications used to treat allergic rhinitis.

Key Concepts

❶ Allergic rhinitis may be classified as seasonal or perennial.
❷ Allergic rhinitis is the most common atopic disease in the United States.
❸ In allergic rhinitis, the normal mechanisms by which the nasal mucosa humidifies and filters inspired air are disrupted due to an immunoglobulin E (IgE)–mediated immunologic reaction.
❹ The most common symptoms associated with allergic rhinitis are sneezing, nasal pruritus, rhinorrhea, and nasal congestion.
❺ Goals of allergic rhinitis treatment are to reduce the patient's symptoms, minimize adverse effects, and increase patient productivity (i.e., reduce lost school and work days).
❻ Antihistamines and intranasal corticosteroids are considered first-line therapy for allergic rhinitis, whereas decongestants, mast cell stabilizers, leukotriene modifiers, and systemic corticosteroids are secondary treatment options.
❼ The anti-inflammatory actions of intranasal corticosteroids make them highly effective agents for allergic rhinitis treatment, especially as first-line treatment for patients presenting with persistent or moderate to severe allergic rhinitis.
❽ In allergen immunotherapy, specific allergen extracts (also called *allergen vaccines*) are administered in order to modify or eliminate allergic rhinitis symptoms.
❾ Patients who may benefit from allergen immunotherapy include those who do not tolerate traditional drug therapy (e.g., nosebleeds with intranasal steroids or sedation with antihistamines), suffer from severe symptoms, have comorbid conditions (e.g., asthma or sinusitis), fail drug therapy, or prefer not to take long-term medication.
❿ Consensus-based guidelines indicate that the management of allergic rhinitis in children follows the same principles as those in adults, with special considerations for dose adjustments and adverse effects.

Allergic rhinitis (AR) is a highly prevalent allergen-induced upper airway inflammatory disease that is characterized by chronic hyperreactive airway mucosa with periods of acute exacerbations. ❶ *AR may be classified as seasonal or perennial.* Those with seasonal allergic rhinitis (SAR) experience symptoms primarily during the pollenating seasons of plants (i.e., spring or fall) because they are sensitive to the pollens of grasses, trees, or various weeds. Sufferers of perennial allergic rhinitis (PAR) have year-round symptoms to allergens that have no seasonal



Patient Encounter 1, Part 1

A 28-year-old woman with no significant past medical history presents to your clinic with complaints of sneezing, rhinorrhea, and nasal congestion persisting for the previous 3 weeks. On further questioning, she reports that the symptoms began this spring and worsen when she is outdoors.

- What symptoms are suggestive of AR?
- Would this patient's AR be classified as seasonal or perennial?
- What initial measure(s) would you recommend for this patient?

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TABLE 59–1. Environmental Controls to Prevent Allergic Rhinitis

Pollens
- Keep windows and doors closed during pollen season
- Avoid fans that draw in outside air
- Use air conditioning
- If possible, eliminate outside activities during times of high pollen counts
- Shower, shampoo, and change clothes following outdoor activity
- Use a vented dryer rather than an outside clothesline

Molds
- Use similar controls as above
- Avoid walking through uncut fields, working with compost or dry soil, and raking leaves
- Clean indoor moldy surfaces
- Fix all water leaks in home
- Reduce indoor humidity to less than 50% if possible

House dust mites
- Encase mattress, pillow, and box springs in an allergen-impermeable cover
- Wash bedding in hot water weekly
- Remove stuffed toys from bedroom
- Minimize carpet use and upholstered furniture
- Reduce indoor humidity to less than 50% if possible

Animal allergens (if removal of pet is not acceptable)
- Keep pet out of patient's bedroom
- Isolate pet from carpet and upholstered furniture
- Wash pet weekly

Cockroaches
- Keep food and garbage in tightly closed containers
- Take out garbage regularly
- Clean up dirty dishes promptly
- Use roach traps

Other recommendations
- Do not allow smoking around the patient, in the patient's house, or in the family car
- Minimize the use of wood-burning stoves and fireplaces

Adapted from American Academy of Allergy.[3] (From May JR, Smith PH. Allergic Rhinitis. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1734, with permission.)

variation (e.g., dust mites, mold spores, and animal dander). Symptoms of PAR typically are less severe than those of SAR due to continuous exposure to low-level allergen concentrations.[1]

EPIDEMIOLOGY

❷ *AR is the most common **atopic** disease in the United States*. It affects between 9% and 24% of adults and up to 42% of children.[2,3] More than 80 million Americans experience 7 or more days of nasal-ocular symptoms annually as a result of AR.[3] Additionally, AR is responsible for 3.5 million lost work days and 2 million missed school days annually in the United States.[4] In addition to decreased quality of life from AR symptoms, patients also suffer from disrupted sleep, resulting in fatigue, irritability, memory deficits, excessive daytime somnolence, and depression that further reduce quality of life.[5]

Factors thought to increase the likelihood of AR include positive allergy skin tests and increasing age. Prevalence of AR appears to be higher with increasing socioeconomic status, as well as in nonwhites, those who live in some polluted areas, people with a family history of allergies, those born during pollen seasons, and those who are first-born. Studies in pediatric patients indicate that children's AR risk increases with early introduction of food or formula, heavy maternal smoking during the first year of life, indoor allergen exposure (e.g., animal dander and dust mites), and parental allergic disorders.[6]



Patient Encounter 1, Part 2

The 28-year-old female patient returns to your clinic 1 month later with worsening complaints of AR symptoms. She purchased Afrin (oxymetazoline) intranasal spray at her local pharmacy and has been using it daily for the past 2 weeks. She is reluctant to continue with an intranasal product.

- What treatment regimen would you recommend for this patient? Your plan should include specific nonpharmacologic and pharmacologic interventions.
- What would you advise the patient regarding Afrin (oxymetazoline) intranasal spray use?

PATHOPHYSIOLOGY

❸ *In AR, the normal mechanisms by which the nasal mucosa humidifies and filters inspired air are disrupted due to an immunoglobulin E (IgE)–mediated immunologic reaction* (Fig. 59–1). Following sensitization, repeat exposure to allergens triggers the allergic cascade. This allergic response is categorized as either an early- or a late-phase response. Degranulation of mast cells near the surface of the nasal mucosal epithelium is a critical component of the early-phase response that occurs within minutes of allergen challenge. Histamine is a predominant mediator of the early-phase response. Release of proinflammatory mediators such as histamine, cytokines (e.g., tumor necrosis factor α, and interleukin 4), chemotactic factors (e.g., interleukin 5), and inflammatory mediators such as leukotrienes, prostaglandins, platelet-activating factor, and bradykinin occurs, resulting in nasal obstruction, nasal itching, sneezing, and nasal drainage.

Basophils, neutrophils, eosinophils, and T lymphocytes migrate to the site of the allergen exposure; this action sustains the late-phase response, which occurs hours after allergen challenge. Nasal obstruction is the primary characteristic of the late-phase response; however, sneezing and rhinorrhea persist from the early phase. Cytokines, including cysteinyl leukotrienes and interleukins 4, 5, and 13, are the more significant proinflammatory mediators to perpetuate inflammation and nasal symptoms.[7]

Allergens, or "triggers," differ between PAR and SAR. Common triggers in PAR are dust mites, mold, and animal or

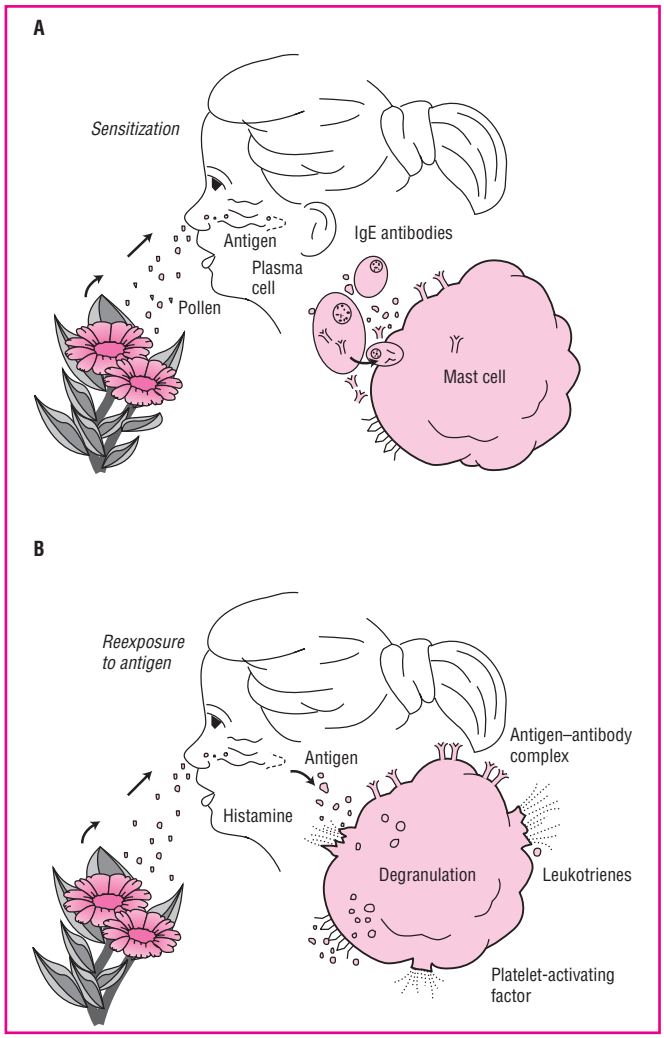


FIGURE 59–1. Allergen sensitization and the allergic response. (From DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005, Figure 93–1, p. 1730.)

cockroach allergens. In SAR, triggers vary depending on the time of year and include plant pollens and outdoor molds. Symptoms develop after the triggers initiate the allergic response.[8]



Patient Encounter 1, Part 3

The patient calls back to the clinic the next day. Her insurance company denied coverage for the antihistamine-decongestant combination and also will not cover these as single-entity products. She requests an alternate prescription.

- What agent(s) do you recommend?



Clinical Presentation and Diagnosis of Allergic Rhinitis[4–6,8]

Typical Symptoms
- Sneezing
- Pruritus (of nose, eyes, throat, and ears)
- Clear rhinorrhea
- Nasal congestion

Other Symptoms
- Chronic cough
- Fatigue
- Irritability
- Malaise
- Recurrent sinusitis
- Sleep disturbances
- Weakness

Signs in Children
- Periorbital "shiners" (edema and darkened tissues)
- "Allergic gape" (chronic mouth breathing)
- "Allergic salute" (open-palm upward nose rubbing that produces nasal crease)
- In severe cases, children may develop facial bone development abnormalities and dental malocclusion.

Diagnosis
- Temporal relationship of symptoms with triggers
- Empirical pharmacologic treatment
- Diagnostic tests optional [e.g., skin test (skin prick or intradermal), serum IgE antibody immunoassay]

TREATMENT

Desired Outcomes and Goals

Although a cure for AR does not exist, therapeutic modalities are aimed at minimizing symptoms. ❺ *Goals of treatment are to reduce the patient's symptoms, minimize adverse effects, and increase patient productivity (i.e., reduce lost school and work days)*. Specifically, therapeutic options may

- Decrease rhinorrhea, sneezing, and nasal pruritus
- Reduce nasal congestion
- Improve quality of life and sleep quality
- Improve productivity
- Prevent complications[5,8]

Nonpharmacologic Therapy

The first step in managing a patient with AR is to recommend lifestyle modifications. Patients should be encouraged to avoid allergens whenever possible (see Table 59–1). This may be difficult, however, especially for those with PAR who have continuous exposure to allergens. In PAR, several environmental adjustments should be made. For example, patients with sensitivity to dust mites should use impermeable covers for



Patient Encounter 1, Part 4

One year later, the female patient returns to your clinic for a routine examination. She reports that she is 8 weeks' pregnant, so she has not been taking her AR medication. She is especially troubled by severe congestion but also reports rhinorrhea and sneezing. She asks you to recommend a medication that will be "safe for her baby." She also would like to breast-feed after her baby is born and wonders if any medications are safe in breast-feeding.

- What do you recommend to manage her symptoms?
- What do you tell her about medication use and breast-feeding?

pillows and mattresses, wash bedding in hot (greater than 130°F) water, and minimize carpeting (i.e., use tile or hardwood floors). The only completely effective measure to eliminate animal dander is to remove the pet from the home. In SAR, outdoor allergens, such as plant pollens and molds, may not be avoided completely. Patients should keep windows and doors closed and use an air conditioner. Since symptoms worsen with increased allergen exposure, patients also should minimize time outdoors, especially during times of high pollen counts (i.e., 11 AM to 3 PM) or certain mold peaks (i.e., late evening and early morning). Despite environmental modifications, patients with significant symptoms of either perennial or seasonal AR often require treatment.[4,8]

Pharmacologic Therapy

Pharmacotherapy has an important role in managing AR symptoms (Table 59–2). Intranasal corticosteroids, systemic and topical antihistamines and decongestants, mast cell stabilizers, and immunotherapy all are beneficial in treating symptoms of AR.[9] ❻ *Antihistamines and intranasal corticosteroids are considered first-line therapy for AR, whereas decongestants, mast cell stabilizers, leukotriene modifiers, and systemic corticosteroids are secondary treatment options*[10–12] (Fig. 59–2). Whenever exposure to allergens can be predicted (e.g., SAR or visiting homes with a pet), medications should be used prophylactically to maximize effectiveness.[11]

H_1 Antihistamines

H_1 antihistamines are the most commonly prescribed medications for AR. H_1 antihistamines bind to and stabilize the H_1 histamine receptor, thereby inhibiting mast cell and basophil mediator release and resulting in reduction of sneezing, itching, rhinorrhea, and ocular irritation. Antihistamines do not prevent histamine release, nor do they bind to already-released histamine. For this reason, maintenance therapy is considered optimal. However, antihistamines are also effective when taken on an as-needed basis.[4,11,12] Antihistamines only minimally reduce nasal congestion, if at all.[8,11–13] Both oral and intranasal antihistamines are classified as first-line therapy in mild to moderate AR.[11,12] Traditionally, antihistamines have been designated by their chemical structure (i.e., ethanolamines, ethylenediamines, alkylamines, piperazines, piperidines, and phenothiazines). Today, H_1 antihistamines are described more commonly as first- or second-generation agents.[13]

First-generation antihistamines (e.g., brompheniramine, chlorpheniramine, clemastine, diphenhydramine, and pyrilamine) were the first to be developed, and most have not been studied in randomized, double-blind, controlled clinical trials.[13] These agents cross the blood-brain barrier and bind to the H_1 receptor, as well as dopamine, serotonin, and cholinergic receptors. These actions result in central nervous system (CNS) adverse effects such as sedation and cognitive impairment, as well as anticholinergic adverse effects (e.g., dry mouth and eyes, constipation, and urinary retention). Patients may develop a tolerance to sedation over a few days, but most of the adverse effects do not subside during treatment.[8] Even with bedtime-only dosing, residual daytime reduction in alertness and performance impairment occur.[14] Due to their adverse-effect profile, first-generation antihistamines should be avoided in patients with high-risk occupations (e.g., pilots and heavy machinery operators), benign prostatic hypertrophy, and elevated intraocular pressure.[4,8] Most first-generation agents have a short half-life that necessitates frequent dosing, often every 4 to 6 hours. First-generation antihistamines are available over the counter (OTC) as either single- or combination-agent products.[8]

Due to the significant adverse effects of the first-generation antihistamines, the second-generation agents were developed. These agents are dosed less frequently than first-generation agents at once or twice daily. The results of several well-designed studies demonstrate that second-generation antihistamines (e.g., cetirizine, fexofenadine, loratadine, and desloratadine) effectively relieve symptoms associated with seasonal or perennial AR.[13] These agents often are referred to as *nonsedating antihistamines.* Larger and more lipophobic than the first-generation agents, second-generation antihistamines penetrate the blood-brain barrier poorly, resulting in decreased CNS adverse effects. Of these agents, cetirizine has the most potential to cause sedation, with 30% greater propensity to occupy CNS H_1 receptors than fexofenadine.[4,13]

Second-generation agents are also more specific to the H_1 receptor, minimizing anticholinergic effects such as constipation and dry mouth.[8] Loratadine became available OTC in December 2002, but the other agents remain available only by prescription. The OTC status of loratadine has had an impact on physician prescribing patterns, as well as resulting in reduced or eliminated insurance coverage of second-generation antihistamines for many patients.[13]

Locally acting antihistamines act more quickly than oral agents but need to be administered intranasally at least twice daily due to the potential for removal by nasal secretions.[13] Azelastine, an intranasal antihistamine, is as effective as systemic antihistamines in the treatment of perennial and seasonal AR.

TABLE 59–2. Effectiveness of Medications for Allergic Rhinitis Symptoms

	Sneezing	Pruritus	Rhinorrhea	Nasal congestion	Comments
Intranasal (Local)					
Antihistamines	√	√	√	√	First-line therapy
Corticosteroids	√	√	√	√	First-line therapy
Cromolyn	√	—	√	√	
Decongestants	—	—	√	√	
Ipratropium	—	—	√	—	
Oral (Systemic)					
Antihistamines	√	√	√	*	First-line therapy
Corticosteroids	√	√	√	√	For severe cases only
Decongestants	—	—	√	√	Often in combination products
Leukotriene receptor antagonists	√	√	√	*	

√, effective; —, no effect; *, debated efficacy for nasal congestion; not as effective as other agents.

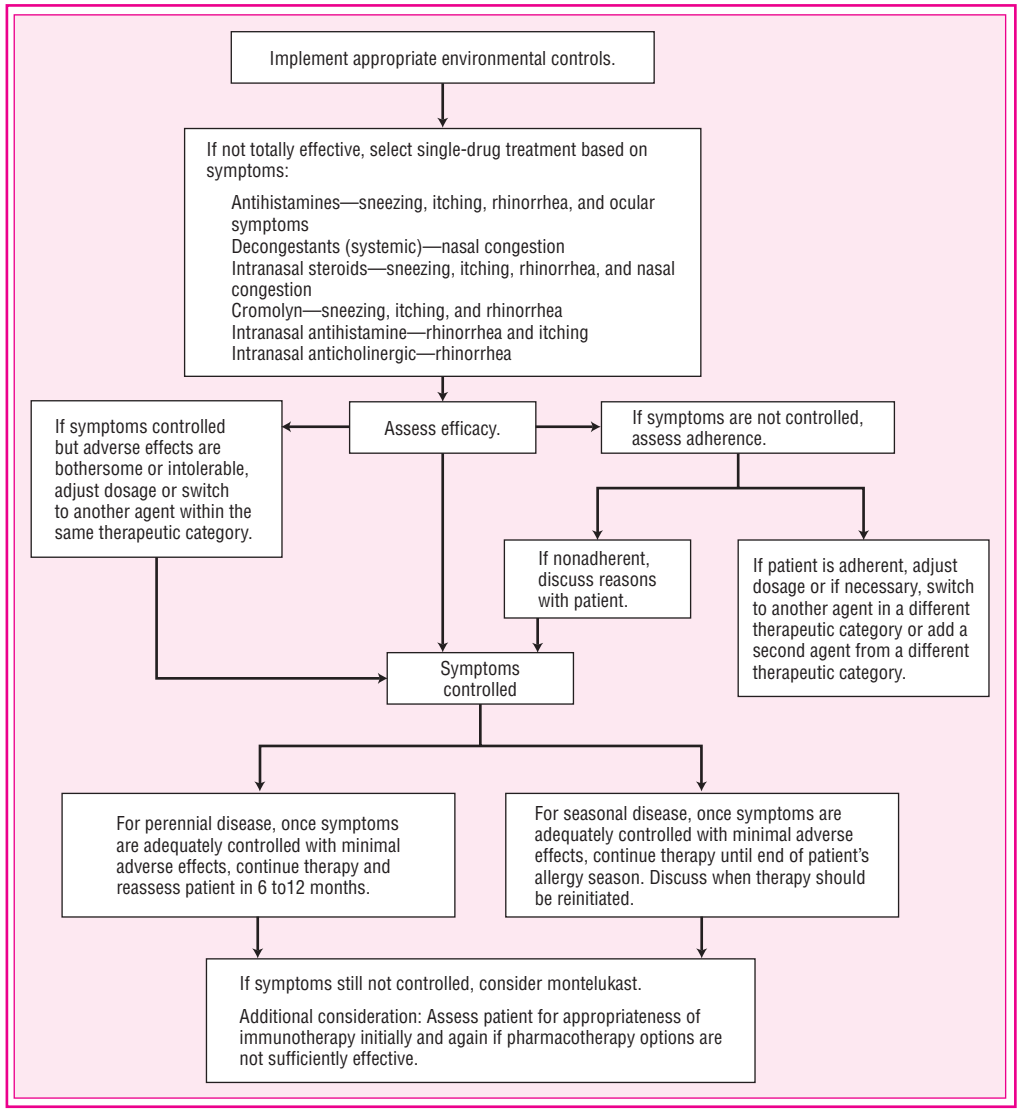


FIGURE 59–2. Treatment algorithm for allergic rhinitis. (From DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005, Figure 93–2, p. 1733.)

Azelastine acts locally to reduce the same symptoms treated by oral antihistamines; it also may reduce nasal congestion to a greater extent. Azelastine is administered twice daily and has a rapid onset of action. Many patients managed with azelastine complain of bitter taste. Drowsiness also has been reported, likely due to systemic absorption.[11–13]

Since comparative data are lacking, H_1 antihistamine selection is based on patient response and preference while minimizing adverse effects and potential drug-drug interactions. Due to the potential for once-daily dosing and a lower incidence of adverse effects compared with first-generation agents, the second-generation agents are prescribed more frequently. However, they are more costly.[12,13]

Intranasal Corticosteroids

❼ *The anti-inflammatory actions of intranasal corticosteroids make them highly effective agents for AR treatment, especially as first-line treatment for patients presenting with persistent or moderate to severe AR.* Intranasal corticosteroids prevent and relieve nasal symptoms associated with early-phase allergic responses such as nasal congestion and itching, rhinorrhea, and sneezing. Additionally, use of intranasal steroids may completely prevent late-phase AR symptoms.[9,10,12] Intranasal corticosteroids reduce inflammatory cell infiltration; decrease the numbers of basophils, eosinophils, neutrophils, and mast cells in the nasal epithelium and nasal secretions; reduce the number of inflammatory mediators from mast cells and other immune cells; decrease capillary permeability; decrease mucus production; and provoke vasoconstriction, resulting in decreased edema.[7]

Currently, six intranasal corticosteroids—beclomethasone, budesonide, flunisolide, fluticasone, mometasone, and triamcinolone—are available commercially. Although all available agents are effective and well tolerated, differences in potency and lipophilicity exist. Fluticasone and mometasone are more potent than the other commercially available intranasal steroids.[9,10] Highly lipophilic agents are associated with a greater degree and faster rate of absorption into the nasal mucosa than less lipophilic agents. The order of lipophilicity from highest to lowest is as follows: mometasone, fluticasone, beclomethasone, budesonide, triamcinolone, and flunisolide.[9]

Intranasal steroids are considered to have a slow onset of action (12–24 hours). Some patients may experience relief within a few days. Maximum treatment response may take up to several weeks to be observed.[9,10,12] To achieve optimal effects, use at regular intervals is recommended.[15] With the exception of beclomethasone and flunisolide, which are administered twice daily, the recommended doses for the intranasal corticosteroids are one to two sprays in each nostril once daily.[15]

Intranasal corticosteroids generally are well tolerated. Local effects such as dryness, burning and stinging, sneezing, headache and epistaxis occur in 5% to 10% of patients regardless of agent or formulation.[9] These adverse effects often resolve with dosage reduction.[10,12] Concerns about adverse effects due to systemic absorption exist with this class of drugs; however, systemic bioavailability is very low (less than 2%) for fluticasone, mometasone, and triamcinolone. Intranasal administration in recommended doses does not appear to affect hypothalamic-pituitary-adrenal axis function.[9,10] Additionally, systemic adverse effects linked to inhaled steroid therapy (e.g., cataract, glaucoma, and dermal thinning) do not seem to occur in patients treated exclusively with intranasal steroids.[10] Slight reductions in growth velocity in children prescribed intranasal steroids have been observed in clinical trials.[9,10,15] The long-term effects, including impact on final adult height and potential for "catchup" growth following discontinuation, have not been studied adequately. Growth of pediatric patients prescribed intranasal steroids should be monitored routinely via stadiometry.[15]

Patients prescribed intranasal steroids should be instructed to shake the product gently before each use and prime the pump before the first use or if not used for more than 1 week. Clear nasal passages before use, and avoid nose blowing for 10 to 15 minutes after use. Rare cases of septal perforation have been reported; therefore, administration of the spray away from the septum should be stressed. Effects are not immediate, and regular use is



Patient Encounter 2, Part 1

A 4-year-old, 20-kg (44 lbs) boy is seen in your practice setting for a routine check-up. His physical examination reveals dark and swollen circles under his eyes, a nasal crease, and mouth breathing. His mother reports that he has suffered from a constant runny and stuffy nose for the past 9 months. She attributed the symptoms to "preschool germs." She reports administering small doses (6.25 mg) of diphenhydramine to him before bedtime two to three times weekly. She states that his symptoms improve following diphenhydramine, but she has a very difficult time arousing him the following morning.

- What signs and symptoms are suggestive of AR?
- Would this patient's AR be classified as seasonal or perennial?
- What treatment regimen would you recommend for this patient? Your plan should include specific nonpharmacologic and pharmacologic interventions, including frequency.
- What monitoring should be performed in the patient? When should the patient be reevaluated?



Patient Encounter 2, Part 2

The patient returns in 1 month for follow-up. He and his mother report improvement in symptoms, and observation reveals less mouth breathing than the month before. The mother discusses her concerns about long-term use of steroids and is not convinced that the plan to monitor growth is sufficient.

- What options are available for the patient?

necessary to experience benefits. If symptoms worsen or do not improve within 3 weeks of treatment, the prescriber should be contacted.[12,15] If symptoms are not controlled with intranasal corticosteroid alone, addition of oral antihistamines may be warranted.[16] Patients with SAR should start therapy before the beginning of the pollen season to achieve maximal benefit.[16]

Decongestants

Decongestants such as OTC pseudoephedrine are sympathomimetic agents that constrict capacitance vessels in the nasal **turbinates.**[17] Decongestants effectively reduce nasal congestion and to some extent rhinorrhea associated with AR.[8,12] The recommended dose of pseudoephedrine is 30 to 60 mg every 4 to 6 hours for a maximum daily dose of 240 mg.[15] Systemic adverse effects such as irritability, dizziness, headache, tremor, tachycardia, and insomnia can occur. Additionally, use is associated with increased blood pressure and intraocular pressure and urinary obstruction.[8,12]

Topical intranasal decongestants (e.g., oxymetolazine, xylometolazine, phenylephrine, and naphazoline) are OTC options that provide prompt relief of nasal congestion. Nasal decongestants are dosed multiple times daily.[15] Tachyphylaxis, rebound congestion, and **rhinitis medicamentosa** may occur with chronic use; therefore, use should be limited to 3 to 5 days.[8,12] These may be used 5 to 10 minutes before administration of intranasal corticosteroids in patients with blocked nasal passages.[15]

Combination Products

Because of their limited effects on allergic symptoms, decongestants often are used in combination with antihistamines.[8] Many antihistamines are available in fixed-dose combinations with pseudoephedrine, which enhances the reduction in nasal congestion and allows for the patient convenience of one tablet. Optimally, therapy should be initiated with an antihistamine alone, adding the adrenergic agent only if nasal congestion does not resolve with antihistamine monotherapy. Use of separate antihistamine and pseudoephedrine also permits independent dose titration.[4,11,12]

Cromolyn

Cromolyn is an OTC nasal spray that inhibits degranulation of sensitized mast cells (i.e., stabilizes mast cells), reducing release of mediators that trigger inflammation and allergic response. Cromolyn also inhibits macrophages, eosinophils, monocytes, and platelets. Studies have demonstrated that intranasal cromolyn is effective in both early and late phases of AR, reducing symptoms of nasal congestion, rhinorrhea, and sneezing. The dose of cromolyn is one spray per nostril four times daily; its frequent dosing interval deters many patients from this treatment option.[18] Patients should use the nasal spray before anticipated allergen exposure and on a regular basis during the season associated with the patient's symptoms.[11] Adverse effects are local, occurring in less than 10% of patients, and include nasal burning, stinging, and epistaxis. No tachyphylaxis has been observed, nor have any drug interactions been reported. These qualities make cromolyn an option for patients with multiple comorbidities and concomitant medications. Cromolyn is an alternative for patients in whom antihistamines are too sedating and impair work and school performance. Additionally, cromolyn helps to prevent AR when taken prior to exposure, such as visiting a home with a pet.[18] Due to its excellent safety profile, cromolyn is a first-line agent in children with AR.[11,12]

Leukotriene Receptor Antagonists

Leukotrienes are inflammatory mediators (similar to histamine) that contribute to the symptoms of the allergic response. Cysteinyl leukotrienes are significant mediators associated with nasal congestion during the late-phase response. Leukotriene receptor antagonists would be expected to block the effects of leukotrienes on nasal congestion, but results of clinical trials have not conclusively demonstrated benefit.[7] Leukotriene receptor antagonists reduce sneezing, rhinorrhea, nasal pruritus and improve the quality of life with rhinoconjunctivitis.[19] Leukotriene receptor antagonists are no more effective than antihistamines at improving nasal congestion.[7] Combination therapy with leukotriene receptor antagonists and antihistamines was more effective than either agent alone but still less effective than intranasal corticosteroids.[19] Although montelukast and zafirlukast are both available commercially in the United States, montelukast is the only leukotriene receptor antagonist indicated for SAR and PAR.[15,20] The recommended dose of montelukast is 4, 5, or 10 mg once daily depending on patient age. Zafirlukast is dosed twice daily, but the ideal dose for AR has yet to be identified. When administered in the evening, montelukast improves nighttime nasal symptoms.[17] Leukotriene receptor antagonists are well tolerated, with headache being the most common adverse effect.[15,20]

Intranasal Anticholinergics

Intranasal anticholinergic agents (e.g., ipratropium) reduce the severity and duration of rhinorrhea but have no effect on other nasal symptoms.[11,12,21] Ipratropium reduces cholinergic hyperreactivity and cholinergically mediated histamine- and antigen-induced secretion. Intranasal ipratropium acts locally, with only minimal systemic absorption. Clinical trials demonstrated that ipratropium bromide 0.3% reduced rhinorrhea in adults and children with PAR.[11,12] Intranasal ipratropium is an option for patients in whom rhinorrhea is refractory to topical intranasal corticosteroids and/or antihistamines.[8,12] Intranasal ipratropium is available only by prescription, and the dose is two sprays nasally two to three times daily.[15] Adverse effects are minimal, but dry nasal membranes have been reported.[11,12]

Systemic Corticosteroids

Systemic corticosteroids, administered orally or by depot injection, are considered last-resort options when all other treatments for SAR are inadequate. Systemic steroids may be used to control rhinitis symptoms in patients with severe PAR or **nasal polyposis.** Data comparing oral and parenteral steroid therapy are lacking; however, oral therapy is preferred due to its low cost

and flexibility in dosing. Due to the risk of adverse effects related to hypothalamic-pituitary-adrenal axis suppression, only short courses (less than 3 weeks) of oral therapy are recommended no more often than every third month. Systemic corticosteroids should be avoided in children and pregnant women.[12,16]

Prescription versus OTC/Self-Treatment

Since many AR treatment options are available OTC, patients often self-treat unless symptoms are intolerable. Additionally, patients without medical insurance or formulary coverage are more likely to purchase OTC agents. Health care providers should ask patients about OTC medication history (i.e., effectiveness of and adverse effects with previously used agents) when selecting AR therapy.

Immunotherapy

Allergen Immunotherapy

Allergen immunotherapy (AIT) is an option in the management of AR, especially in patients who react to limited antigens. ❽ *In AIT, specific allergen extracts (also called allergen vaccines) are administered in order to modify or eliminate AR symptoms.* Patients receive a series of allergen injections beginning with a small quantity of allergen and building up to a maintenance dose. During the upward titration, injections are administered at varied intervals, ranging from several in one day to weekly. Maintenance doses are given every 4 to 6 weeks for 3 to 5 years. Duration of effect is uncertain, but an effect has been noted at least 6 years after discontinuing AIT.[22,23]

The mechanism of AIT is uncertain. It is theorized that AIT modulates allergen-specific T cells, attenuating early- and late-phase allergic responses. Results of clinical trials have demonstrated the effectiveness of AIT in SAR due to grass, ragweed, and birch pollen. AIT is even effective in patients who fail conventional drug therapy. In PAR, a longer duration of AIT is necessary to alleviate symptoms. Despite lengthening therapy duration, AIT may be less effective in patients with PAR than in those with SAR.[22]

In AIT, patient selection is critical. The allergic cause of AR should be verified by history and skin or blood tests. Additionally, the responsible antigen(s) must be identified. ❾ *Patients who may benefit from AIT include those who do not tolerate traditional drug therapy (e.g., nosebleeds with intranasal steroids and sedation with antihistamines), suffer from severe symptoms, have comorbid conditions (e.g., asthma and sinusitis), fail drug therapy, or prefer not to take long-term medication.*[11,22–24]

Local and systemic adverse effects are associated with AIT. Patients may experience pain or subcutaneous nodules at the injection site. In patients who suffer systemic symptoms soon after the injection, the AIT plan should be assessed and may need to be advanced more gradually. Systemic reactions, including anaphylaxis, are most likely to occur during the titration phase. Patients with asthma are at higher risk for systemic and fatal reactions. Patients should be monitored for adverse effects for at least 20 minutes after the antigen injection. Emergency agents, including epinephrine and an injectable corticosteroid, should be readily available.[23,24]

Omalizumab

Clinical trials have indicated that omalizumab, a recombinant humanized monoclonal IgE antibody approved for use in moderate to severe persistent asthma in patients with reactivity to a perennial allergen, is effective in the treatment of SAR.[25–27] Omalizumab inhibits the binding of IgE to mast cell and basophil receptors, resulting in a reduction of allergic mediator release.[25] Additionally, serum free IgE levels are decreased.[25–27] In SAR patients, omalizumab improves quality of life and nasal symptoms and reduces antihistamine needs. The most effective dose in SAR appears to be omalizumab 300 mg administered subcutaneously every 3 to 4 weeks depending on baseline IgE levels.[26,27]

The most common adverse effect with omalizumab is injection-site reaction, reported in 45% of patients in clinical trials. Other adverse effects include viral and upper respiratory tract infections, sinusitis, headache, and pharyngitis. Rare cases of malignant neoplasms and anaphylaxis were reported during clinical trials of omalizumab in asthma. Patients should be monitored for at least 2 hours following the injection so that anaphylaxis and/or injection-site reactions may be managed.[25]

Omalizumab is substantially more costly than other AR treatment options and must be administered in the clinic setting.[28] Comparative trials are needed to determine the role of omalizumab in AR.

Complementary and Alternative Medicines

Complementary and alternative medicine therapies, such as acupuncture, biofeedback, chiropractic manipulation, dietary supplements, herbal therapy, and homeopathic preparations, are used by individuals with allergic rhinitis.[29,30] Use of bromelain, gingko, ginseng, licorice, quercetin, and *Urtica dioica* has been reported, but large-scale studies documenting efficacy are lacking.[31,32] Caregivers should inquire routinely about patients' use of alternative therapies and counsel patients about the lack of validated data to support such practices.[12]

Special Populations

Children

Allergic rhinitis can have a large impact on the health and quality of life of children by causing absenteeism from school, reduced learning, depression, anxiety, and family dysfunction. If left untreated, serious complications such as asthma, sinusitis, nasal polyposis, respiratory infections, and otitis media can occur. ❿ *Consensus-based guidelines indicate that the management of allergic rhinitis in children follows the same principles as in adults, with special considerations for dose adjustments and adverse effects.* Allergen avoidance and environmental control are first priorities. Subsequent treatment recommendations depend on symptom severity. A number of treatment options

are available for pediatric patients with AR. As with adults, second-generation antihistamines and intranasal corticosteroids are first-line treatment options.

First-generation antihistamines are effective, but associated sedation and psychomotor impairment limit chronic use. Efficacy and safety of second-generation antihistamines in children have been demonstrated in clinical trials.[33] Cetirizine is indicated for children 6 months of age and older, loratadine for children 2 years of age and older, and fexofenadine for children 6 years of age and older.[15]

Intranasal corticosteroids are the most effective anti-inflammatory agents used in pediatric patients with allergic rhinitis. Although fewer studies have been conducted in children, results demonstrate that intranasal corticosteroids are effective and well tolerated, with an adverse-effect profile similar to placebo. Mometasone is indicated for children as young as 2 years of age, fluticasone is indicated for children 4 years of age and older, and beclomethasone, budesonide, flunisolide, and triamcinolone are indicated for children 6 years and older.[15] Because concerns regarding effect of intranasal steroids on growth exist, the growth of pediatric patients prescribed intranasal steroids should be monitored routinely via stadiometry.

Azelastine nasal spray is indicated for children 5 years of age and older and is considered an alternative to intranasal corticosteroids in patients with persistent severe symptoms. Intranasal cromolyn, another commonly used agent in children, is indicated in patients 2 years of age and older and has an acceptable safety profile. However, limited efficacy and multiple daily administrations limit its use to mild and early rhinitis or for prophylaxis of a known imminent exposure.

Oral pseudoephedrine should not be used in children under 1 year of age due to safety concerns. Intranasal ipratropium can be used as intermittent therapy for mild rhinitis or as add-on therapy in more severe cases. AIT is recommended for persistent rhinitis, particularly severe disease, because studies have shown that children respond better than adults. Montelukast is indicated for children 2 years of age and older with SAR and for infants 6 months of age and older with PAR. Studies evaluating leukotriene receptor antagonists as monotherapy or in combination with antihistamines have contradictory results.[33]

Pregnancy

Rhinitis symptoms are common during pregnancy and can occur in more than 20% of pregnant women. Approximately one-third of pregnant women experience worsening of AR symptoms during pregnancy. Because the bothersome symptoms of AR affect the quality of life of pregnant women and increase the likelihood of sinusitis, treatment should be optimized during pregnancy. Vasomotor rhinitis of pregnancy results from increased blood flow to the nasal turbinates, increased nasal glandular activity, and relaxation of the nasal vascular smooth muscle from increases in estrogen and progesterone.

As with any other AR patient, avoidance practices are the mainstay of therapy in pregnant AR patients. Elevation of the head of the bed and use of saline nasal spray are helpful in relieving nasal congestion. Intermittent use of intranasal decongestants can be useful for vasomotor rhinitis of pregnancy. Ideally, avoiding all medications during the first trimester, the primary period of organogenesis, is recommended. Cromolyn nasal spray is considered first-line therapy for AR in pregnant patients. The first-generation antihistamines chlorpheniramine and tripelennamine are the recommended antihistamines for use during pregnancy. For women unable to tolerate the first-generation agents, the use of second-generation agents such as loratadine and cetirizine may be considered. No data on adverse effects of azelastine nasal spray in this population are available. Pseudoephedrine is the preferred decongestant during pregnancy. However, an association between use of oral decongestants during the first trimester and infant **gastroschisis**—a rare congenital fissure of the abdominal wall—has been observed. Intranasal steroids may be considered in patients who do not experience adequate symptom relief from antihistamines and decongestants. Because budesonide and beclomethasone have been available for a longer period of time, these may be preferred in pregnancy. AIT is considered safe and effective for pregnant women and may be continued during pregnancy. However, it is not recommended to start AIT during pregnancy nor increase the strength of the allergen.[34]

Lactation

Drug selection in lactating women may be difficult. A number of factors must be considered when responding to questions regarding safety of drugs in nursing mothers. The American Academy of Pediatrics' (AAP) Committee on Drugs provides recommendations on the safety of drugs in lactating women. AR agents considered by the AAP as compatible with breast-feeding include fexofenadine, loratadine, and pseudoephedrine. Limited data are available on the safety of the inhaled corticosteroids in lactating women. However, their low systemic absorption and the classification of systemic (intravenous and oral) prednisone and prednisolone as compatible with breast-feeding should be considered when addressing questions about intranasal corticosteroids in nursing mothers.[35]

OUTCOME EVALUATION

AR is a bothersome and costly disorder affecting large numbers of patients. Clinicians encountering AR patients in their practice settings should be familiar with treatment options. Lifestyle modifications and many pharmacologic agents are effective in reducing symptoms and improving quality of life.

- Educate patients about environmental control measures (see Table 59–1).
- Routinely assess patients for response to treatment and adverse effects.
- Mild or intermittent symptoms are treated with second-generation antihistamines.

- Moderate or frequent symptoms require treatment with an intranasal corticosteroid.
- After 3 months of successful treatment, therapy may be interrupted and started again if symptoms return.
- Patients with severe symptoms or those that persist despite intranasal corticosteroid treatment are treated with a combination of intranasal corticosteroid and antihistamine.
- Investigate for underlying diseases of nonallergic origin (i.e., anatomic abnormalities, chronic sinusitis, or nasal polyps) if combination therapy does not provide sufficient relief.
- For resistant cases of nasal obstruction, evaluate the need for topical decongestants, oral decongestants, or short-course oral steroids.
- Consider intranasal ipratropium for resistant rhinorrhea and immunotherapy for those with symptoms that persist despite treatment.[16]



Patient Care and Monitoring

1. Assess the patient's symptoms to determine if self-treatment is appropriate or evaluation by a physician is necessary. Determine type of symptoms, frequency (seasonal or chronic), and precipitating triggers. Does the patient have any AR-related complications (e.g., nasal polyposis, sinusitis, or otitis media)?
2. Review any diagnostic data (e.g., skin test and serum IgE-antibody immunoassay) to determine to which allergens the patient is sensitized.
3. Obtain a thorough history of nonprescription, prescription, and natural drug product use. Determine which treatments have been helpful in the past.
4. Educate the patient on environmental modifications that may reduce symptoms (see Table 59–1).
5. Is the patient taking antihistamines and/or intranasal steroids? Is the patient experiencing adverse effects (e.g., sedation from antihistamines or nasal itching, burning, or bleeding from intranasal corticosteroids)?
6. Develop a plan to assess the effectiveness of the antihistamine and/or intranasal corticosteroid therapy after 3 months.
7. Determine if long-term therapy is warranted.
8. Assess improvements in symptom control and quality of life, including productivity and sleep.
9. Evaluate the patient for adverse drug reactions.
10. Stress the importance of adherence to the regimen including environment avoidance measures.
11. Provide patient education regarding allergen triggers, avoidance measures, and drug therapy:

- What causes AR?
- Possible complications of AR.
- When to take medications?
- What potential adverse effects may occur?
- What to report to physician (lack of symptom resolution)?

ABBREVIATIONS

AAP:	American Academy of Pediatrics
AIT:	allergen immunotherapy
AR:	allergic rhinitis
CNS:	central nervous system
H_1 antihistamine:	histamine-1 receptor antagonist
IgE:	immunoglobulin E
OTC:	over the counter
PAR:	perennial allergic rhinitis
SAR:	seasonal allergic rhinitis

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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60 Minor Ophthalmic Disorders

Kendra J. Grande



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Differentiate between the various minor ophthalmic disorders based on patient-specific information.
2. Choose an appropriate treatment regimen for an ophthalmic disorder.
3. Discuss the product differences that direct the selection of ophthalmic medications.
4. Assess when further treatment is required based on patient-specific information.
5. Recommend an ophthalmic monitoring plan given patient-specific information, a diagnosis, and a treatment regimen.
6. Educate patients about ophthalmic disease states and appropriate drug and non-drug therapies.

Key Concepts

❶ The clinician must be able to distinguish ophthalmic conditions that lead to significant morbidity, including blindness.
❷ The choice of topical antibiotic in patients who wear contact lenses must cover *Pseudomonas aeruginosa.*
❸ Both acute and chronic bacterial conjunctivitis are self-limiting, except if caused by staphylococci.
❹ Viral conjunctivitis is usually self-limiting, worsening after 4 to 7 days, but then resolving within 2 to 4 weeks.
❺ Nonpharmacologic measures are critical to prevent the spread of viral conjunctivitis.
❻ Use a step-care approach for treatment of allergic conjunctivitis.
❼ Untreated bacterial keratitis is associated with corneal scarring and potential loss of vision. Corneal perforation may cause the loss of the eye.
❽ There is no cure for age-related macular degeneration and the efficacy of most treatments is low.
❾ Dry eye is a chronic condition in which symptoms can be improved with treatment, but it is not usually curable. Patient education is critical.

This chapter provides an overview of common ophthalmic disorders and their treatments. ❶ *Many ophthalmic disorders are benign or self-limited, but the practitioner must be able to distinguish conditions that lead to serious morbidity, including blindness.* Preserving both visual function and cosmetic appearance must be done whenever possible.[1] The clinician must understand when referral is appropriate and the appropriate time frame for follow-up. These vary greatly by condition.

OCULAR EMERGENCIES

Etiology and Epidemiology

Ophthalmic problems encompass 3% to 10% of all emergency department visits.[1] Falls are a frequent cause of traumatic eye injury in the elderly.[2] Corneal abrasions are the most common eye injury in children and are often due to fingernail scratches or objects swung near the eye. Accidental cigarette burns are common in children, but may be a sign of child abuse. Even aggressive eye rubbing may damage the cornea.[3,4]

Health care practitioners must know the proper treatment for ocular emergencies and the time frame for follow-up in order to prevent further morbidity (Table 60–1).

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Corneal Abrasions



Clinical Presentation and Diagnosis of Corneal Abrasions[3]

Symptoms
- Photophobia
- Pain with extraocular muscle movement
- Foreign body sensation
- Recent ocular trauma
- Gritty feeling
- Headache

Signs
- Excessive tearing
- Blepharospasm
- Blurred vision

Diagnostic Test
Use sterile fluorescein dye strips and visualize the cornea under a cobalt-blue filtered light; abrasions appear green; ensure that no foreign body remains in the eye

Treatment

Desired Outcomes
- Complete healing of the corneal abrasion with no scarring or vision impairment
- Prevent infection and pain
- Prevent corneal loss or corneal transplant

General Approach to Treatment
The five layers of the cornea contain no blood vessels but are nourished by tears, oxygen, and aqueous humor. Minor corneal abrasions heal quickly. Moderate abrasions take 24 to 72 hours to heal. Deep scratches may scar the cornea and require corneal transplant if vision is impaired. Do not use eye patches to treat corneal abrasion, as they decrease oxygen delivery, increase pain, and increase the chance of infection.[3]

TABLE 60–1. Ophthalmic Emergencies: Time to Follow-up by Ophthalmologist[1]

Immediate Consult Required	Within 24 Hours
Foreign body in eye	Acute angle-closure glaucoma
Acute, painless loss of vision	Orbital cellulitis
Acute chemical burn	Blood in the eye (hyphema)
Blunt trauma to eye	Macular edema
	Retinal detachment
	Sudden congestive proptosis (bulging of eye forward)
	Corneal ulcer
	Corneal abrasion

Corneal Abrasion Prevention[3]
- Wear eye protection during sports
- Wear industrial safety lenses
- Clip fingernails of infants and children
- Remove low-hanging branches and objects
- Tape the patient's eyelids closed or use gels or soft contacts during general anesthesia to prevent lag-ophthalmos
- Carefully fit and place contact lenses

Pharmacologic Therapy

Topical NSAIDs
Topical non-steroidal anti-inflammatory drugs (NSAIDs) decrease pain from corneal abrasion. Available ocular NSAIDs are diclofenac 0.1%, ketorolac 0.5%, nepafenac 0.1%, and bromfenac 0.09%. The usual dose for diclofenac and ketorolac is one drop four times daily; nepafenac is dosed three times daily and bromfenac is dosed twice daily. Use topical NSAIDs with caution in patients with clotting disorders or those who are on systemic NSAIDs or warfarin therapy. Topical administration of NSAIDs may delay wound healing, especially with concurrent topical corticosteroid use.[3,5] Oral analgesics are not well studied for use in corneal abrasion; they may have decreased efficacy. They are less expensive than topical NSAIDs and may be an option for some patients.[3]

Topical Antibiotics
Because an infection slows the healing of a corneal abrasion, prophylactic antibiotics are often used. Studies on the efficacy of this are mixed. Discontinue the use of contact lenses until the abrasion is healed and the antibiotic course complete. ❷ *In contact lens wearers, choose an antibiotic that covers* Pseudomonas aeruginosa, *like gentamicin ointment or solution or a fluoroquinolone.*[3] Antibiotic resistance is an increasing problem. Resistance occurs primarily with older antibiotics, but has been reported for fluoroquinolones as well. Two newer fluoroquinolones, gatifloxacin and moxifloxacin, do not yet have reports of resistance. These agents are more expensive.[6]

Outcome Evaluation

1. Re-evaluate patients in 24 hours.
2. If symptoms worsen, recheck for foreign bodies.
3. If not fully healed, evaluate again in 3 to 4 days.
4. Refer to ophthalmologist if:

- No improvement in 3 days
- Worsening symptoms
- Symptoms do not improve daily
- Symptoms do not improve within a few hours of contact lens removal[3]

Other Ocular Emergencies: Treatment

Traumatic Injuries

Attempt to remove loose foreign bodies by gentle irrigation with artificial tears or sterile saline. If successful, a topical broad-spectrum antibiotic, such as erythromycin, will prevent infection. Some patients may need a short-acting cycloplegic mydriatic-like cyclopentolate or tropicamide to help with pain.[7] Do not use cycloplegic mydriatics in children.[8] If irrigation is unsuccessful, mechanical removal of foreign objects should be completed only by ophthalmologists using a slitlamp. Protect the eye with a metal eye shield or a paper cup taped over the eye while awaiting the ophthalmologist.[7]

Splash Injuries and Chemical Exposure

Instruct patients over the phone to irrigate the eye immediately with water or saline continuously for at least 15 minutes before seeking a clinician. Irrigation dilutes and removes the chemical agent, and is the best way to decrease ocular tissue damage. Patients should then seek immediate care from an ophthalmologist or emergency facility.[7]

Loss of Vision

A variety of disorders may lead to rapid, painless, monocular or binocular vision loss. This may include central retinal artery occlusion, acute narrow-angle glaucoma, trauma, or others. The differential diagnosis is complex and needs to be undertaken by an emergency department or ophthalmologist.[9]

CONJUNCTIVITIS

While no exact numbers are available, conjunctivitis, which is also known as red eye, is one of the most common ophthalmic complaints seen by general clinicians. An inflamed conjunctiva is the most common cause of red eye.[10] Use the differential diagnosis algorithm shown in Fig. 60–1 to determine the proper treatment or need for referral.

Bacterial Conjunctivitis

Etiology

The vast majority of conjunctivitis cases are viral in nature. For acute bacterial **conjunctivitis**, the cause is primarily gram-positive organisms.[11] The primary pathogens in acute bacterial conjunctivitis are *Streptococcus pneumoniae, Staphylococcus aureus,* or *Haemophilus influenzae.*[12]

Staphylococcus, *Moraxella*, or other opportunistic bacteria typically cause chronic conjunctivitis.[10] *Moraxella* infections may cluster in groups of women who share makeup.[12] ❸ *Both acute and chronic bacterial conjunctivitis are self-limiting except if caused by staphylococci.*[13] Because of this, the pathogens are rarely cultured unless the case is unresponsive to treatment. While infection typically begins in one eye, it will often spread to both within 48 hours.[11]

Hyperacute bacterial conjunctivitis is associated with gonococcal infections in sexually active patients. The causative agents are *Neisseria gonorrhoeae* or *N. meningitidis.* Prompt work-up and treatment is required, as corneal perforation occurs in 10% of cases within 48 hours.[12] An ophthalmologist should complete a conjunctival scraping and susceptibility testing.[10]

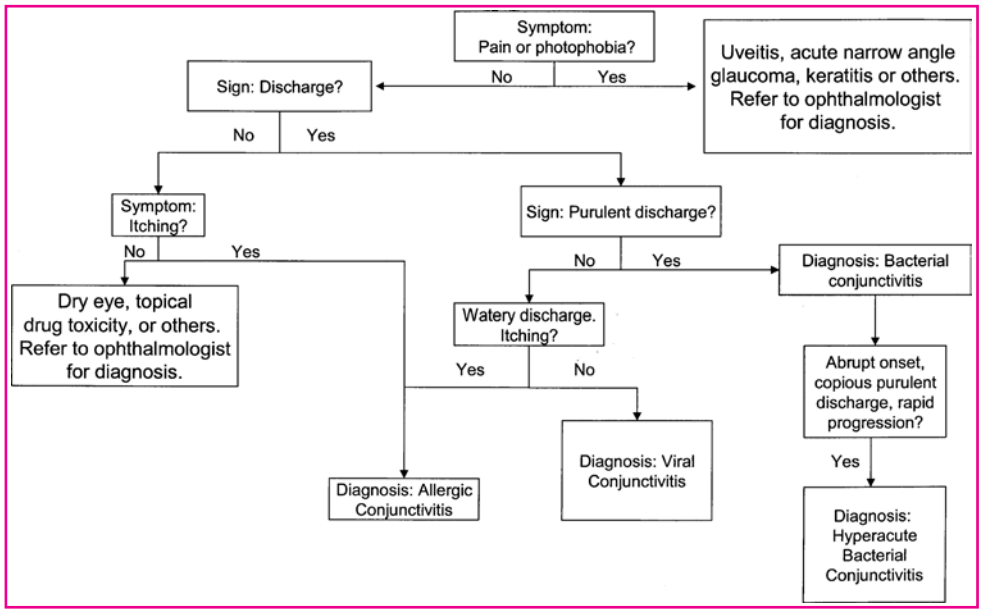


FIGURE 60–1. Differential diagnosis for red eye.

Treatment

Desired Outcomes

- Complete resolution of the bacterial conjunctivitis
- Prevent adverse consequences of the infection
- Preserve functionality of the eye

General Approach to Treatment

Treat acute bacterial conjunctivitis with broad-spectrum antibiotics. Although the condition is usually self-limiting, antibiotic treatment decreases the spread of disease to other people and prevents extraocular infection. Additionally, treatment may help decrease the risk of corneal ulceration or other complications that affect sight. Finally, treatment speeds recovery.[14]

Pharmacologic Therapy

The choice of an antibiotic agent for acute bacterial conjunctivitis is largely empiric. The initial treatment needs to include *Staphylococcus* coverage, but also may be chosen on the basis of cost and side-effect profile.[13,14] In general, ointments are a good dosage form for children. Adults prefer drops because they do not interfere with vision.[14]

Many broad-spectrum topical antibiotics are approved to treat acute bacterial conjunctivitis (Table 60–2). Trimethoprim /polymyxin B solution, polymyxin B with bacitracin ointment, or erythromycin ointment are cost-effective, first-line treatments. The aminoglycosides (tobramycin, neomycin, and gentamicin) are alternatives but have incomplete gram-positive coverage.[14] The aminoglycosides can cause corneal epithelial toxicity. Neomycin often causes allergic reactions. Tobramycin is the best tolerated of the class but is also the most expensive. Sulfacetamide 10% drops show increasing resistance. If infection recurs, use a topical fluoroquinolone like ofloxacin, ciprofloxacin, norfloxacin, gatifloxacin, moxifloxacin, or levofloxacin.[12] Fluoroquinolones are not used first-line for conjunctivitis because they have poor *Streptococcus* coverage and are expensive. Development of resistance is also a concern with fluoroquinolones.[14]

Treat hyperacute bacterial conjunctivitis with a single dose of 1 g of intramuscular ceftriaxone in combination with topical antibiotics.[11]

Patients with chronic bacterial conjunctivitis often have a concurrent case of blepharitis. Add a lid hygiene regimen to topical antibiotic treatment.[12]

TABLE 60–2. Bacterial Conjunctivitis Dosing Guidelines for Topical Ophthalmic Antibiotics[32]

Trimethoprim/polymyxin B solution	1 drop every 3 hours for 7–10 days
Polymyxin B with bacitracin ointment	Apply thin ribbon every 3–4 hours for 7–10 days
Erythromycin 0.5% ointment	Apply a thin ribbon up to six times daily
Tobramycin 0.3% solution	1–2 drops every 4–6 hours
Gentamicin 0.3% solution	1–2 drops every 4 hours
Sulfacetamide 10% solution	1–2 drops every 2–3 hours for 7–10 days
Ofloxacin 0.3% solution	Days 1 and 2: 1–2 drops every 2–4 hours Days 3–7: 1–2 drops four times daily
Ciprofloxacin 3.5 mg/mL solution	Days 1 and 2: 1–2 drops every 2 hours while awake Days 3–7: 1–2 drops every 4 hours while awake
Levofloxacin 0.5% solution	Days 1 and 2: 1–2 drops every 2 hours while awake, up to 8 times per day Days 3–7: 1–2 drops every 4 hours while awake, up to four times per day
Gatifloxacin 0.3% solution	Days 1 and 2: 1 drop every 2 hours while awake up to eight times per day Days 3–7: 1 drop every 4 hours while awake
Moxifloxacin 0.5% solution	1 drop three times a day for 7 days

Outcome Evaluation

Significant improvement of acute bacterial conjunctivitis should be seen within 1 week.[11] Terminate treatment with topical antibiotics when the inflammation is resolved.[12]

Viral Conjunctivitis

Etiology

The most common cause of viral conjunctivitis is adenovirus. It is often called "pink-eye."[10] Viral conjunctivitis infections are easily spread through swimming pools, camps, and contaminated fingers and medical instruments.[14] Patients often present with an upper respiratory tract infection or recent exposure to viral conjunctivitis. While the infection begins in one eye, it will spread to both eyes 50% of the time. ❹ *Viral conjunctivitis is usually self-limiting, worsening after 4 to 7 days but then resolving within 2 to 4 weeks.*[10] Five percent of patients remain contagious 16 days after the appearance of symptoms.[11]



Patient Encounter 1

A 40-year-old woman presents complaining of irritation, redness, and "stickiness" of the right eye for the past 48 hours. Today she woke up with the lids of the right eye stuck together and it took a warm washcloth to get her eye open. Examination reveals a whitish discharge from the right eye and a redness of the left eye. She has worn contact lenses for 6 years.

- What is the probable diagnosis?
- On physical assessment, how do you differentiate between bacterial, viral, and allergic causes?
- What is a reasonable treatment regimen for her?

Treatment

Desired Outcomes

- Complete resolution of the viral conjunctivitis
- Prevent adverse consequences of the infection
- Avoid spreading infection to other patients

Nonpharmacologic Therapy

❺ *Nonpharmacologic measures are critical to prevent the spread of viral conjunctivitis.* Patients should not share towels or other contaminated objects, should avoid close contact with other people and avoid swimming for 2 weeks.[10] The virus remains viable on dry surfaces for more than 2 weeks.[13] Take care in the medical setting to thoroughly decontaminate instruments and wash hands.[11]

Patients may obtain symptomatic relief by using cold compresses and artificial tears.[10] If artificial tear solutions sting, recommend a preservative-free formula.

Pharmacologic Therapy

Topical antivirals are not used to treat adenovirus conjunctivitis. Topical antibiotics are often prescribed for viral conjunctivitis, ostensibly to prevent bacterial superinfection. In reality, this is a case of the patient insisting on a medication to speed healing.[11] Avoid the use of antibiotics for a viral infection.[12] Eliminating superfluous antibiotic use also helps prevent the development of antibiotic resistance.

If patients have a severe subepithelial infiltration, a topical steroid may be required. However, topical steroids may cause serious ocular complications and may worsen herpetic conjunctivitis, which has symptoms similar to viral conjunctivitis. Additionally, the period of virus shedding may be prolonged by up to 50% by topical prednisolone. Only ophthalmologists should prescribe topical steroids.[10]

Outcome Evaluation

Refer patients that do not see improvement within 7 to 10 days to an ophthalmologist to rule out herpetic and other infectious processes.[11] If pain or photophobia occurs, suspect corneal involvement and refer the patient. This typically occurs 10 to 14 days after the onset of conjunctivitis.[13]

Allergic Conjunctivitis

Etiology

Ocular allergy is a broad term that includes several diseases with the hallmark symptom of itching, often accompanied by tearing, conjunctival swelling, and nasal congestion.[14] Seasonal ocular allergy is the most common type of allergic conjunctivitis. This is an IgE-mediated hypersensitivity to pollen or other airborne allergens.[11] Often, the patient's history is positive for atopic conditions such as allergic rhinitis, asthma, or eczema.[14] Perennial allergic conjunctivitis has similar but less severe symptoms and may not be tied to a specific time of year. Finally, **conjunctivitis medicamentosa** is a contact allergy to a topical medication, often an antibiotic.[11]

Pathophysiology

The conjunctiva of the eye is often the first site of contact with an environmental allergen. Mast cell degranulation occurs, resulting in the release of mediators. The earliest mediator is histamine, which causes itching, redness, and swelling. Leukotrienes and prostaglandins cause increased mucus secretion and cellular infiltration along with chemosis, resulting in conjunctival vasodilation. The mast cells also release cytokines, chemokines, and growth factors which trigger inflammatory processes.[15]

Treatment of ocular allergy is aimed at slowing or stopping these processes. Antihistamines block the histamine receptors and some prevent histamine production and/or inhibit mediator release from the mast cells.[15] Mast cell stabilizers inhibit the degranulation of mast cells, preventing mediator release. Some topical agents have multiple mechanisms of action, combining antihistaminic, mast cell stabilization, and anti-inflammatory properties (Tables 60–3 and 60–4).[16]

Treatment

Desired Outcomes

- Relief of current allergic symptoms
- Prevention of future allergic symptoms
- No adverse effects from treatment

Nonpharmacologic Therapy

The primary treatment is removal and avoidance of the allergen.[17] For conjunctivitis medicamentosa, discontinue the offending medication.[11] Apply cold compresses three to four times daily to reduce redness and itching and to provide symptomatic relief.[18]

Pharmacologic Therapy

❻ *Use a step-care approach for the treatment of allergic conjunctivitis.* The first step is a non-medicated, artificial tears solution. The solution dilutes or removes the allergen, providing relief while lubricating the eye. Solutions are applied two to four times daily as needed. Ointments may be used in the evenings to further moisturize the surface of the eye.[17] There are many products on the market. Try a preservative-free formulation if other products sting or burn. Unit-dose preservative-free products are more expensive. Some newer multi-dose products, such as sodium perborate (Purite®), have rapidly dissociating preservatives and are more cost-effective.

If artificial tears are insufficient, the second treatment step is a topical antihistamine or antihistamine/decongestant combination. The antihistamine/decongestant combination is more effective than either agent is alone. Decongestants are vasoconstrictors that reduce redness and seem to have a small synergistic effect with the antihistamine. The only topical

TABLE 60–3. Mechanisms of Action of Ocular Allergy Drugs[15,16,17]

Drug	Mechanisms	Notes
Pheniramine	H_1-receptor antagonist	Available only in combination with naphazoline
Antazoline	H_1-receptor antagonist	Available only in combination with naphazoline
Levocabastine	H_1-receptor antagonist	Downregulates intracellular adhesion molecules, decreasing the inflammatory response; may be used for up to 2 weeks
Olopatadine	Antihistaminic, mast cell stabilizer	
Emedastine	H_1-receptor antagonist; inhibits eosinophil chemotaxis	Superior H_1-receptor binding ability
Ketotifen	H_1-receptor antagonist, mast cell stabilizer, eosinophil inhibitor, platelet-activating factor inhibitor	May inhibit eosinophil chemotaxis
Azelastine	H_1-receptor antagonist, mast cell stabilizer	May inhibit cytokine release
Epinastine	H_1- and H_2-receptor antagonist, mast cell stabilizer, anti-inflammatory	
Nedocromil	Mast cell stabilizer, H_1-receptor antagonist	May inhibit eosinophils
Cromolyn sodium	Mast cell stabilizer	
Lodoxamide	Mast cell stabilizer	May be used for up to 3 months
Pemirolast	Mast cell stabilizer	
Ketorolac	Prostaglandin inhibitor	
Loteprednol	Corticosteroid	Only 0.2% approved for seasonal allergic conjunctivitis

decongestant used in combination products is naphazoline. Topical decongestants burn and sting on instillation and commonly cause mydriasis, especially in patients with lighter-colored eyes. Long-term use leads to rebound congestion or conjunctivitis medicamentosa. Topical decongestant use should be limited to less than 10 days.[17]

There is still debate whether oral antihistamines control ocular allergy as well as topical antihistamines. Topical antihistamines are recommended before oral agent in step therapy because of the increased risk of systemic side effects with oral drugs. Additionally, topical antihistamines provide faster relief of ocular symptoms. Consider oral antihistamines

TABLE 60–4. Dosing and Common Side Effects of Ocular Allergy Drugs

Drug	Dosing[32]	Common Side Effects[17]
Pheniramine	Varies by manufacturer and product	Ocular stinging
Antazoline	Varies by manufacturer and product	Ocular stinging
Levocabastine	1 drop in affected eye(s) four times daily	Ocular stinging, headache
Olopatadine	1–2 drops in affected eye(s) two times daily at 6- to 8- hour intervals	Headache
Emedastine	1 drop in affected eye up to four times daily	Headache
Ketotifen	1 drop in affected eye(s) twice daily	Red eyes (conjunctival injection), headache
Azelastine	1 drop in affected eye(s) twice daily	Ocular stinging, headache, bitter taste
Epinastine	1 drop in each eye twice daily	Ocular stinging, cold symptoms
Nedocromil	1–2 drops in each eye twice daily	Ocular stinging, bitter taste
Cromolyn sodium	1–2 drops in each eye 4–6 times daily	Ocular stinging
Lodoxamide	1–2 drops in affected eye(s) four times daily	Ocular stinging, foreign body sensation
Pemirolast	1–2 drops in affected eye(s) four times daily	Headache, cold symptoms
Ketorolac	1 drop four times a day	Ocular stinging, irritation
Loteprednol	1 drop in affected eye(s) four times daily	Elevated intraocular pressure, cataracts, decreased wound healing, secondary ocular infections, systemic side effects possible

when systemic symptoms are present.[15] Oral antihistamines are reviewed elsewhere in this text.

If insufficient relief is obtained from these products, either a mast cell stabilizer or a multiple-action agent is appropriate.[17] Use mast cell stabilizers prophylactically throughout the allergy season. Full response may take 4 to 6 weeks.

If mast cell stabilizers or multiple-action agents are not successful, a trial of a topical NSAID is appropriate. Ketorolac is the only approved topical agent for ocular itching. NSAIDs do not mask ocular infections, affect wound healing, increase intraocular pressure, or contribute to cataract formation like the topical corticosteroids. However, for allergic conjunctivitis, topical ketorolac is not as effective as olopatadine or emedastine in trials.[15] Full efficacy of ketorolac takes up to 2 weeks. [17]

If all these avenues are ineffective, short-term topical corticosteroids and immunotherapy are the third-line treatments for ocular allergy.[17]

Outcome Evaluation

Monitor patients for relief of symptoms. Ensure an adequate trial of the agent. If no improvement is seen, follow a stepped-care approach to treatment. Refer severe cases that do not respond to an ophthalmologist for short-term topical corticosteroids.

BACTERIAL KERATITIS

Epidemiology

Thirty thousand cases of microbial **keratitis** occur annually in the United States.[18] Microbial keratitis encompasses bacterial, fungal, and *Acanthamoeba* keratitis.[19] Only bacterial keratitis, the most common form, is discussed here.

Pathophysiology

Bacterial keratitis is a broad term for a bacterial infection of the cornea. This includes corneal ulcers and corneal abscesses. The cornea in a healthy eye has natural resistance to infection, making bacterial keratitis rare. However, many factors predispose a patient to bacterial infection by compromising the defense mechanisms of the eye (Table 60–5).[19]

The most common pathogens in bacterial keratitis are *Pseudomonas* (including *Pseudomonas aeruginosa*) and other gram-negative rods, staphylococci, and streptococci. If the keratitis is related to the use of contacts, *Pseudomonas* is the most common cause followed by *Serratia marcescens*. For hospitalized infants and adults on respirators, *Pseudomonas* is the most common.[19]

❼ *Untreated bacterial keratitis is associated with corneal scarring and potential loss of vision. Corneal perforation may occur and the patient may lose the eye.* In virulent organisms, this destruction may occur within 24 hours. Central corneal scarring may result in vision loss even after successful eradication of the organism.



Clinical Presentation and Diagnosis of Bacterial Keratitis[10]

General

The rate of progression of signs and symptoms varies depending on the infecting organism. A differential diagnosis for keratitis must include viral, fungal, and nematodal infections in addition to bacterial causes.[19]

Symptoms

- Photophobia
- Rapid onset of ocular pain

Signs

- Red eye
- Conjunctival discharge
- Decreased vision

Laboratory Tests

Culture if keratitis is severe or sight-threatening. Otherwise, cultures or smears are used only if the corneal infiltrate is chronic or unresponsive to broad-spectrum antimicrobial therapy.[19]

Treatment

Desired Outcomes

- Resolution of infection
- Resolution of corneal inflammation
- Reduced corneal pain
- Restored corneal integrity with minimal scarring
- Restored visual function[19]

TABLE 60–5. Risk Factors for Bacterial Keratitis[19]

Exogenous Factors	**Medications**
Contact lenses	Contaminated ocular medications
Trauma	Topical non-steroidal anti-inflammatory drugs
Previous ocular or eyelid surgery	Anesthetics
Loose sutures	Steroids
Previous corneal surgery	Antimicrobials
Ocular Surface Disease	Preservatives
Misdirection of eyelashes	Glaucoma medications
Abnormal lid anatomy or function	**Corneal Epithelial Abnormalities**
Tear film deficiencies	Herpes zoster ophthalmicus
Ocular infection such as conjunctivitis or blepharitis	Herpes simplex keratitis
Systemic Conditions	Corneal epithelial edema
Diabetes mellitus	Predisposition to recurrent erosion of the cornea
Debilitating illness (malnourishment or respiratory)	
Connective tissue disease	
Substance abuse	
Stevens-Johnson syndrome	
Immunocompromised	
Atopic dermatitis	
Gonococcal infection	
Vitamin A deficiency	

TABLE 60–6. Pharmacologic Therapies for Bacterial Keratitis[19]

Organism	Drug	Topical Dosing
Unknown or multiple organisms	Fluoroquinolones 3 mg/mL	Severe keratitis: loading dose every 5–15 minutes for the first hour, then every 15 minutes to 1 hour around the clock
Gram-positive cocci	Cefazolin 50 mg/mL *or* Vancomycin 15–50 mg/mL	Less severe keratitis may use less frequent dosing
Gram-negative rods	Tobramycin 3–14 mg/mL *or* Gentamicin 3–14 mg/mL *or* Ceftazidime 50 mg/mL *or* Fluoroquinolones 3 mg/mL	Antibiotics may be alternated each hour for ulcers and contact lens wearers as indicated
Gram-negative cocci	Ceftriaxone 50 mg/mL *or* Ceftazidime 50 mg/mL *or* Fluoroquinolones 3 mg/mL	
Non-tuberculous mycobacteria	Amikacin 20–40 mg/mL *or* **Oral** clarithromycin 500 mg every 12 hours	
Nocardia	Amikacin 20–40 mg/mL *or* Trimethoprim 16 mg/mL and sulfamethoxazole 80 mg/mL	

General Approach to Treatment

All cases of suspected bacterial keratitis require prompt ophthalmology consultation to prevent permanent vision loss.[10]

Pharmacologic Therapy

Dosage Considerations

Topical antibiotic drops are preferred. Consider subconjunctival antibiotics if compliance is a concern. Systemic therapy is useful in cases of systemic infection (e.g., gonorrhea) or if the sclera is infected. Reserve ointments for minor cases or adjunctive nighttime therapy.[19]

Drug Choice

Start topical broad-spectrum antibiotics empirically. Use a loading dose for severe keratitis (Table 60–6). Single-drug therapy with a fluoroquinolone is as effective as combination therapy. Resistance is seen with some fluoroquinolones. Because of this, choose a newer fluoroquinolone such as moxifloxacin or gatifloxacin in severe keratitis cases.[6] Fortified antibiotic therapy is an option for severe or unresponsive infections, but may increase toxicity to the cornea and surrounding tissues. Fortified antibiotics must be compounded.[19] All compounded formulations must comply with governmental 797 regulations concerning compounding of drug preparations.

Topical corticosteroids are employed in some cases of bacterial keratitis. The suppression of inflammation may reduce corneal scarring. However, local immunosuppression, increased ocular pressure, and reappearance of the infection are disadvantages to their use. There is no conclusive evidence that they alter clinical outcomes. If the patient is already on topical corticosteroids when the keratitis occurs, discontinue use until the infection is eliminated.[19]

Outcome Evaluation[19]

- Monitor patient symptoms for improvement to determine therapeutic efficacy
- Modify treatment regimen based on results of culture and sensitivity testing, if necessary
- Modify the treatment regimen if the patient does not show improvement within 48 hours
- Gram-negative keratitis will have increased inflammation in the first 24 to 48 hours, even on appropriate therapy
- Taper therapy based on clinical response
- Reculture or biopsy if negative clinical response; discontinue antibiotics for 12 to 24 hours before culture to improve culture results

MACULAR DEGENERATION

Epidemiology and Etiology

Age-related macular degeneration (AMD) is the primary cause of irreversible vision loss in developed countries (Figs. 60–2 and 60–3). The prevalence increases with age.[20] In the United States, 1.75 million people age 40 or older have AMD; another 7 million people are at substantial risk of developing it. Because of the rapid aging of the United States population, it is projected that almost 3 million people will develop AMD by 2020.[21] The causes of AMD are not completely known (Table 60–7).

Pathophysiology

AMD is a deterioration of the central portion of the retina (the **macula**). The macula facilitates central vision and high-resolution visual acuity because it has the highest concentration of photoreceptors in the retina. The loss of central



FIGURE 60–2. Normal vision. (From the National Eye Institute, National Institutes of Health Ref. No. EDS01. Accessed online at: http://www.nei.nih.gov/photo/)

vision leads to irreversible loss of the ability to drive, read, and perform other fine visual tasks like recognize faces.[22] Peripheral vision is preserved, allowing mobility.[20]

Early macular changes are often called age-related maculopathy and are characterized by large **drusen** and pigmentary abnormalities in the macula.[20] Age-related maculopathy accounts for 85% to 90% of all age-related macular changes. Ten to fifteen percent of these patients will develop advanced atrophy and/or develop abnormal blood vessels in and under the retina called **choroidal neovascular membranes**. Patients are then classified as having AMD.[23]

There are two forms of AMD: atrophic (also called the non-exudative or dry form) and neovascular (the exudative or wet form). Ten to twenty percent of patients with the atrophic form will progress to the neovascular form.[23] The neovascular form is responsible for the majority of the cases of blindness; however, vision loss is seen in both forms.[20]

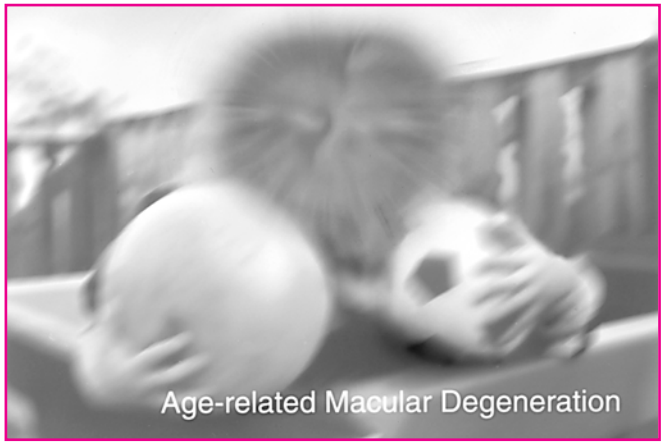


FIGURE 60–3. The scene in Fig. 60–2 as it might be viewed by a person with age-related macular degeneration. (From the National Eye Institute, National Institutes of Health Ref. No. EDS05. Accessed online at: http://www.nei.nih.gov/photo/)

TABLE 60–7. Risk Factors for AMD[20,33]

Definite Risk Factors	Potential Risk Factors
Advancing age (greater than 60 years)	Female gender
Light pigmentation (white ethnicity)	Cardiovascular disease
Cigarette smoking	Hypertension
Family history	Increased body mass index (especially in women)
Low dietary intake of antioxidant vitamins or zinc	Higher dietary fat intake
	Light-colored irides
	Increased exposure to sunlight

Treatment

Desired Outcomes

The primary goal of treatment for AMD is to slow the disease progression. This includes slowing the loss of visual acuity and the progression to legal blindness, along with maintaining contrast sensitivity and slowing the rate of progression to late AMD. The secondary goals are maintaining quality of life for the patient and minimizing the adverse effects of treatment.[22]



Clinical Presentation and Diagnosis of AMD

Symptoms

Age-related maculopathy:

- Mild blurry central vision
- Difficulty reading
- Trouble with color and contrast[23]

Age-Related Macular Degeneration[20,23]

- Painless, progressive moderate to severe blurring of central vision
- Sudden loss or distortion of vision possible

Signs[23]

- Drusen
- Retinal pigment epithelial mottling

Other Diagnostic Tests[20,23]

- Amsler's grid abnormalities indicate fluid in subretinal space (Figs. 60–4 and 60–5)
- Dilated fundus examination shows drusen and pigmentary abnormalities in the macula
- Rapid sequence fluorescein angiography shows leakage in the neovascular form

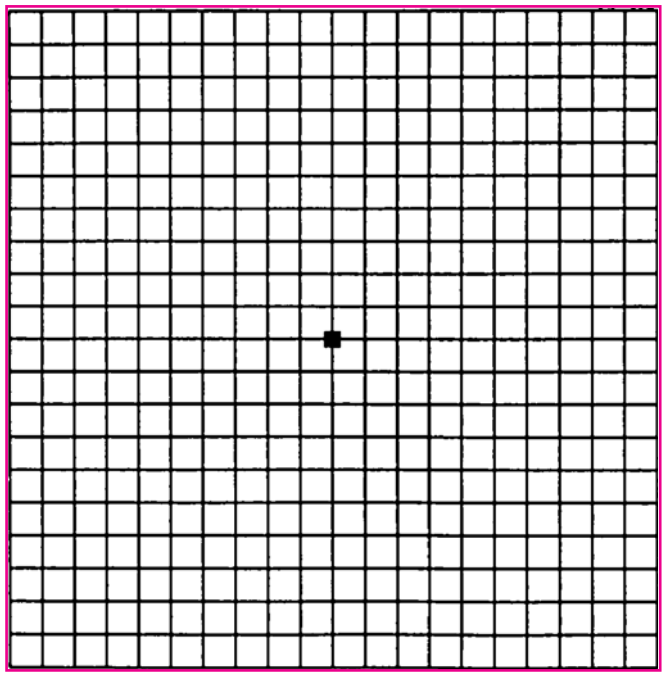


FIGURE 60–4. Amsler's grid distortions in the lines of the grid may be caused by subtle changes in central vision due to fluid in the subretinal space. This is the Amsler's grid as it appears to someone with normal vision. (From the National Eye Institute, National Institutes of Health Ref. No. EC03. Accessed online at: http://www.nei.nih.gov/photo/)

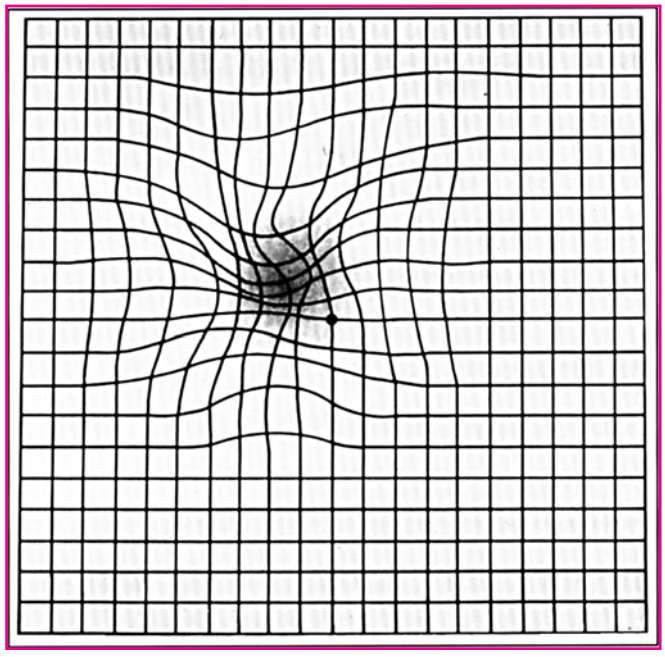


FIGURE 60–5. Amsler's grid as it might appear to someone with AMD. (From the National Eye Institute, National Institutes of Health Ref. No. EC04. Accessed online at: http://www.nei.nih.gov/photo/)

General Approach to Treatment

There is no cure for AMD and the efficacy of most treatments is low. Newer drug developments show promise but no treatment can reverse damage that has already occurred.[23] Early diagnosis is critical. High-risk patients need periodic eye examinations because some patients do not notice any changes, even when neovascularization has occurred.[20]

Nonpharmacologic Treatment

Age-Related Maculopathy and Atrophic Age-Related Macular Degeneration

Drusen ablation may help patients with multiple large drusen in both eyes that have not progressed to neovascular macular degeneration. These laser treatments may lead to resolution of the drusen and improved visual acuity. However, it is not clear if progression to choroidal neovascular membranes and neovascular macular degeneration is reduced.[23] There is a possibility that the laser treatments may induce choroidal neovascularization and retinal atrophy.[22]

Neovascular Age-Related Macular Degeneration

Until recently, the only treatments for neovascular AMD were nonpharmacologic. Thermal laser photocoagulation reduces severe visual loss 2 to 5 years after the procedure, but leads to an immediate and permanent reduction in central vision. There is a 50% chance that leakage will recur in the next 2 years after the procedure.[20,22]

Photodynamic therapy uses non-thermal red light to activate verteporfin, which produces reactive oxygen species that locally damage the neovascular endothelium.[24] Verteporfin treatment reduces the risk of loss of visual acuity and legal blindness over 1 to 2 years. Long-term results are not yet available. Severe photosensitivity for 3 to 5 days after the procedure is common and some patients experience a severe loss of vision. Eventually, most patients have some visual recovery. This procedure requires multiple treatments over time.[22]

Pharmacologic Therapy

Atrophic Age-Related Macular Degeneration

There are no approved pharmacologic treatments for atrophic AMD. The Age-Related Eye Disease Study showed that a supplement containing ascorbic acid 500 mg, vitamin E 400 IU, beta carotene 15 mg, zinc oxide 80 mg, and cupric oxide 2 mg reduced the rate of clinical progression of all types of AMD by 28% in patients with at least intermediate macular degeneration. No benefit was seen in patients with earlier stages of age-related maculopathy; however, the duration of the study may have been insufficient to detect this benefit.[25]

Supplementation is not without risk. For example, beta carotene supplementation in smokers may increase the risk of developing lung cancer.[23] At this time, it is not clear from the

evidence if a patient at high risk but without symptoms of AMD would benefit from supplementation.[26]

Neovascular Age-Related Macular Degeneration

Vascular endothelial growth factor induces **angiogenesis**, increases vascular permeability, and increases inflammation, all of which are thought to contribute to neovascular AMD. A new class of drugs, the vascular endothelial growth factor antagonists, binds to these growth factors in an attempt to suppress neovascularization. Pegaptanib is the only approved drug in this class at this time.[27]

Pegaptanib 0.3 mg is administered as an intravitreous injection every 6 weeks. In clinical studies, patients treated with pegaptanib experienced a slower rate of visual decline than patients treated with a sham injection.[28] Vision loss continued to occur in patients and the drug was less effective in the second year of treatment. Long-term efficacy studies are not available yet.[27]

Outcome Evaluation

Monitor patients for acute and chronic vision changes or loss. The Amsler's grid and frequent eye examinations may detect changes more quickly. The long-term prognosis for AMD is poor. Monitor patients for inability to drive and remove driving privileges as appropriate. Work with patients and family members to plan for lifestyle changes as vision decreases.

DRY EYE

Epidemiology

Dry eye is a frequent cause of eye irritation. A lack of a single diagnostic test for the condition limits the available epidemiologic data. One study estimated the prevalence of dry eye in the United States population age 65 and older at 14.6%, which is approximately 4.3 million Americans.[29]

The risk factors for dry eye are listed in Table 60–8. Of interest, the use of caffeine is associated with a decreased risk of dry eye. Dry eye that is left untreated can cause loss of vision or other morbidities over time.[30]

TABLE 60–8. Risk Factors for Dry Eye[30]

Older age
Female gender
Arthritis
Smoking
Multivitamin use
Estrogen replacement therapy

Pathophysiology

The ocular surface and the tear-secreting glands of the eye are now known to function as an integrated unit. This unit refreshes the tear supply and clears used tears. An autonomic neural reflex loop stimulates secretion of tear fluid and proteins by the lacrimal glands. The sensitivity of the ocular surface decreases as aqueous tear production and tear clearance decreases. This results in a decrease in sensory-stimulated reflex tearing which exacerbates dry eye.[29,30] Over time, wearing contact lenses also desensitizes the cornea by constant stimulation.[12]

Dysfunction may be caused by aging, systemic inflammatory diseases, a decrease in androgen hormones, surgery, ocular surface diseases (such as herpes zoster), systemic diseases, or medications that affect the efferent cholinergic nerves. Decreased tear secretion produces an inflammatory response on the ocular surface called **keratoconjunctivitis sicca**. This inflammation is now a target for new medications that treat dry eye.[29,30]

Conditions that increase the evaporative loss of tears also worsen dry eye. In addition to environmental causes (Table 60–9) an abnormal blink reflex is a common cause of increased evaporative loss.[30]

TABLE 60–9. Associated Conditions That Cause or Worsen Dry Eye[30]

Ocular Conditions	**Local Trauma**
Blepharitis	Orbital surgery
Meibomian gland dysfunction	Radiation
Systemic Diseases	Injury
Sjögren's syndrome	Chemical exposure
Rosacea	**Systemic Medications**
Lymphoma	Diuretics
Sarcoidosis	Antihistamines
Hemochromatosis	Anticholinergics
Amyloidosis	Antidepressants
Human immunodeficiency virus	Systemic retinoids
Hepatitis C	Isotretinoin
Epstein-Barr virus	Hormones
Graft-versus-host disease	Hormone therapy
Rheumatoid arthritis	Cardiac antiarrhythmic
Systemic lupus erythematosus	Diphenoxylate/atropine
Scleroderma	β-Blockers
Neuromuscular diseases	Chemotherapy agents
Bell's palsy	
Parkinson's disease	
Environmental Factors	
Wind	
Reduced humidity	
Air conditioning or heating	
Exogenous irritants or allergens	
Prolonged use of computer or reading	
Contact lenses	
Air travel	
Smoke exposure	



Clinical Presentation and Diagnosis of Dry Eye[30]

General

Many other ocular diseases have similar symptoms. Patients with suggestive symptoms without signs should be placed on a treatment trial. Repeated observations over time may be required for a clinical diagnosis.

Symptoms

- Dry or foreign body sensation
- Mild itching
- Burning
- Stinging
- Photophobia
- Ocular irritation or soreness
- Blurry vision
- Contact lens intolerance
- Diurnal fluctuation
- Symptoms that worsen later in the day

Signs

- Redness
- Mucus discharge
- Increased blink frequency
- Tearing

Other Diagnostic Tests

- The tear break-up time test assesses the stability of precorneal tear film. Break-up times of less than 10 seconds are considered abnormal.
- Ocular surface dye staining assesses the ocular surface and will show blotchy or exposure-zone punctate areas in the dry eye.
- Schirmer's test evaluates aqueous tear production but is not diagnostic for dry eye. Results of 5 mm or less are considered abnormal.
- Assess corneal sensation if trigeminal nerve dysfunction is suspected.
- Evaluate for an autoimmune disorder if significant dry eyes or other signs and symptoms or family history are present.

Treatment

Desired Outcomes

- Relief of the symptoms of dry eye
- Prevention of recurrence
- Prevention of long-term adverse effects from dry eye

General Approach to Treatment

❾ *Dry eye is a chronic condition. Symptoms can be improved with treatment but unless dry eye is secondary to a disease, it is not usually curable. Because of this, patient education is critical and a periodic reassessment of the efficacy of the treatment is appropriate.* If the patient is unresponsive to treatment, refer to an ophthalmologist for additional options. If the dry eye is secondary to a systemic disease, the disease should be managed by the appropriate medical specialist.[30]

Nonpharmacologic Therapy

Behavioral and environmental modifications may significantly improve dry eye, especially in mild cases. Evaluate the patient's environment for air drafts. Consider adding a humidifier in low-humidity areas. Schedule regular breaks from computer work or reading. Lower the computer screen to below eye level to decrease lid aperture. Evaluate medication use and make therapeutic substitutions to medications that do not exacerbate dry eye. Spectacle sideshields or goggles may reduce tear evaporation.[30]

If pharmacologic and other therapies are not sufficient, punctal occlusion or lateral tarsorrhaphy may be an option. Punctal occlusion is the plugging of the punctal drainage sites with collagen (temporary) or Silastic (permanent) plugs. Lateral tarsorrhaphy sutures portions of the lid margins together to decrease evaporative tear loss. These procedures are reserved for severe cases of dry eye secondary to other diseases. [12]

Pharmacologic Therapy

Regardless of the cause, the mainstay of treatment for dry eye is artificial tears. Artificial tears augment the tear film topically and provide relief. If a patient uses artificial tears more than four times daily, recommend a preservative-free formulation. Preservative-free formulations are also appropriate if the patient develops an allergy to ophthalmic preservatives. Artificial tears are available in gel, ointment, and emulsion forms that provide a longer duration of relief and may allow for less frequent instillation. Ointment use is appropriate at bedtime.[30]

Anti-inflammatory agents may be used in conjunction with artificial tears. The only approved agent is cyclosporine emulsion. Administered topically, it is thought to act as a partial immunomodulator suppressing ocular inflammation, but the exact mechanism is unknown. Cyclosporine emulsion increases tear production in some patients. Fifteen minutes should elapse after instillation of cyclosporine before artificial tears are instilled.[31] Use of topical corticosteroids for short periods (e.g., 2 weeks) may suppress inflammation and ocular irritation symptoms. No topical corticosteroid is approved for this indication, however.[30]

The oral cholinergic agonists pilocarpine and cevimeline are used for patients with combined dry eye and dry mouth (e.g., Sjögren's syndrome) or severe dry eye. By binding to muscarinic receptors, the cholinergic agonists may increase tear production. Excessive sweating is a common side effect with pilocarpine and may limit its use (Table 60–10).

TABLE 60–10. Pharmacologic Therapies for Dry Eye[32]

Drug (Brand Name)	Dosing
Pilocarpine 5 mg tablet (Salagen®)	5 mg orally four times daily
Cevimeline 30 mg capsule (Evoxac®)	30 mg orally three times daily
Cyclosporine ophthalmic emulsion 0.05% (Restasis®)	One drop in each eye twice daily



Patient Encounter 2

A 60-year-old woman presents with complaints of redness, burning, and watering of both eyes. She does not have any itching of the eyes or other visible discharge. She has had the symptoms, which are more severe when she arises in the morning, for several years. The symptoms have become worse recently. Your physical examination reveals red and teary eyes.

Her medical history includes osteoarthritis, mild osteoporosis, and hypertension. She also has recurrent sinus infections associated with seasonal allergic rhinitis. She is a medical transcriptionist.

Meds

Metoprolol 100 mg daily
Premarin 0.3 mg daily
Calcium carbonate 1200 mg daily
Ibuprofen 600 mg as needed for joint pain
Loratadine 10 mg as needed for allergies
Senior over-the-counter multivitamin daily

- What is the probable diagnosis?
- What are the other contributing factors that may be worsening her condition?
- What nonpharmacologic interventions might she benefit from?
- What treatment option is best for her?

Outcome Evaluation[29]

- Monitor patient for relief of symptoms
- Periodically reassess the patient's compliance and understanding of the disease
- It may take 6 weeks before improvement is seen with pilocarpine therapy
- Cyclosporine therapy may take up to 6 months for full efficacy
- If a patient presents with visual loss, moderate or severe pain, corneal ulceration, or a lack of response to therapy, refer the patient to an ophthalmologist for prompt evaluation

DRUG-INDUCED OCULAR DISORDERS

Table 60–11 shows some ocular changes due to the use of certain drugs.



Nasolacrimal Occlusion[37]

Use of nasolacrimal occlusion decreases systemic absorption up to 60% and may increase ocular bioavailability of the drug. After instillation of the eye drop, the patient should close the eye and press a finger gently against the nasolacrimal duct (tear duct) for 2 to 3 minutes.

TABLE 60–11. Selected Drug-Induced Ocular Changes

Miosis[34]	**Mydriasis[34]**
Narcotics	Anticholinergics
Barbiturates	Tricyclic antidepressants
Phenothiazines	Sympathomimetics
Decreased Tear Volume[34]	**Corneal Deposits[35]**
Anticholinergics	Amiodarone
Antihistamines	Chloroquine and hydroxychloroquine
Diuretics	Tamoxifen
β-Blockers	Gold
Tricyclic antidepressants	Ibuprofen, naproxen, and indomethacin
Nystagmus[34]	Phenothiazines
Phenytoin	**Cause or Worsen Cataracts[34]**
Barbiturates	Corticosteroids
Increased Tear Volume[34]	**Decreased Blink Rate[34]**
Cholinergic agents	Sedative-hypnotics
Benzodiazepines	Ethanol
Phenothiazines	**Lid and Corneal Edema[34]**
Induce Uveitis[36]	Chlorthalidone
Rifabutin	Oral contraceptives
Bisphosphonates	Ibuprofen
Sulfonamides	Digoxin
Cidofovir	Phenothiazines
Topical metipranolol	
Topical corticosteroids	
Latanoprost	

ABBREVIATIONS

AMD: age-related macular degeneration
NSAID: non-steroidal anti-inflammatory drug

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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61 PSORIASIS

Rebecca M.T. Law



LEARNING OBJECTIVES

UPON COMPLETION OF THE CHAPTER, THE READER WILL BE ABLE TO:

1. Discuss the etiology of psoriasis including genetic and immune changes.
2. Describe the pathophysiology of psoriasis including types of psoriasis and clinical presentations.
3. Compare and contrast the treatment modalities for psoriasis, including topical and systemic therapies and phototherapy.
4. Recommend an appropriate treatment plan for a patient with psoriasis.
5. Recommend appropriate monitoring parameters for a patient on drug treatment for psoriasis.
6. Provide appropriate counseling information to a patient with psoriasis.

KEY CONCEPTS

❶ Patients with psoriasis have a lifelong illness that may be very visible and emotionally distressing. There is a strong need for empathy and a caring attitude in interactions with these patients.

❷ Psoriasis is a T-lymphocyte–mediated inflammatory disease that results from a complex interplay between multiple genetic factors and environmental influences. Genetic predisposition coupled with some precipitating factor triggers an abnormal immune response, resulting in the initial psoriatic skin lesions. Keratinocyte proliferation is central to the clinical presentation of psoriasis.

❸ Diagnosis of psoriasis is usually based on recognition of the characteristic plaque lesion, and not based on lab tests.

❹ Treatment goals for patients with psoriasis are to minimize signs such as plaques and scales, alleviate symptoms such as pruritus, reduce the frequency of flare-ups, and ensure appropriate treatment of associated conditions such as psoriatic arthritis or clinical depression, and minimize treatment-related morbidity.

❺ Management of patients with psoriasis generally involves both nonpharmacologic and pharmacologic therapies.

❻ Nonpharmacologic alternatives such as stress reduction and the liberal use of moisturizers may be extremely beneficial and should always be considered and initiated when appropriate.

❼ Pharmacologic alternatives for psoriasis include topical agents, phototherapy, and systemic agents including the use of biologic response modifiers.

❽ In initiating pharmacologic treatment, the choice of therapy is generally guided by the severity of disease: topical agents would be appropriate for mild to moderate disease while a systemic agent would be a more appropriate choice for moderate to severe disease. Phototherapy or photochemotherapy are used for patients with moderate to severe psoriasis, generally when topical therapies alone are inadequate. Patient-specific concerns such as existing comorbid conditions (e.g., renal impairment or hepatic disease) must also be taken into consideration in the choice of therapy. Once the disease is under control, it would be important to step down to the least potent, least toxic agent(s) that maintain control.

❾ Rotational therapy (i.e., rotating systemic drug interventions in a sequential manner) is a means to minimize drug-associated toxicities, since systemic agents for psoriasis often have differing toxicities. This may be considered for psoriasis patients who require systemic treatments long-term to manage their condition.

❿ Some biologic response modifiers have proven efficacy for psoriasis; however, there are differences among these agents, including mechanism of action, duration of remission, and adverse-effect profile. In general, due to their immunosuppressive effects, there is an increased risk of infection with most of these agents. The use of live or live-attenuated vaccines during therapy is generally not recommended. Currently, biologic response modifiers are often considered for patients with moderate to severe psoriasis when other systemic agents are inadequate. It has also been

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recommended that biologic response modifiers be considered as first-line therapy, alongside conventional systemic agents, for patients with moderate to severe psoriasis; however, in practice, cost may be a limiting factor.

Psoriasis is a disease that waxes and wanes. It is a chronic illness that is never cured; however, the signs and symptoms of psoriasis may go into remission (subside totally) and then return again (flare-up, exacerbation, or reactivation). Remission may last for years in some patients, while in others exacerbations may occur every few weeks. Triggers include stress, seasonal changes, and some drugs. Disease flare-ups may also occur at times of life crises. Disease severity may vary from mild to disabling. Thus, management of this condition is necessarily long-term, and management modalities may change according to the severity of illness at the time.

❶ *Patients with psoriasis have a lifelong illness that may be very visible and emotionally distressing. There is a strong need for empathy and a caring attitude in interactions with these patients.*

EPIDEMIOLOGY AND ETIOLOGY

Psoriasis is a common inflammatory skin disorder which is estimated to affect 1.5% to 3% of the Caucasian population.[1,2] It may present at any age.[3,4] Ethnic factors influence disease prevalence. In the United States, prevalence among blacks (0.45% to 0.7%) is lower than in the remainder of the United States population (1.4% to 4.6%).[1] Between 10% and 30% of patients with psoriasis will also have psoriatic arthritis.[5] In 10% to 15% of psoriatic patients with arthritis, joint symptoms actually appear prior to skin involvement.[3] Clinical depression is another frequent comorbid illness in these patients. A recent United States survey showed that 8% to 10% of psoriatic patients aged 18 to 54 years old actively contemplated suicide because of their psoriasis.[6]

❷ *Psoriasis is a T-lymphocyte–mediated inflammatory disease that results from a complex interplay between multiple genetic factors and environmental influences.[1] Genetic predisposition coupled with some precipitating factor triggers an abnormal immune response, resulting in the initial psoriatic skin lesions.* Other risk factors may exacerbate preexisting psoriasis and cause disease flare-ups. Precipitating factors include skin trauma such as a horse-fly bite (known as the **Koebner phenomenon),** an environmental change such as cold weather, stress, a viral or streptococcal infection, or use of a β-adrenergic blocker.[2] Factors exacerbating psoriasis include drugs (e.g., lithium, nonsteroidal anti-inflammatory drugs, antimalarials, β-adrenergic blockers, and withdrawal of corticosteroids), and psoriatic patients commonly have exacerbations during times of stress.[2]

There is a polygenic inheritance pattern which may account for disease susceptibility and expression.[7] Family linkage studies have identified several genetic loci that are potentially responsible: the *PSOR1* gene on chromosome 6p21.3, the *PSOR2* gene on chromosome 17q25, the *PSOR3* gene on chromosome 4q34, the *PSOR4* gene on chromosome 1q21, the *PSOR5* gene on chromosome 3q21, the *PSOR6* gene on chromosome 19p13, the *PSOR7* gene on chromosome 1p, the *PSOR8* gene on chromosome 16q12-13 (which links to both psoriasis and Crohn's disease), and the *PSOR9* gene on chromosome 4q31.[1,4,7,8] There are possibly other genetic loci. *PSOR1* has been considered the major gene locus for psoriasis;[1,4] it appears to be associated with up to 50% of cases of psoriasis.[1]

Studies conducted in twins show a threefold increased risk of psoriasis in monozygotic twins versus fraternal twins.[7] In addition, based on a study in 3,095 families with psoriasis, the calculated lifetime risk of developing psoriasis if no parent, one parent, or both parents have psoriasis was found to be 0.04, 0.28, and 0.65, respectively. If there was already one affected child in the family, the risks were increased to 0.24, 0.51, and 0.83, respectively.[7,9] As many as 71% of patients with psoriasis during childhood have some positive family history.[1] Similarly, psoriatic arthritis is heritable, with a prevalence 19 times higher in first-degree relatives of patients with psoriatic arthritis than in the general population.[7]

PATHOPHYSIOLOGY

❷ *Keratinocyte proliferation is central to the clinical presentation of psoriasis.* **Keratinocytes** are skin cells producing keratin which act as a skin barrier. Increased keratinocyte cell turnover (hyperkeratosis) results in the characteristic thick scaly skin lesions seen in patients with psoriasis.[10,11] Hyperkeratosis results from immune derangements.

The abnormal immune response seen in psoriasis is mediated primarily by T lymphocytes (T cells).[1] In patients with psoriasis, certain types of T cells are overactive and migrate to the skin in large numbers. T cells access the skin by binding to activated endothelial cells via intracellular cell adhesion molecules (ICAM-1).[1,12] These naïve T cells then encounter antigens in the skin, which are presented to the T cells by antigen-presenting cells (APCs), and become activated. There is an LFA-3–CD2 signal which plays an important part in T-cell activation: LFA-3 is the leukocyte-function-associated antigen type 3 found on APCs; CD2 is a cell-surface glycoprotein expressed on T-cell subtypes.[1] When LFA-3 interacts with CD2, there is an increased proliferation of T cells.[13]

Activated T cells begin releasing cytokines including interleukin-2 (IL-2), interferon-γ, (IFN-γ), tumor necrosis factor (TNF-α), and others.[4,13] Cytokine activity leads to a rapid proliferation and turnover of skin cells, triggering the inflammatory process and the development of psoriatic skin lesions.[4,13,14] TNF-α may have a role in disease severity; it upregulates endothelial and keratinocyte expression of ICAM-1,



Patient Encounter, Part 1

A 25-year-old Caucasian man presents with itchy lesions on his scalp, chest, back, elbows, and knees. He says these lesions started about a month ago, and seem to be spreading. Upon examination, the lesions are well-demarcated and are reddish-violet in color—easily distinguished from normal skin. They appeared raised and are covered with loose scales. Removing the scales caused pinpoints of bleeding to show up.

- What information is consistent with psoriasis in this patient?

activates T cells, enhances T-cell infiltration, and augments keratinocyte proliferation.[12]

Treatment of psoriasis is based on an understanding of the underlying pathophysiology. Agents that modulate the abnormal immune response, such as corticosteroids and biologic response modifiers, are important treatment strategies for psoriasis. In addition, topical therapies that affect cell turnover are effective for psoriasis. Clinically, a treatment regimen should always be individualized, taking into consideration severity of disease, patient responses, and tolerability to various interventions.

CLINICAL PRESENTATION

❸ *Diagnosis of psoriasis is usually based on recognition of the characteristic plaque lesion, and not based on lab tests.*



Clinical Presentation of Plaque Psoriasis

General
- Patients have small discrete to generalized confluent lesions over the entire body.

Symptoms
- Patients may complain of severe itching.

Signs
- Lesions are raised and are red to violet in color (commonly known as plaques).
- Lesions have sharply demarcated borders except where confluent.
- Lesions are loosely covered with silvery-white scales, which if lifted off, show small pinpoints of bleeding (Auspitz sign).
- Plaques appear most commonly on the elbows, knees, scalp, umbilicus, and lumbar areas, and often extend to involve the trunk, arms, legs, face, ears, palms, soles, and nails.
- Nail involvement presents as pitting, discoloration ("oil spots"), crumbling, splinter hemorrhages, growth arrest lines, or tissue build-up around the nails.



Clinical Presentation of Other Types of Psoriasis

Inverse psoriasis spares the areas commonly involved in plaque psoriasis and instead appears in intertriginous areas, where scaling is minimal.
Guttate psoriasis presents as a sudden eruption of small, disseminated erythematosquamous papules and plaques, and is often preceded by a streptococcal infection 2 to 3 weeks prior.
Pustular psoriasis may be localized or generalized and may be an acute emergency requiring systemic therapy.
Generalized pustular psoriasis is characterized by disseminated deep-red erythematous areas and pustules, which may merge to become "lakes of pus."
Erythrodermic psoriasis is a generalized, life-threatening condition that presents with erythema, desquamation, and edema, and may require life support measures as well as systemic therapy.
Psoriatic diaper rash is the most common type of psoriasis in children under 2 years old. This usually affects inguinal folds and greater than 90% of psoriatic diaper rash cases may have involvement outside the diaper area.

TREATMENT

Desired Outcomes and Goals

❹ *Since psoriasis is a chronic illness with no known cure, the goals of treatment focus on controlling the signs and symptoms of disease,* including:

- Minimizing or eliminating the signs of psoriasis such as plaques and scales.
- Alleviating pruritus and minimizing excoriations.
- Reducing the frequency of flare-ups.
- Ensuring appropriate treatment of associated conditions such as psoriatic arthritis.
- Avoiding or minimizing adverse effects from topical or systemic treatments used.
- Providing cost-effective therapy.
- Providing guidance or counseling as needed (e.g., stress-reduction techniques).
- Maintaining or improving the patient's quality of life.

General Approach to Treatment

❺ *Management of patients with psoriasis generally involves both nonpharmacologic and pharmacologic therapies.* Pharmacologic alternatives for plaque psoriasis include topical treatments, **phototherapy**, **photochemotherapy**, and systemic therapies alone (orally or by injection). The choice of treatment is usually dictated by the severity of disease.[15–17] In some cases, a combination of treatment options may be preferred. Topical therapies can be used in patients with limited or mild



Patient Encounter, Part 2

Additional relevant information was obtained from the patient, including the following history.

FH
His father and one of his brothers have psoriasis; his only sister has atopic dermatitis

SH
He works as an assistant copywriter in a busy publishing house, and is constantly struggling with multiple deadlines; he is an occasional social drinker and nonsmoker; he is a single father to a 6-year-old boy

PE
He appears anxious and embarrassed about the lesions

VS: Blood pressure 125/70 mm Hg, pulse 72 bpm, respiratory rate 16/minute, temperature 37°C (98.6°F)
CV: Regular rate and rhythm, normal S1, S2; no murmurs, rubs, or gallops
Abd: Soft, nontender; bowel sounds present
Exts: Within normal limits; no joint pains
Skin: Multiple lesions on the scalp, chest, back, elbows, and knees; evidence of excoriation on the chest.

- What risk factors does he have for psoriasis?
- Identify your treatment goals for the patient.

to moderately severe disease. Phototherapy and photochemotherapy are used in moderate to severe disease. Systemic therapies are used for patients with extensive or moderate to severe disease. To minimize drug toxicities in these patients, systemic therapies are often used in rotation, or used in conjunction with topical or phototherapy.[16,17] Biologic agents are becoming incorporated into the same category as other systemic agents and are currently recommended for consideration as first-line therapies alongside conventional systemic agents for moderate to severe disease.[17] However, since there is a significant cost difference, biologic agents are often reserved for cases in whom traditional systemic agents provide inadequate control. There are two recently published treatment guidelines including a general consensus on psoriasis treatments by the American Academy of Dermatology,[16] and a consensus on moderate to severe psoriasis by the Canadian Psoriasis Expert Panel.[17]

Nonpharmacologic Treatment

❻ *Nonpharmacologic alternatives may be extremely beneficial in the patient with psoriasis and complement pharmacologic therapies; thus should always be considered and initiated when appropriate.* These include the following management strategies:[10]

- *Stress reduction techniques*. Psychotherapy including stress management, guided imagery, and relaxation techniques are being used more frequently as adjunctive therapies for patients with psoriasis. Stress reduction has been shown to improve both the extent and severity of psoriasis.
- *Oatmeal baths*. Regular use of oatmeal baths in tepid water may help soothe the itching associated with psoriasis and reduce the need for systemic anti-pruritic agents.
- *Non-medicated moisturizers*. Maintaining adequate skin moisture helps to control the scaling associated with psoriasis. Emollients restore skin pliability, reduce skin shedding, reduce pruritus, and help prevent painful cracking and bleeding.[2] Non-medicated moisturizers may be liberally applied several times daily to help prevent skin dryness. Fragrance-free products should be selected when available.
- *Avoid irritant chemicals on the skin*. Harsh soaps or detergents should not be used. Cleansing should be done with tepid water, preferably using lipid-free and fragrance-free cleansers.
- *Avoid skin trauma*. Sunburns can induce a flare-up of psoriasis. Sunscreens with a sun protection factor of at least 15 should be routinely used when outdoors; often a sun protection factor of 30 is recommended. Avoid scratching the skin, which could lead to excoriations and exacerbate psoriasis. Loose-fitting cotton garments should be worn to minimize skin irritation.

Pharmacologic Treatment

❼ *Pharmacologic alternatives for psoriasis include topical agents, phototherapy, and systemic agents including the use of biologic response modifiers. See Figs. 61–1 and 61–2 for treatment algorithms.*



Patient Encounter, Part 3

The diagnosis is that the patient has new-onset mild to moderate plaque psoriasis.

- What nonpharmacologic alternatives are appropriate for this patient?
- What pharmacologic treatments would be appropriate as initial therapy for this patient?
- Create a care plan for this patient's psoriasis, including statement of the drug-related problems, goals of therapy, patient-specific detailed therapeutic plan, and monitoring plan and follow-up.

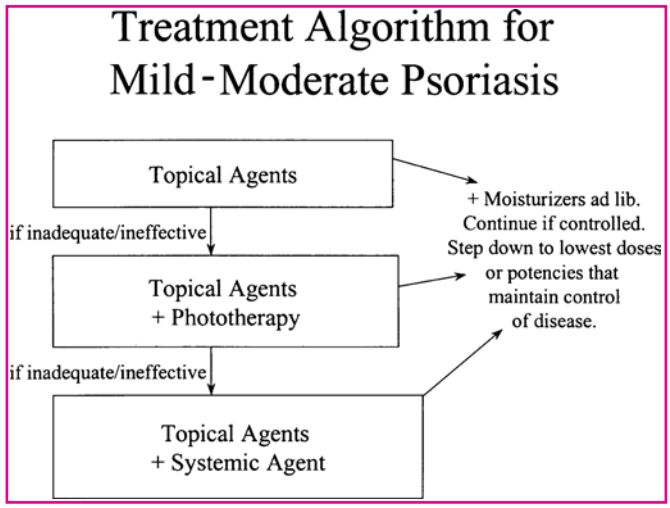


FIGURE 61–1. Treatment algorithm for mild to moderate psoriasis.

Topical Therapy for Psoriasis

❽ *Topical therapy is the initial drug treatment strategy for patients with mild to moderate psoriasis. It is estimated that approximately 70% to 80% of all patients with psoriasis can be treated adequately with use of topical therapy.*[1] Topical therapies include corticosteroids, coal tar products, anthralin, vitamin D_3 analogues such as calcipotriol, retinoids such as tazarotene, and topical immunomodulators such as tacrolimus and pimecrolimus.[18] Vitamin D_3 analogues and topical retinoids all affect keratinocyte functions and the immune response. Currently, these are in wider use than is either anthralin or coal tar preparations.

Topical agents may be incorporated into various vehicles including ointments, creams, gels, lotions, foams, pastes, and shampoos. Ointments provide occlusion which may increase drug penetration and enhance efficacy. Creams and lotions are easier to spread, especially in hairy areas. Gels may have drying and cooling effects in addition to easy spreadability. Foams may have enhanced delivery and/or efficacy in comparison to lotions or creams and become a cosmetically elegant liquid upon skin contact, with good patient acceptance.[18] Shampoos incorporating tar distillates or salicylic acid are useful for scalp psoriasis. Pastes such as Lasar's paste have an inherent stiffness which minimizes the spread of medication and are useful for incorporating drugs such as anthralin. Anthralin, especially in higher concentrations used in short-contact methods, may cause skin irritation and burning if in contact with normal skin. The selection of an appropriate vehicle is often an important consideration.

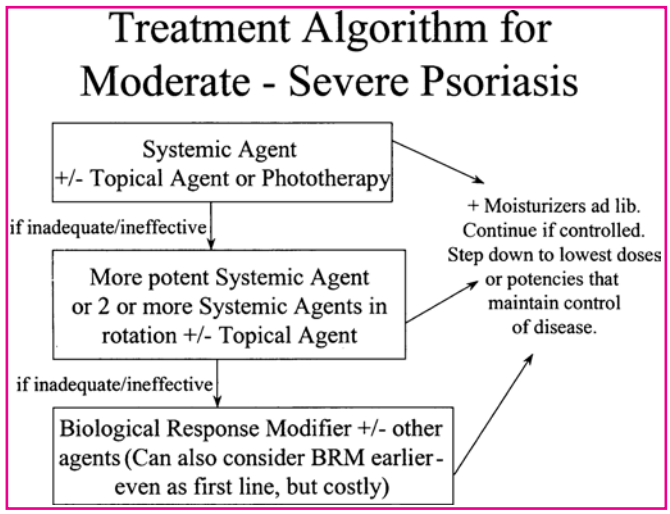


FIGURE 61–2. Treatment algorithm for moderate to severe psoriasis.

For mild to moderate psoriasis, mid-potency corticosteroids such as betamethasone valerate (0.05% to 1%) are most frequently selected first, with escalation to higher-potency corticosteroids if needed, and stepping down to lower-potency corticosteroids when the psoriasis improves. High-potency corticosteroids may be used initially in thicker plaque areas such as palms and soles, but should be considered for short-term use only. These include fluocinonide, clobetasol, halobetasol, and betamethasone dipropionate in optimized base. Low-potency corticosteroids such as hydrocortisone (0.5% to 2%) are appropriate choices if treatment of the face or flexures is necessary. Topical corticosteroids are available as ointments, creams, lotions including scalp lotions, and a few foam products, and should be applied in a thin layer on the skin. Intralesional triamcinolone may be useful for specific lesions such as nail matrix psoriasis. Tachyphylaxis due to down-regulation of steroid receptors can occur with prolonged use, making the treatment regimen ineffective.[2,18] Using a potent corticosteroid for only 1 to 2 days per week ("weekend therapy") has been shown to lengthen the duration of effectiveness.[18] Combining this regimen with calcipotriol used during the week may provide greater efficacy.[18]

It is important to remember that adverse effects of *topical* corticosteroids may be *systemic* in nature and hypothalamic-pituitary-adrenal axis suppression can occur, especially when high-potency corticosteroids are used. Infants and small children may be more susceptible due to their increased skin surface:body mass ratio.[18] Topical corticosteroids may also cause **striae**, skin atrophy, acne, **telangiectasias**, and rosacea.[2,10,18] Atrophy can result in thin, fragile, easily lacerated skin. Striae are caused by tearing of dermal connective tissue and are irreversible.[18] Due to their significant adverse-effect profile, it has been recommended that no topical corticosteroid be used regularly for more than 4 weeks without review and reassessment.[2]

Vitamin D analogues (calcipotriol, calcitriol, and tacalcitol) are also frequently selected as initial pharmacotherapy in the management of mild to moderate psoriasis.[2] These inhibit keratinocyte differentiation and proliferation and may be anti-inflammatory.[2] Unlike corticosteroids, tachyphylaxis does not occur with prolonged use. Clearance of lesions should occur after 4 to 6 weeks of treatment.[2] Lack of response by 8 weeks

indicates treatment failure.[2] These analogues may cause skin irritation leading to erythema, dryness, stinging, or burning. They may also cause hypercalcemia secondary to excessive absorption or use.[2,10,18] Calcipotriol (50 mcg/g) is currently available in the United States and Canada as ointment, cream, and solution. Topical calcitriol has been studied for treatment of psoriasis and appears almost as effective as betamethasone dipropionate in clearance of lesions, with a longer remission period.[2] It is less irritating than calcipotriol and can be used for the face and flexures.[2] Calcipotriol plus betamethasone is available as a combination product in Canada.[10] In contrast, salicylic acid can completely inactivate calcipotriol on contact.[18] Tacalcitol is a newer vitamin D_3 analogue available in the UK.[1]

Keratolytic agents such as salicylic acid are often added to bath oil or shampoos (typically 3% to 4%) for scalp psoriasis.[10] Salicylic acid can also be added to topical corticosteroid preparations to enhance steroid penetration (salicylic acid breaks down keratin).

Coal tar is keratolytic and may have anti-proliferative and anti-inflammatory effects.[2] Coal tar products include crude coal tar and tar distillates (liquor carbonis detergens) available as ointments, creams, and shampoos in various strengths. Preparations containing coal tar may precipitate folliculitis,[10] will stain clothing, and have an unpleasant odor. They are also photosensitizing and can be combined with UVB phototherapy (Goekermann's regimen) to increase treatment response.[19,20]

Anthralin (dithranol) has a direct anti-proliferative effect on epidermal keratinocytes[2] and is generally used only on thick plaque areas. It can be used continuously or as short-contact anthralin therapy (SCAT): 1% to 4% applied for minutes to up to 2 hours.[18] Anthralin, including SCAT with high anthralin concentrations, may be highly irritating, especially if SCAT treatments are misused or used continuously.[10] It is important to remember when compounding anthralin preparations that prescribed concentrations can range from 0.1% (meant for continuous use) to 1% to 4% (meant for short-contact use).[18] Normal skin surrounding the psoriasis plaques should be protected by using non-medicated paste or zinc oxide. People who handle the dry anthralin powder should avoid skin contact (e.g., by wearing gloves while compounding).

Tazarotene is a topical retinoid used for mild to moderate psoriasis and is also effective for acne. It normalizes keratinocyte differentiation and has anti-proliferative and anti-inflammatory effects.[2] Tazarotene is available commercially as a 0.05% or 0.1% gel. It may cause significant skin irritation including erythema, pruritus, and burning, especially upon initial use.[2,10,18] Combining tazarotene use with a topical corticosteroid in an alternate-day regimen or morning corticosteroid–evening tazarotene dosing fashion may minimize skin irritation and steroid-induced skin atrophy, and enhance efficacy.[18] Avoid its use in women of childbearing age unless effective contraception is being used; there is a potential risk of systemic drug absorption[2] and systemic retinoids are known teratogens. Concomitant use of other topical preparations or cosmetics with a strong drying effect should be avoided when possible.[10]

Phototherapy for Psoriasis

Phototherapy or photochemotherapy is used for patients with moderate to severe psoriasis, generally when topical therapies alone are inadequate. Photochemotherapy is the concurrent use of phototherapy together with topical agents[18,21] or systemic drugs.[1,21] Phototherapy of psoriasis involves the use of either ultraviolet A (UVA) or ultraviolet B (UVB). UVA is a longer wavelength, and therapy with UVA is always combined with psoralens (e.g., methoxsalen or trioxsalen), which are used as photosensitizers to increase efficacy (PUVA = psoralens + UVA). There may be an increased risk of skin cancers after prolonged use of phototherapy and risks are greater with PUVA than UVB.[10,21]

There is a bath PUVA and an oral PUVA. Bath PUVA therapies involve soaking in a bath of psoralens liquid for 15 minutes prior to UVA treatment. Oral PUVA involves taking an oral psoralens capsule the day prior to a UVA treatment. Oral psoralens such as methoxsalen cause nausea in many patients. Other adverse effects of PUVA include photosensitivity, which necessitates the use of eye protection and UVA-blocking sunscreen for 24 hours after a PUVA treatment; macular **melanosis** at exposed sites (PUVA **lentigines**); and increased risk of skin cancers, especially squamous cell carcinoma.[21]

PUVA has been used in conjunction with other topical agents to increase treatment efficacy. Calcipotriol when added to a regimen of PUVA may reduce the number of PUVA treatments and the total UVA dosage needed for clearing lesions.[18,22,23] The rate ratio for marked improvement in patients receiving PUVA plus calcipotriol versus PUVA alone was 1.2 in a recent meta-analysis of 11 controlled studies.[24] If calcipotriol and PUVA are used together, calcipotriol must be applied *after* PUVA, since irradiation with UVA will inactivate calcipotriol.[25] Use with other topical agents has been limited. One small study of PUVA with tazarotene in 12 patients with extensive plaque psoriasis showed a statistically significant improvement after 3 weeks;[26] however, UVA doses should be reduced by at least one-third if tazarotene is added, since it increases the risk for immediate pigment darkening caused by UVA.[27] Coal tars are photosensitizing[18] and are not generally used with PUVA,[21] and PUVA plus topical corticosteroids have yielded conflicting results.[21]

UVA can be used with other systemic agents including oral retinoids (RePUVA) and methotrexate. This will be discussed later in greater detail.

UVB treatments are often used alone. However, they have also been given in combination with topical or systemic agents to increase treatment efficacy. Topical regimens include UVB with tazarotene,[21] UVB with crude coal tar (Goekermann regimen),[19–21] UVB with anthralin (Ingram regimen),[21] and UVB with calcipotriol.[21] UVB with tazarotene (a retinoid) may be synergistic; the effect of each agent seems to be enhanced when used together. However, all retinoids can cause skin thinning, which may allow for easier burning to occur. The erythema induction threshold is lowered by about 25%.[21] Therefore, doses of UVB should be reduced by at least one-third when tazarotene is added.[18,21] UVB with crude coal tar is a regimen developed early in the twentieth century which is still considered one of



Patient Encounter, Part 4

The patient's psoriatic condition remains well controlled for about 10 years, then flare-ups become a frequent occurrence. The patient did not respond well to UVB therapy used alone. He is currently presenting with fairly extensive plaque psoriasis, affecting about two-thirds of his body surface area.

Create a care plan for this patient's psoriasis, including statement of the drug-related problems, goals of therapy, patient-specific detailed therapeutic plan, and monitoring plan and follow-up.

the most effective regimens available.[21] However, many patients consider it messy and time-consuming. UVB with short-contact anthralin therapy (SCAT) may not be consistently effective, and UVB with topical steroids may actually shorten the remission period.[22,28]

Several UVB and systemic therapy combinations have shown efficacy. These include UVB with acitretin (ReUVB) and UVB with methotrexate, and will be discussed later.

Systemic Therapy for Psoriasis

❸ *Systemic therapies are seldom used for mild to moderate psoriasis, and are generally reserved for patients with moderate to severe psoriasis.*[17,29] Oral agents include sulfasalazine, acitretin, methotrexate, cyclosporine, mycophenolate mofetil, azathioprine, tacrolimus, and hydroxyurea. Parenteral agents include the biologic response modifiers alefacept, efalizumab, etanercept, infliximab, and many others, currently at various stages of research or approval for psoriasis.

❾ *Rotational therapy (i.e., rotating systemic drug interventions in a sequential manner) is a means to minimize drug-associated toxicities, since systemic agents for psoriasis often have differing toxicities. This may be considered for psoriasis patients who require systemic treatments long-term to manage their condition.* Systemic therapies are optimally used in a rotating fashion to minimize drug toxicities (e.g., methotrexate–acitretin–cyclosporine or methotrexate–PUVA–acitretin).[10]

Sulfasalazine has variable efficacy and is of limited potency. However, its side-effect profile is better than other systemic therapies and it is sometimes tried as an initial systemic agent for moderate to severe psoriasis. Usual doses are 2 to 4 g/day in divided doses.[10]

Acitretin is an oral retinoid that is likely safer than methotrexate or cyclosporine, especially when considering continuous use over many years.[21] The initial dose is 25 mg/day which can be increased to a maximum of 75 mg/day if needed.[17] When acitretin is used concurrently with phototherapy (ReUVB or RePUVA), there appears to be a synergistic treatment effect, and the number and duration of phototherapy sessions needed to achieve clearance is reduced.[21] RePUVA is a well-established treatment regimen for psoriasis.[1] When acitretin is used with calcipotriol, improvement and clearance of lesions may be achieved with significantly lower cumulative acitretin dosages.[21,30] However, acitretin is teratogenic and relatively contraindicated in women of childbearing potential. It must not be used in pregnant women, those with unreliable contraception, or those who intend to become pregnant at any time during or for 3 years after discontinuation of therapy.[10,29] Ethanol should be avoided during therapy and for 2 months after drug discontinuation since it causes the transesterification of acitretin to etretinate, which has a much longer elimination half-life.[10,29] Other side effects include ophthalmologic, neuromuscular, hyperlipidemic, and hepatic enzyme changes.[10,29] Long-term continuous use has caused a syndrome of **disseminated idiopathic skeletal hyperostosis** and mild osteoporosis, found in a few case reports.[21,31]

Methotrexate used in low doses is one of the mainstays of systemic therapy in the treatment of psoriasis. An initial test dose of 2.5 to 5 mg is recommended.[17] If lab values are normal after 1 week, the dose can be increased to a range of 7.5 to 30 mg/wk.[17] This can be given as a single dose or split into two or three doses given 12 hours apart to minimize gastrointestinal side effects. Always titrate to the lowest effective dose for maintenance. There is a significant risk of hepatotoxicity which is greater than that seen in patients with rheumatoid arthritis given similar cumulative doses of methotrexate.[29] In psoriatic patients with no hepatic risk factors, a liver biopsy is recommended when the cumulative dose of methotrexate reaches 1.5 g. In high-risk psoriatic patients, it is preferable to also perform a biopsy during initial therapy with methotrexate.[10,17,29,32] Monitoring PIIINP (the aminoterminal propeptide of type III procollagen) at least three times yearly may reduce the number of repeat liver biopsies required.[10,29] Liver biopsies are not recommended in the elderly, those with limited life expectancy, or those with significant medical problems.[29] Periodic complete blood cell counts, renal and liver function tests, and pulmonary toxicity testing should also be conducted.[10,29]

The combination of methotrexate and UVB seems to be synergistic; responses may occur with lower cumulative doses of both methotrexate and UVB. However, stopping methotrexate may cause rebound[21,33] and there is some concern about photosensitivity.[21] Methotrexate and PUVA have been used together in patients refractory to other treatments; however, there is additive carcinogenesis (especially increasing the risk of squamous cell cancer) and subacute phototoxicity.[21]

Methotrexate has been used successfully with cyclosporine, either concurrently[34] or in rotation. Rotational therapy is particularly effective since it minimizes the serious adverse effects of both agents: hepatotoxicity from methotrexate and hypertension and nephrotoxicity from cyclosporine. Having an overlapping treatment period may not be necessary and patients have been successfully switched after a 1-week washout period.[21,35] This is a very useful combination of systemic agents in the long-term management of this chronic disease.

Cyclosporine is used in low doses whether alone or in combination with other agents. The usual dose range is 2 to 2.5 mg/kg

per day, given orally in two divided doses, for patients with stable generalized psoriasis or for moderate to severe disease. For patients with severe inflammatory flares of psoriasis, or recalcitrant cases who fail to respond to numerous other therapies, or for a highly distressed patient in a crisis situation, the starting dose is higher at 5 mg/kg per day in two divided doses.[29] This dose should not be exceeded[17] and once there is a clear response should be decreased by 0.5 to 1 mg/kg per day at weekly or longer periods, to the lowest effective maintenance dose. If started at 2.5 mg/kg per day, and the response is inadequate, it is recommended to wait at least 1 month before considering a dosage increase. If necessary, the dosage may be increased by 0.5 to 1 mg/kg per day[9,28,35] monthly[17] to a maximum of 5 mg/kg per day.[17] Always titrate to the lowest effective dose for maintenance.[17]

Blood pressure and serum creatinine (SCr) should be assessed prior to beginning cyclosporine therapy to obtain accurate baselines, and should be reassessed biweekly once therapy is started for at least the first 12 weeks of therapy (until values stabilize), and then closely monitored during therapy. If SCr increases to 30% above the patient's baseline, the cyclosporine dosage needs to be decreased and SCr rechecked in a month. If the SCr is still above 30% of the patient's baseline, cyclosporine should be discontinued and only resumed when the SCr returns to within 10% of the patient's baseline. Cyclosporine should also be discontinued for inadequate response after 3 months' use at the maximum dose.[10,36]

The combination of cyclosporine with calcipotriol may be more efficacious than either agent used alone.[21,37] Cyclosporine and SCAT may also be effective.[21,38] However, cyclosporine *should not* be used concurrently with PUVA; there is a well-documented increased risk of squamous cell cancer and the combination may have a negative effect on lesion clearance.[21] The combination of cyclosporine with methotrexate is extremely effective and minimizes toxicity from either agent as discussed. Cyclosporine has also been used successfully with mycophenolate mofetil[38] and etanercept.[29]

Mycophenolate mofetil in doses of 1 to 1.5 g twice daily (maximum dose 3 g/day) is effective as adjunctive therapy in patients with resistant psoriasis on cyclosporine.[29,38] As monotherapy, there may be some benefit in patients with moderate psoriasis and psoriatic arthritis, but not in severe psoriasis.[29]

Hydroxyurea is an older agent still used occasionally today for patients with psoriasis; however, there have been recent precautions about its use in the elderly and cutaneous vasculitic toxicities in patients with myeloproliferative disorders.[29] Toxicity associated with tacrolimus has limited its use in psoriasis. Azathioprine has a slow onset and significant toxicity.[29] Oral corticosteroids are reserved for severe or life-threatening conditions such as severe psoriatic arthritis or exfoliative psoriasis; prolonged oral steroid use should be avoided.[10]

Biologic Response Modifiers

Based on the recent advances in our understanding of the pathogenesis and pathophysiology of psoriasis, there was accompanying research into the development and use of biologic response modifiers for psoriasis and psoriatic arthritis. ⓾ *Some biologic response modifiers have proven efficacy for psoriasis; however, there are differences among these agents, including mechanism of action, duration of remission, and adverse-effect profile. Currently, biologic response modifiers are often considered for patients with moderate to severe psoriasis when other systemic agents are inadequate. It has also been recommended that biologic response modifiers be considered as first-line therapy, alongside conventional systemic agents, for patients with moderate to severe psoriasis;[17] however, in practice, cost may be a limiting factor.* Biologic response modifiers with proven efficacy for psoriasis include alefacept, etanercept, and efalizumab. These agents employ the following targeted immunosuppressive strategies: alefacept inhibits T-cell activation by targeting LFA-3–CD2 and inducing apoptosis in memory T cells,[1] etanercept inhibits T1 cytokines by targeting tumor necrosis factor-α, and efalizumab inhibits T-cell activation by targeting CD11a, the α subunit of LFA-1 (ICAM-1).[1,10,39] Other biologic agents in clinical trials for psoriasis include infliximab, adalimumab, HuMax-CD4, siplizumab, daclizumab, and denileukin diftitox.[10,39] ⓾ *In general, due to their immunosuppressive effects, there is an increased risk of infection with most of these agents. The use of live or live-attenuated vaccines during therapy is generally not recommended.*

The most promising types of biologic response modifiers are monoclonal antibodies, cytokines, and fusion proteins.[1] Monoclonal antibodies may be chimeric (fused mouse and human segments; designated "-ximab"), humanized with intermittent murine sequences (designated "-zumab"), human backbone with monkey sequences, or fully human.[40]

Alefacept is a recombinant fusion protein composed of LFA-3 linked to the constant portion of human IgG.[40,41] Alefacept inhibits T-cell activation by binding to their CD2 sites, thus impairing co-stimulatory signals; and alefacept also interacts with natural killer cells to destroy already activated T cells.[1,10] This agent is useful for moderate to severe chronic plaque psoriasis. About one-third of alefacept-treated patients enter prolonged remissions ranging from 6 to 18 months. Alefacept appears to spare helper T-cell function and does not significantly impair primary or secondary antibody responses (for example, the ability to combat infections or respond to vaccinations). There is a significant risk of malignancy and common side effects include lymphopenia, myalgias and chills, pharyngitis, cough, nausea, and for IM injections pain and inflammation at the injection site.[10,42,43] The dosage recommended is 15 mg IM once weekly for 12 weeks. The regimen may be repeated in 12 weeks if needed, provided the CD4+ T-cell count is normal (defined as greater than or equal to 250 cells/μL).[10]

Etanercept is a fully human dimeric fusion protein composed of human TNF-α p75 receptor fused to the Fc portion of human IgG1.[41] It acts as a tumor necrosis factor-α (TNF-α) inhibitor by binding to and inactivating TNF-α, thus preventing interactions with its cell surface receptors.[41] This agent is useful for chronic moderate to severe plaque psoriasis and for psoriatic

arthritis. In clinical trials, 49% of patients given 50 mg subcutaneously twice weekly showed a 75% improvement in the psoriasis area-and-severity index by 12 weeks.[10,44] The drug appears to be well tolerated; common side effects include injection site reactions, headache, increased respiratory tract infections (colds and sinusitis), and gastrointestinal symptoms.[10,44] There is an increased risk of tuberculosis and hepatitis B reactivation. Serious infections including fatalities have been reported with etanercept and there were reports of worsening congestive heart failure (CHF) and new-onset CHF.[10] Due to rare reports of blood disorders (anemia, aplastic anemia, leukopenia, neutropenia, pancytopenia, and thrombocytopenia), patients are advised to contact their doctor if they experience persistent fever, bruising, bleeding, or paleness.[10] A systemic lupus erythematosus (SLE)-like syndrome has been rarely reported.

Efalizumab is a humanized murine antibody directed against CD11a, the α subunit of leukocyte-function-associated antigen type 1 [LFA-1]. This inhibits T-cell activation, cutaneous T-cell trafficking, and T-cell adhesion to keratinocytes. Efalizumab has a rapid onset of action with symptom improvement seen in about 4 weeks. About 25% of psoriatic patients receiving either 1 or 2 mg/kg per week improved by at least 75% at 12 weeks of treatment.[11,45–47] Treatment should be continued; with cessation of therapy, the median time to relapse is 60 to 80 days. Long-term safety and efficacy are still being evaluated. Thrombocytopenia occurs rarely.[18] Common side effects include headache, fever, chills, nausea, and myalgias, which usually diminish after the first or second weekly dose. Worsening psoriasis may occur during treatment or after drug discontinuation, and there is an increased risk of infection.[11,45–47]

Infliximab is a chimeric human/murine monoclonal antibody against TNF-α. It is approved for reducing the signs and symptoms of psoriatic arthritis and clinical studies in patients with psoriasis are showing benefit. Good responses have been seen in patients with moderate to severe plaque psoriasis receiving infliximab 5 to 10 mg/kg at 0, 2, and 6 weeks. Median time to response was 4 weeks.[48] If the treatment is continued it should be given every 8 weeks thereafter. Infliximab is also approved for rheumatoid arthritis and significant adverse effects from post-marketing experience and clinical trials have included hematologic abnormalities (leukopenia, neutropenia, thrombocytopenia, and pancytopenia), hepatotoxicity (rarely: acute liver failure, jaundice, hepatitis, and cholestasis), hypersensitivity reactions (anaphylaxis, urticaria, and serum sickness), ocular toxicity (optic neuritis and optic neuropathy), and increased infections (tuberculosis, hepatitis B reactivation, *Listeria monocytogenes* infections, fungal infections, and sepsis). There is an increased risk of infection by live vaccines and vaccination with live vaccines while receiving infliximab therapy is not recommended. Patients should be evaluated for active or latent tuberculosis (tuberculosis skin test) prior to therapy.

Adalimumab is a TNF-α inhibitor initially approved for the treatment of rheumatoid arthritis in 2003. It is approved for treatment of psoriatic arthritis and off-label uses and clinical studies in patients with psoriasis are showing benefit. The dosage is 40 mg subcutaneously every 2 weeks. Patients should be evaluated for active or latent TB infection (TB skin test) prior to therapy. There is an increased risk of serious infections (in particular, respiratory infections including pneumonia and tuberculosis, and hepatitis B reactivation), of exacerbation in patients with heart failure, and increased risk of lymphoma. Hematologic abnormalities (pancytopenia, thrombocytopenia, and leukopenia) have been rarely reported. Positive antinuclear antibody titers and a lupus syndrome have been reported. Anti-dsDNA antibody determinations are recommended in patients presenting with lupus-like symptoms during adalimumab therapy. A pruritic urticarial eruption that lessens in severity with each subsequent injection has recently been reported.



Patient Encounter, Part 5

It was decided to begin methotrexate in this patient, rotating with cyclosporine.

- What lab tests would be important to perform prior to starting therapy with methotrexate? With cyclosporine?
- What dosage regimen would be appropriate?
- What monitoring plan would be appropriate?
- What information would be important to provide this patient with?

OUTCOME EVALUATION

- Monitor the patient for clearance of skin lesions. Depending on the agent(s) used and site of lesions it may take 2 to 6 weeks or longer to see a response. Complete clearance may not be achieved for all patients.
- Monitor the patient for specific adverse effects, depending on agent(s) used. Some agents are discussed below, and others are discussed earlier in this chapter.
- Methotrexate: Monitor complete blood cell count and liver function tests at baseline and regularly, and consider liver biopsy prior to treatment and at a cumulative dose of 1.5 g. If available, monitor PIIINP at least three times yearly.
- Cyclosporine: Monitor SCr, blood urea nitrogen, and blood pressure at baseline and reassess biweekly for at least 12 weeks (or longer until values stabilize), then regularly. Adjust doses when needed in response to SCr changes as discussed above.[9,35]
- Acitretin: Monitor serum lipids and liver function tests.
- Topical corticosteroids: Monitor for skin thinning, telangiectasias, and possible hypothalamic-pituitary-adrenal axis suppression.
- Interact with the patient's other health care providers as needed to discuss patient concerns or issues.



Patient Care and Monitoring

With respect to pharmacologic therapies, it is important to:

- Provide patients with an approximate time frame for improvement based on the patient's areas of involvement and type of drug therapy. For example, a statement such as: "There should be less scaling and redness of your scalp lesions and a reduction in the thickly crusted areas within 1 to 2 weeks. You should notice a general improvement in your condition by 6 to 12 weeks. Your palms, soles, elbows, and knees may take longer to clear."[9]
- Provide appropriate advice about drug regimens including how to apply a specific topical agent, how to use a specific systemic agent, and precautions and possible toxicities of any drug therapy, remembering that topical therapies can have significant systemic adverse effects.
- Check the patient profile and talk with the patient to ensure that there are no significant drug interactions with other concurrent medications and therapies.
- Reinforce the importance of adherence to therapies and specific drug regimens.
- Reinforce the importance of regular follow-up with the patient's health care providers including all appointments for follow-up care and lab work (if any).
- Interact with the patient's other health care providers as needed to discuss patient concerns or issues detected including drug interactions, nonadherence, and adverse effects.

SUMMARY

We must remember that psoriasis is a lifelong illness with no known cure and often has a significant psychosocial component. Author John Updike has said about his own psoriatic condition, that "my torture is skin deep" and that "we hate to look upon ourselves," calling himself a "leper."[49,50] This disease may be very visible and emotionally distressing, and can cause significant disability both physically and psychologically, affecting psychosocial functioning and quality of life. Empathy and a caring attitude can go a long way in the care of these patients.[50]

ABBREVIATIONS

APC:	Antigen-presenting cell
CHF:	congestive heart failure
ICAM-1:	Intracellular cell adhesion molecule-1
IFN-γ:	interferon-γ
IL-2:	Interleukin-2
IM:	intramuscular
LFA-1:	leukocyte-function-associated antigen type 1
LFA-3:	leukocyte-function-associated antigen type 3
PIIINP:	the aminoterminal propeptide of type III procollagen
PUVA:	psoralens + ultraviolet A
RePUVA:	oral retinoid + PUVA
ReUVB:	acitretin + ultraviolet B
SCAT:	Short-contact anthralin therapy
SCr:	serum creatinine
SLE:	systemic lupus erythematosus
TNF:	Tumor necrosis factor
UVA:	Ultraviolet A
UVB:	Ultraviolet B

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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Useful websites: National Psoriasis Foundation, at www.psoriasis.org; PsoriasisNet, at www.skincarephysicians.com; American Academy of Dermatology, at www.aad.org; Canadian Dermatology Association, at www.dermatology.ca.

62 Common Skin Disorders

Angie L. Goeser



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Describe the pathophysiology of common skin disorders.
2. Assess the signs and symptoms of common skin disorders in a presenting patient.
3. List the goals of treatment for patients with common skin disorders.
4. Select appropriate nonpharmacologic and pharmacologic treatment regimens to patients presenting with common skin disorders.
5. Identify adverse effects that may result from pharmacologic agents used in the treatment of common skin disorders.
6. Develop a monitoring plan that will assess the safety and efficacy of the overall disease management of common skin disorders.
7. Create educational information for patients about common skin disorders, including appropriate self-management, available drug treatment options, and anticipated therapeutic responses.

Key Concepts

❶ The development of acne lesions results from four pathogenic factors, which include excess sebum production, keratinization, bacterial growth, and inflammation.

❷ The treatment goals for acne vulgaris are to eliminate existing lesions and prevent new lesions from developing, as well as to decrease discomfort and the incidence of scarring.

❸ Acne is categorized as mild, moderate, or severe based on lesion type and severity and successful treatment approaches are developed based on these categories.

❹ Irritant contact dermatitis results from first-time exposures to irritating substances such as soaps, plants, cleaning solutions, or solvents. Allergic contact dermatitis occurs after an initial sensitivity and further exposure to allergenic substances, including poison ivy, latex, and certain types of metals.

❺ The initial treatment goal of contact dermatitis is identifying the causative substance and eliminating its exposure. The second treatment goal is symptom relief.

❻ Although many factors contribute to the etiology of diaper rash, it is most likely the result of prolonged contact of the skin with urine and feces in the diaper.

❼ The primary goal in the treatment of diaper rash is prevention and is most often accomplished through frequent diaper changes.

❽ When a diaper rash is already present, repairing the damaged skin, relieving discomfort, and preventing infection are important factors to consider when developing an effective treatment regimen.

The skin is the largest organ of the human body. One of its most important functions is to assist the immune system by serving as a barrier that protects underlying structures from trauma, infection, and exposure to harmful environmental elements. The skin also holds in place essential organs and fluids necessary for life. Any significant injury to this outer protective layer may potentially compromise an individual's overall health.

Several thousand skin disorders are currently documented, and many patients will seek the assistance of a health care provider when a problem with their skin develops. Others will utilize methods of self-care to effectively treat their symptoms. Some skin problems, such as mild acne or diaper rash, may be successfully treated with over-the-counter medications and lifestyle modifications. However, if left untreated or treated inadequately, these seemingly simple disorders can worsen and require more advanced care.

As health care providers, it is important to be familiar with the diagnosis and treatment of disorders of the skin. Providing

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patients with appropriate nonpharmacologic and pharmacologic therapy options, as well as patient education on methods of treatment and prevention, will assist in the successful resolution of many common skin disorders.

ACNE VULGARIS

Acne vulgaris, an inflammatory skin disorder of the pilosebaceous units of the skin, is the most common dermatologic reason for physician visits in the United States.[1] Although most commonly seen on the face, acne can also present on the chest, back, neck, and shoulders (Fig. 62–1). While generally a self-limiting condition, long-term physical complications of acne may include extensive scarring and psychological distress.[1,3]

EPIDEMIOLOGY

With an estimated 40 to 50 million people affected, acne vulgaris is the number one skin disease in the United States.[4] While acne affects approximately 85% of adolescents and adults aged 12 to 25 years, the disease can develop or recur in adults aged 30 to 50 years.[5] The prevalence of acne among Caucasians, African-Americans, Hispanics, and Asians is similar, with acne occurring more often in males during adolescence and females during adulthood.[6,7]



FIGURE 62–1. A spectrum of acne lesions is seen on the face of a 17-year-old male: comedones, papules, pustules, and erythematous macules and scars at the site of resolving lesions. The patient was successfully treated with a 4-month course of isotretinoin; there was no recurrence over the next 5 years. (From Wolff K, Johnson RA. Disorders of sebaceous and apocrine glands. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology. 5th ed. New York: McGraw-Hill, 2005: 5.)

PATHOPHYSIOLOGY

❶ *The development of acne lesions results from four pathogenic factors: excess sebum production, keratinization, bacterial growth, and inflammation.*[3]

The pilosebaceous unit of the skin consists of a hair follicle and the surrounding sebaceous glands. An initial acne lesion called a comedo forms when there is a blockage in the pilosebaceous unit.[8]

Sebum is released by the sebaceous glands and naturally maintains hair and skin hydration. An increase in androgen levels, especially during puberty, can cause an increase in the size of the sebaceous gland and the production of abnormally high levels of sebum within those glands. This excess sebum can result in plugged follicles and acne formation.

Keratinization, the sloughing of epithelial cells in the hair follicle, is also a natural process. In acne, however, *hyper*keratinization occurs and causes increased adhesiveness of the sloughed cells. Accumulation of these cells clogs the hair follicle, blocks the flow of sebum, and forms an acne lesion called an **open comedo** or "blackhead."

Propionibacterium acnes (P. acnes), an anaerobic organism, is also found in the normal flora of the skin. This bacteria proliferates in the mixture of sebum and keratinocytes and can result in an inflammatory response producing a **closed comedo** or "whitehead." More severe acne lesions such as pustules, papules, and nodules can also form with inflammatory acne and result in significant scarring if treated inadequately (Fig. 62–2).

TREATMENT

Desired Outcomes and Goals

❷ *While eliminating existing lesions and preventing the development of new lesions are primary goals of acne therapy, secondary goals include relieving pain or discomfort and preventing permanent scarring.*[8] In addition, acne can cause patients a significant amount of stress, anxiety, frustration, embarrassment, and even depression.[10] Because of these psychological symptoms, treatment compliance and patient education on both physical and psychological aspects of this skin disorder are also imperative.

General Approach to Treatment

❸ *Acne is categorized as mild, moderate, or severe based on the lesion type and lesion severity that present* (Table 62–1).

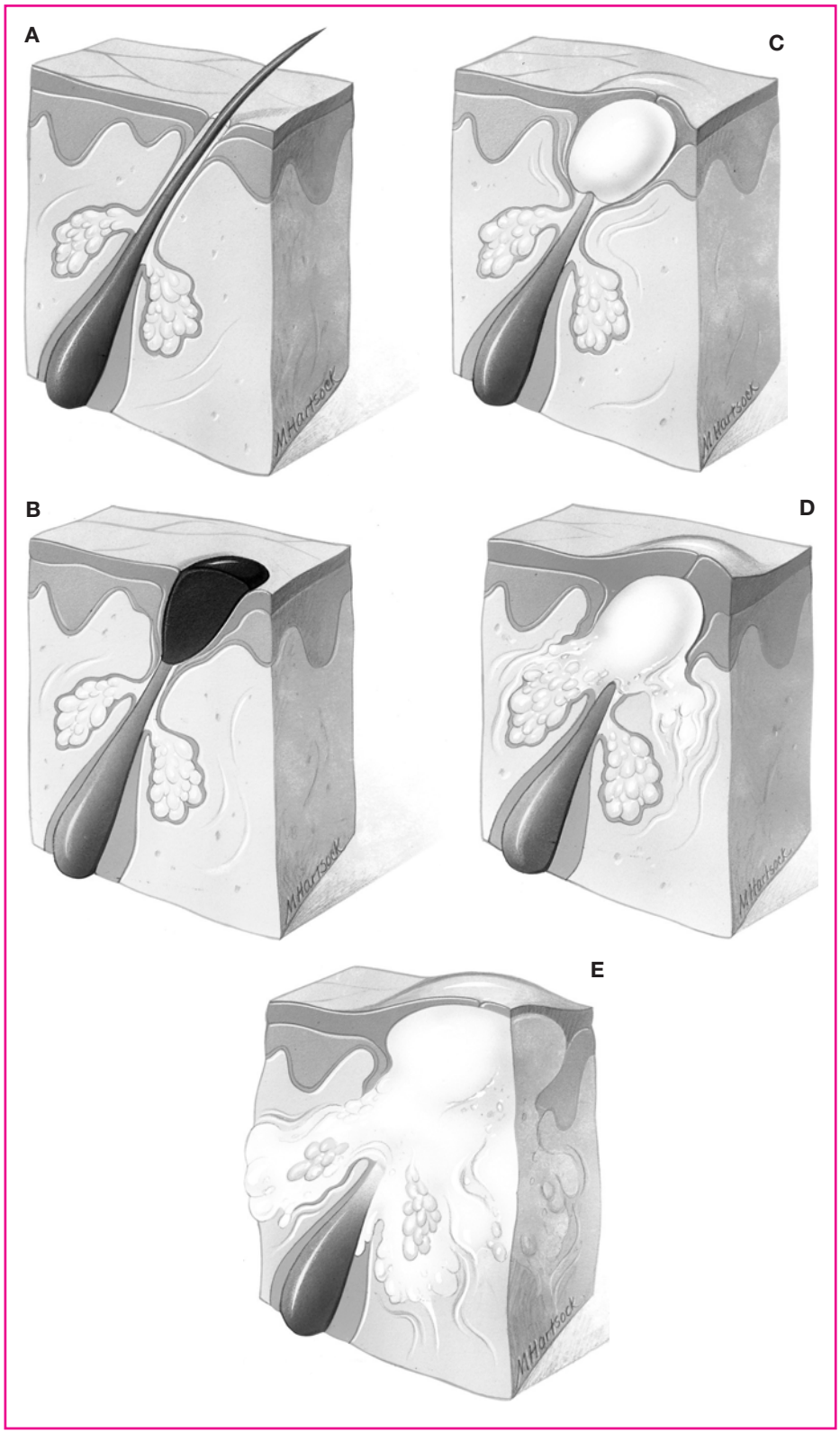


FIGURE 62–2. Stages of acne. *A.* Normal follicle. *B.* Open comedo (blackhead). *C.* Closed comedo (whitehead). *D.* Papule. *E.* Pustule.[9]

TABLE 62–1. Predominance of Acne Lesion Type by Acne Severity

		Typical Frequency of Lesion Type					
Acne Severity	**Predominant Lesions**	**Closed Comedones**	**Open Comedones**	**Papules**	**Pustules**	**Nodules**	**Scarring**
Mild	Noninflammatory lesions (open and closed comedones)	Few to numerous	Few to numerous	Possible	Possible	None	None
Moderate	Inflammatory papules and pustules with some noninflammatory lesions	Few to numerous	Few to numerous	Numerous	Numerous	Few	Possible
Severe	Inflammatory lesions and scarring with some noninflammatory lesions	Few to numerous	Few to numerous	Extensive	Extensive	Extensive	Extensive

From West DP, West LE, Musumeci ML, Micali G. Acne vulgaris. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1757, with permission.

Successful treatment approaches are developed based on these categories, as well as any previous treatment information presented by the patient. Improvement of symptoms following treatment occurs gradually, sometimes taking 6 to 8 weeks for results to be physically apparent.[8] Patients need to be educated on continual treatment compliance during this time and should not get discouraged if acne lesions appear to worsen before getting better during the initial 2 to 3 weeks of therapy.[11]



Clinical Presentation of Acne

Acne lesions are most often seen on the face, but can also present on the chest, back, neck, and shoulders and are described as either noninflammatory or inflammatory. In addition, severe inflammatory lesions can lead to scarring and hyperpigmentation.

Non-Inflammatory Lesions

Open comedo or "blackhead": a plugged follicle of sebum, keratinocytes, and bacteria that protrudes from the surface of the skin and appears black or brown in color. Although dark in color, blackheads do not indicate the presence of dirt, but rather an accumulation of melanin.

Closed comedo or "whitehead": a plugged follicle of sebum, keratinocytes, and bacteria that remains beneath the surface of the skin. Closed comedos usually appear as small white bumps about 1 to 2 mm in diameter.

Inflammatory Lesions

Papules: solid, elevated lesions less than 0.5 cm in diameter

Pustules: vesicles filled with purulent fluid less than 0.5 cm in diameter

Nodules: lesions greater than 0.5 cm in both width and depth

Cysts: nodules filled with a fluid or semisolid which can be expressed

Scars: inflammatory acne can result in permanent scarring that ranges from small depressed pits to large elevated blemishes

Hyperpigmentation: inflammatory acne may cause hyperpigmentation of the skin that can last for weeks to months

Nonpharmacologic Therapy

There is significant variance in the clinical benefit of many nonpharmacologic interventions for acne vulgaris. Among non-drug treatment alternatives, mild, non-comedogenic facial soap used twice daily, as well as the avoidance of oily skin products and the avoidance of manipulating or squeezing lesions are helpful self-treatment recommendations.

Pharmacologic Therapy

Topical Agents

Benzoyl Peroxide

Benzoyl peroxide is easy to use and recommended as first-line therapy in the treatment of mild to moderate noninflammatory acne. Benzoyl peroxide has a **comedolytic** effect that increases the rate of epithelial cell turnover and helps to unclog blocked pores. It also has antibacterial activity against *P. acnes*, which appears to be the main reason for the effectiveness of this product.[13]

It is available with or without a prescription and remains the most commonly purchased over-the-counter topical treatment for acne.[12] Benzoyl peroxide is available in concentrations ranging from 1% to 10% in various formulations including creams, lotions, gels, and facial washes.

Adverse effects commonly reported with benzoyl peroxide are dryness, irritation, redness, and stinging of the skin. Reducing the incidence of these effects can be achieved by beginning a treatment regimen with the lowest strength of benzoyl peroxide and titrating up to higher effective strengths over several weeks if needed. A disadvantage of benzoyl peroxide is a bleaching effect that tends to discolor hair and fabrics.[12]

A typical regimen for benzoyl peroxide use is to apply the product to clean, dry skin no more than two times a day. The strength and dosage form selected may vary from patient to patient depending on acne severity and the sensitivity of the patient's skin. Since gel preparations are the most potent dosage form, patients with dry or overly sensitive skin should

be recommended a milder cream, lotion, or facial wash.[3] If severe irritation or allergic reaction develops, benzoyl peroxide use should be discontinued.

Retinoids

Retinoids, which are highly effective in the treatment of acne, stimulate epithelial cell turnover and aid in unclogging blocked pores. Retinoids also exhibit anti-inflammatory properties through the inhibition of neutrophil and monocyte chemotaxis.[8] Because of these comedolytic and anti-inflammatory effects, topical retinoids are recommended as first-line treatment for mild to moderate comedonal and inflammatory acne.[3] While success is seen with monotherapy, using a retinoid in combination with benzoyl peroxide or topical antibacterials is also an appropriate and effective therapeutic treatment option.[3] Tretinoin, adapalene, and tazarotene are topical retinoids available for use in the treatment of acne. Table 62–2 describes the strengths and formulations of these agents.

Adverse effects are likely with the use of topical retinoids. Although transient, erythema, irritation, dryness, and peeling at the site of application are all common effects. Photosensitivity can also occur with retinoid use, causing increased skin irritation and redness.[14]

The topical retinoid selected should be used once daily at bedtime, beginning with a low-potency formulation. Increased strengths are then initiated according to treatment results and tolerance. Patients should be advised that a worsening of acne symptoms generally occurs in the first few weeks of therapy, with lesion improvement occurring in 3 to 4 months.[16] The use of topical retinoids should be avoided in children less than 12 years old and in pregnant women.[14]

Antibacterials

Topical antibacterials directly suppress *P. acnes* and are also first-line agents used in the treatment of mild to moderate inflammatory acne.[3,16]

Clindamycin 1% and erythromycin 2% preparations, applied once or twice daily, have similar effects and are the most commonly prescribed topical antibacterial agents.[17] These agents, as well as sodium sulfacetamide, are available in various formulations for the treatment of acne.

Adverse effects are generally mild and include dryness, erythema, and itching.[18] Although rare and seen most often with oral therapy, pseudomembranous colitis can occur with the use of topical clindamycin.[19] As with any antibacterial agent, the possibility of resistance exists with the use of topical erythromycin. However, co-administration of erythromycin and benzoyl peroxide has been shown to decrease the incidence of resistance, as well as to improve symptoms of mild to moderate inflammatory acne.[20]

Azelaic Acid

With antibacterial and anti-inflammatory properties, and the ability to stabilize keratinization, azelaic acid is an effective alternative in the treatment of mild to moderate acne in patients who cannot tolerate benzoyl peroxide or topical retinoids.[3,21] It also has a hypopigmentation effect that may prove effective in patients who are prone to post-inflammatory hyperpigmentation resulting from acne.[22]

Adverse effects are minimal and transient with erythema and skin irritation most commonly reported.[16,21]

Azelaic acid 20% cream should be applied twice daily with improvement of symptoms seen in 1 to 2 months.[21]

Keratolytics

Sulfur, resorcinol, and salicylic acid are not as effective as other topical agents, but can be used as second-line therapies in the treatment of mild to moderate acne.[12]

While these agents may cause less skin irritation than benzoyl peroxide or the topical retinoids, several disadvantages exist. Sulfur preparations produce an unpleasant odor when applied to the skin, while resorcinol may cause brown scaling. And although rare, the possibility of salicylism exists with continual salicylic acid use.[3,12]

TABLE 62–2. Topical Retinoids Available for the Treatment of Acne[15]

Agent	Brand Name	Dosage Form	Dosage	Side Effects
Tretinoin	Retin-A™	0.025%, 0.05%, and 0.1% cream 0.01%, 0.025% gel 0.05% solution	Apply a small amount once daily before bedtime	Skin irritation, dryness, photosensitivity; initially may worsen acne
	Retin-A™ Micro	0.04% and 0.1% gel		Skin irritation, dryness, photosensitivity; initially may worsen acne
Adapalene	Differin®	0.1% cream 0.1% gel	Apply a small amount once daily before bedtime	Same as tretinoin but may be *less* severe
Tazarotene	Tazorac®	0.05% and 0.1% cream 0.05% and 0.1% gel	Apply a small amount once daily before bedtime	Same as tretinoin but may be *more* severe

Oral Agents

Antibacterials

Moderate to severe acne can be effectively treated with oral antibiotics, especially when treatment with topical therapy has failed. Because of their ability to decrease *P. acnes* colonization, oral antibiotics can prevent acne lesions from developing.[8] Improvement of symptoms is generally evident at 6 to 10 weeks, with maximum benefits occurring after 6 months of therapy.[23]

Although tetracycline, doxycycline, and minocycline are the most commonly prescribed oral antibiotics for acne, erythromycin and clindamycin are appropriate second-line agents for use when patients cannot tolerate or have developed resistance to tetracycline or its derivatives.[3] See Table 62–3 for antibiotic dosing guidelines.

Adverse effects with the tetracyclines include gastrointestinal upset; drug interactions with dairy products, antacids, and iron; and phototoxicity. Minocycline can also cause vestibular complications (headache and dizziness) and skin discoloration that is not typical with tetracycline and doxycycline.[16]

Although their effectiveness is similar to the tetracyclines, the use of erythromycin and clindamycin is often limited due to their potential adverse outcomes. Erythromycin has treatment failure due to resistance and a high incidence of gastrointestinal intolerance, while clindamycin causes diarrhea and carries a risk of developing pseudomembranous colitis with long-term use.[3,8]

Isotretinoin

Isotretinoin is effective in up to 80% of patients with severe nodulocystic acne who are unresponsive to other topical and oral treatment regimens.[8,23,24] Isotretinoin works on the four pathogenic factors that contribute to acne development and can produce acne remission for several years.

Adverse effects with the use of isotretinoin are frequent and generally dose-related. About 90% of patients experience drying of the mucosa of the mouth, eyes, and nose.[3] Drying, peeling, and pruritus of the facial skin is also likely. Increases in cholesterol and triglyceride levels have been reported with isotretinoin use; therefore it is recommended to monitor liver function and serum lipids at baseline and 4 and 8 weeks of therapy to identify any complications. Other serious adverse effects from this medication include increased creatine phosphokinase, increased blood glucose, teratogenicity, photosensitivity, muscle pain, suicidality, and depression.[3] Table 62–4 lists the common adverse effects from isotretinoin therapy and management strategies for those symptoms.

Because it is teratogenic and classified as pregnancy category X, the Food and Drug Administration has recently mandated an online registry program called iPledge™ to ensure that females do not become pregnant while taking isotretinoin. Wholesalers, pharmacies, doctors, and patients must be registered in the iPledge™ computer-based system in order to control the distribution, prescribing, and dispensing of isotretinoin. A negative pregnancy test must be obtained and confirmed in the system before a prescription is dispensed to female patients of child-bearing potential. These patients must also commit to using effective measures of birth control during the course of isotretinoin therapy. Contact the program at their web site: https://www.ipledgeprogram.com/.

Initial dose ranges for treatment are 0.5 to 1 mg/kg daily in two divided doses, with beneficial results generally reported at total daily doses of 120 to 150 mg/day.[3]

TABLE 62–3. Oral Agents Used in the Treatment of Moderate to Severe Acne[15]

Drug	Dosage Form	Strength	Regimen	Side Effects
Tetracycline	Tablets, capsules	250, 500 mg	500 mg twice daily before meals Maintenance dose: 500 mg daily	GI upset, phototoxicity, tooth discoloration, drug and food interactions
Doxycycline	Tablets, capsules	50, 100 mg	100–200 mg daily before meals Maintenance dose: 50 mg daily	GI upset, phototoxicity, drug and food interactions
Minocycline	Tablets, capsules	50, 75, 100 mg	50 mg twice daily or 100 mg once daily Maintenance dose: 50 mg daily	GI upset, phototoxicity, drug and food interactions, vestibular toxicity, skin discoloration
Erythromycin	Tablets	250, 500 mg	500 mg twice daily with food Maintenance dose: 500 mg daily	GI intolerance, drug interactions
Clindamycin	Capsules	75, 150, 300 mg	150–300 mg daily Maintenance dose: 150 mg daily	Diarrhea, pseudomembranous colitis
Isotretinoin	Capsules	10, 20, 40 mg	0.5–1 mg/kg/per day in two divided doses Maximum dose: 2 mg/kg per day Cumulative dose: 120–150 mg/day	Dry skin and mucous membranes, muscle and joint pain, elevated liver enzymes and triglycerides, depression, teratogenicity

GI, gastrointestinal.

TABLE 62–4. Isotretinoin's Adverse Effects and Management Strategies

Adverse Effect	Response
Teratogenicity	Contraindicated during pregnancy
Depression	Patient monitoring and counseling; antidepressants
Dryness	
Mouth	Hard candy
Eyes	Eyedrops; avoid contact lenses if possible during treatment course
Nose	Lubricant
Skin	Nondrying gentle skin cleansers; non-comedolytic moisturizers
Lips	Lip moisturizer with sunscreen
Muscle and joint pain	Nonsteroidal anti-inflammatory drugs
Alopecia	Reversible when drug discontinued or dose decreased
Hypertriglyceridemia	Reversible when drug discontinued or dose decreased
Acne flare at start of therapy	Continue therapy
Photosensitivity	Use sunscreens (moisturizing), protective clothing, and sun avoidance

From West DP, West LE, Musumeci ML, Micali G. Acne vulgaris. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1762, with permission.

Oral Contraceptives

Oral contraceptives are a valuable second-line treatment option for moderate to severe acne in female patients. Oral contraceptives decrease the production of androgens by the ovaries, which in turn leads to a decrease in sebum production.[3,16]

Adverse effects include nausea, weight gain, breast tenderness, and breakthrough bleeding. Oral contraceptives have also been associated with an increased incidence of thromboembolic disease, particularly in women who use tobacco products or have other risk factors for thromboembolism. The development of these complications is significantly reduced when low-dose estrogen formulations of oral contraceptives are used.[3]

Other Agents

Although use is infrequent, several other agents are available as second or third-line treatment options for acne when first-line therapies fail and include the following:[3]

- Corticosteroids
- Chemical peels
- Antiandrogens
- Estrogens
- Gonadotropin-releasing hormone agonists

Figure 62–3 shows useful algorithms for the effective treatment of the various stages of acne.

OUTCOME EVALUATION

Depending on severity, complete resolution of acne may take weeks to months. Monitor patients after 6 weeks of pharmacologic therapy for any improvement of signs and symptoms:[12]

- Decreased number of lesions
- Decreased severity of lesions
- Relief of pain/irritation

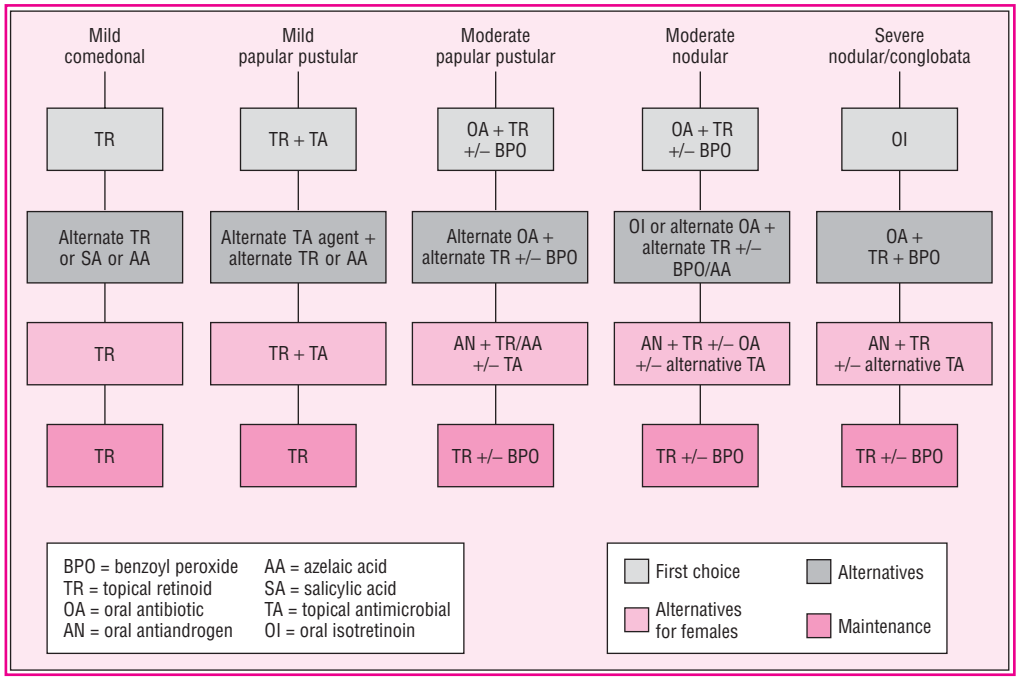


FIGURE 62–3. Algorithms for acne treatment.[3]



Patient Encounter

A 14-year-old female high school student presents to your clinic with complaints of worsening acne. Upon visual examination, you see that she has 4 pustules on her chin, 2 pustules on her forehead, and numerous open and closed comedones on her nose and cheeks. After interviewing the patient, you conclude that her acne lesions are moderately painful and make her feel embarrassed about going to school with so many "zits." She says that she began to have occasional acne at the age of 12, but over the past 6 months symptoms have worsened and states that she always has 4 to 6 lesions present on her face. The patient appears to be a healthy teenager who says that she eats well and is very athletic.

- What reported symptoms support the diagnosis of acne?
- What other information would you obtain from this patient before creating a treatment plan for her?
- Describe your treatment goals for this patient.
- What nonpharmacologic and pharmacologic treatment options are available for this patient?
- Given the information presented, develop a treatment regimen for this patient's acne.

If no improvement is reported or symptoms have worsened, patients should be re-evaluated and a change in the treatment regimen may be necessary.

Educate patients on the possibility of adverse effects. Consider a change in therapy if a patient experiences effects that are not tolerated or are considered a compromise to their health.



Patient Care and Monitoring

1. Assess patient symptoms and the presence of acne lesions. Determine severity of acne: mild, moderate, or severe.
2. Review patient history to determine treatment regimens that have been used in the past, including nonprescription, prescription, and herbal medications.
3. Obtain the patient's allergy status.
4. Develop a treatment plan appropriate for improvement of acne.
5. Discuss any monitoring parameters that may be necessary throughout the course of therapy.
6. Provide patient education on acne and its treatment:
   - What is acne and how does it develop?
   - Describe physical and psychological complications that can result from acne.
   - What drug and non-drug therapies are available for treatment?
   - Describe the possible side effects of drug therapy.
   - Emphasize the importance of treatment regimen compliance to ensure positive results.



FIGURE 62–4. Irritant contact dermatitis. Erythema and edema with spared areas on the back at sites in contact with an irritant in a 30-year-old male. (From Wolff K, Johnson RA. Eczema/dermatitis. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology. 5th ed. New York: McGraw-Hill, 2005: 20.)

CONTACT DERMATITIS

Contact dermatitis is a term used to describe a condition in which exposure to an offending substance produces inflammation, erythema, and pruritus of the skin.[25] More specifically, contact dermatitis can be divided into either irritant or allergic forms.[25,26] ❹ *Irritant contact dermatitis results from first-time exposures to irritating substances such as soaps, plants, cleaning solutions, or solvents. Allergic contact dermatitis occurs after an initial sensitivity and further exposure to allergenic substances, including poison ivy, latex, and certain types of metal*[27] (Figs. 62–4 and 62–5). Table 62–5 lists agents commonly responsible for irritant and allergic contact dermatitis. While generally occurring on the exposed skin such as the hands and face, contact dermatitis can appear anywhere on the body.[25] Although most cases are easily treated, contact dermatitis remains an uncomfortable and sometimes embarrassing skin condition.

EPIDEMIOLOGY

Contact dermatitis is a common reason for dermatology referrals and constitutes up to 90% of all workers' compensation claims for dermatologic conditions. Although most often seen in adulthood, contact dermatitis can affect all age groups, with females at slightly greater risk than males.[28]



FIGURE 62–5. Allergic contact dermatitis of the hand: chromates. Confluent papules, vesicles, erosions, and crusts on the dorsum of the left hand in a construction worker who was allergic to chromates. (From Wolff K, Johnson RA. Eczema/dermatitis. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology. 5th ed. New York: McGraw-Hill, 2005: 27.)

PATHOPHYSIOLOGY

Irritant contact dermatitis is not the result of an immunologic process, but rather occurs from direct injury to the skin. An irritating agent comes into contact with the skin, damages the protective layers of the epidermis and can cause erythema, the formation of vesicles, and pruritus.[25,29,30] Symptoms occur within minutes to hours of exposure and begin to heal soon after removal of the offending substance.[27]

TABLE 62–5. Common Agents Causing Contact Dermatitis

Irritant Contact Dermatitis
Soaps
Detergents
Cosmetics
Solvents
Acid, mild or strong
Alkali, mild or strong
Allergic Contact Dermatitis
Plant resins, poison ivy, poison oak, poison sumac
Metals (nickel or gold in jewelry)
Latex and rubber
Cigarette smoke
Local anesthetics (lidocaine, benzocaine)

Clinical Presentation of Contact Dermatitis

Contact dermatitis is generally confined to the area of contact, but in a highly sensitive person, a widespread or even generalized eruption may occur. Contact dermatitis is divided into two forms: irritant and allergic. Both forms may include, but are not limited to:

- Erythema
- Pruritus
- Vesicles
- Papules
- Crusts
- Burning

Irritant Form

The irritant form usually presents within hours of exposure and the rash is often localized. Irritant contact dermatitis may also include fissuring and scaling.

Allergic Form

The allergic form can take several days to present and the condition may extend beyond the borders of the region exposed. Allergic contact dermatitis may also include oozing pustules and skin erosion.

Allergic contact dermatitis is a delayed hypersensitivity reaction.[30] Upon initial exposure, a substance penetrates the skin, binds to a protein and develops into sensitizing antigens. Subsequent exposures to that substance will then elicit an allergic reaction.[25,29,30] Symptoms of allergic contact dermatitis are similar to those of the irritant type, but may take several hours to several days to develop following re-exposure.[25,26]

TREATMENT

Desired Outcomes and Goals

❺ *Identifying the causative substance and eliminating its exposure is the initial treatment goal for contact dermatitis.* Although physical symptoms can develop almost immediately after contact, removal of the offending agent will improve existing symptoms and prevent the occurrence of further complications. ❺ *The second treatment goal is symptom relief.* Since inflammation and pruritus, as well as lesion formation, are likely to result from contact dermatitis, appropriate selection of nonpharmacologic and pharmacologic agents for these symptoms is necessary.

Nonpharmacologic Therapy

In many cases contact dermatitis may not require medical treatment at all. Non-drug therapy for contact dermatitis is

aimed at relieving pruritus and maintaining skin hydration.[27] Effective agents used for this include the following:[25,27]

- Colloidal oatmeal baths
- Cool or tepid soapless showers
- Cool, moist compresses applied to the area for 30 minutes three times a day
- Emollients or lubricants applied to the area after bathing (mineral oil or petrolatum)

Pharmacologic Therapy

Astringents

The drying effect of astringents will decrease oozing from lesions and relieve itching.[25,26] Due to their ability to cause blood vessel constriction, astringents can also decrease inflammation.

Aluminum acetate (Burow's solution), calamine, and witch hazel are safe and effective products available for use.[25] Patients apply solutions as a compress for 15 to 30 minutes two to four times a day.

Adverse effects reported with these agents are minimal and include drying and tightening of the skin. Because of this, their use should be limited to no more than 7 days.[25,26,28]

Topical Steroids

Erythema, inflammation, pain, and itching caused by contact dermatitis can be effectively treated with topically applied corticosteroids. With such a wide range of products and potencies available, an appropriate steroid selection is based on severity and location of the lesions. Table 62–6 shows a list of topical steroids and their potencies. Higher-potency preparations are used in areas where penetration is poor, such as on the elbows and knees. Lower-potency products should be reserved for areas of higher penetration, such as on the face, axillae, and groin. Low-potency steroids are also recommended for the treatment of infants and children.[32,33]

Adverse effects from topical steroids are usually related to the potency of the steroid used, frequency of application, duration of therapy, and the site of application. Skin atrophy, hypopigmentation, striae, and steroid-induced acne are all possible side effects associated with long-term use.[32,33]

Topical steroids are typically applied two to four times daily. As improvement begins, maintenance therapy should be limited to the lowest-strength steroid that continues to control the condition. Once symptoms are completely resolved, use should be discontinued.

Antihistamines

Whether due to their antihistaminic activity or their sedative side effects, pruritus caused by contact dermatitis can be relieved with the use of sedating oral antihistamines such as diphenhydramine or hydroxyzine. Topical antihistamines are available, but use is limited due to their high sensitizing potential.[25,32]

In addition to sedation, many oral antihistamines can cause hypotension, dizziness, blurred vision, and confusion.[28]

Diphenhydramine and hydroxyzine can be safely administered to children older than 2 years and adults. Table 62–7 outlines the recommended doses for these medications.

OUTCOME EVALUATION

With adequate treatment, most cases of contact dermatitis should improve within 7 days. Complete resolution of symptoms may take up to 3 weeks.[12] If a patient experiences severe symptoms associated with fever or difficulty breathing, they should be instructed to seek medical attention immediately. Furthermore, patients should return to their health care provider if any of the following occur:

- Rash has not improved or has worsened after several days of treatment
- Rash has increased in size or has spread to other locations
- Patient is experiencing adverse effects from the treatment regimen



Patient Encounter

A 45-year-old female presents to a pharmacy with complaints of itching and wants a recommendation to treat it. Upon visual examination you see that she has erythematous papules on both legs. After further questioning, you learn that she has recently spent a great deal of time outside at a family picnic. She states that the picnic was in a wooded area near her home and that she and several others went on a short hike that day. She states that she was wearing shorts and "probably" came into contact with the grasses and weeds that lined the hiking trail. The rash appeared the same day as the picnic and she says that it seems to have spread since it first developed. From the information she has presented, you conclude that she has been exposed to poison ivy.

- What information supports the possibility of poison ivy exposure?
- Describe the symptoms that support this diagnosis.
- Determine what the patient has tried to relieve her symptoms.
- What are your treatment goals for this patient?
- What nonpharmacologic and pharmacologic treatment options are available for this diagnosis?
- Given the information presented, develop a treatment regimen for a patient with contact dermatitis.

TABLE 62–6. Topical Steroids to Treat Contact Dermatitis

Corticosteroids	Dosage Forms	Strength (%)	USP Potency Ratings[a]	Vasoconstrictive Potency Rating[b]
Alclometasone dipropionate	Cream	0.05	Low	VI
	Ointment	0.05	Low	V
Amcinonide	Lotion, ointment	0.1	High	II
	Cream	0.1	High	III
Beclomethasone dipropionate	Cream, lotion, ointment	0.025	Medium	—
Betamethasone benzoate	Cream, gel	0.025	Medium	III
	Ointment	0.025	Medium	IV
Betamethasone dipropionate	Cream AF (optimized vehicle)	0.05	Very high	I
	Cream	0.05	High	III
	Gel, lotion, ointment (optimized vehicle)	0.05	Very high	I
	Lotion	0.05	High	V
	Ointment	0.05	High	II
	Topical aerosol	0.1	High	—
Betamethasone valerate	Cream	0.01, 0.05, 0.1	Medium	V
	Lotion, ointment	0.05, 0.1	Medium	III
	Foam	0.12	Medium	IV
Clobetasol propionate	Cream, ointment, solution, foam	0.05	Very high	I
Clobetasol butyrate	Cream, ointment	0.05	Medium	—
Clocortolone pivalate	Cream	0.1	Low	—
Desonide	Cream, lotion, ointment	0.05	Low	VI
Desoximetasone	Cream	0.05	Medium	II
	Cream, ointment	0.25	High	II
	Gel	0.05	High	II
Dexamethasone	Gel	0.1	Low	VII
	Topical aerosol	0.01, 0.04	Low	VII
Dexamethasone sodium phosphate	Cream	0.1	Low	VII
Diflorasone diacetate	Cream	0.05	High	III
	Ointment	0.05	High	II
	Ointment (optimized vehicle)	0.05	Very high	II
Diflucortolone valerate	Cream, ointment	0.1	Medium	—
Flumethasone pivalate	Cream, ointment	0.03	Low	—
Fluocinolone acetonide	Cream	0.01	Medium	VI
	Cream	0.025	Medium	V
	Cream	0.2	High	—
	Ointment	0.025	Medium	IV
	Solution	0.01	Medium	VI
Fluocinonide	Gel, cream, ointment	0.05	High	II
	Solution	0.05	High	II
Flurandrenolide	Cream, ointment	0.0125	Low	—
	Ointment	0.05	Medium	IV
	Cream, lotion	0.05	Medium	V
	Tape	4 mcg/cm^2	Medium	I
Fluticasone propionate	Cream	0.05	Medium	IV
	Ointment	0.05	Medium	III
Halcinonide	Cream	0.025, 0.1	High	II
	Ointment	0.1	High	III
	Solution	0.1	High	—
Halobetasol propionate	Cream, ointment	0.05	Very high	I
Hydrocortisone	Cream, lotion, ointment	All strengths	Low	VII
Hydrocortisone acetate	Cream, lotion, ointment	All strengths	Low	VII
Hydrocortisone butyrate	Cream	0.1	Medium	V
	Ointment	0.1	Medium	—
Hydrocortisone valerate	Cream	0.2	Medium	V
	Ointment	0.2	Medium	IV
Methylprednisolone acetate	Cream, ointment	0.25	Low	VII
	Ointment	1	Low	VII
Mometasone furoate	Cream	0.1	Medium	IV
	Lotion, ointment	0.1	Medium	II

(*Continued*)

TABLE 62–6. Topical Steroids to Treat Contact Dermatitis (*Continued*)

Corticosteroids	Dosage Forms	Strength (%)	USP Potency Ratings[a]	Vasoconstrictive Potency Rating[b]
Triamcinolone acetonide	Cream, ointment	0.1	Medium	IV
	Cream, lotion, ointment	0.025	Medium	—
	Cream (Aristocort)	0.1	Medium	VI
	Cream (Kenalog)	0.1	High	IV
	Lotion	0.1	Medium	V
	Ointment (Aristocort, Kenalog)	0.1	High	III
	Cream, ointment	0.5	High	III
	Topical aerosol	0.015	Medium	—

[a]USP ratings are low, medium, high, and very high.
[b]Vasoconstriction potency scale is I (highest) to VII (lowest).
—, unknown vasoconstrictive properties; USP, United States Pharmacopeia.
From West DP, West LE, Scuderi L, Micali G. Psoriasis. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1775, with permission.



Patient Care and Monitoring

1. Assess the patient's symptoms. Determine which form of contact dermatitis is present: irritant or allergic.
2. Obtain a thorough patient history. Has there been prior exposure to this agent? If so, what treatment regimens were used in the past to alleviate symptoms?
3. Obtain the patient's allergy status.
4. Develop a treatment plan appropriate for contact dermatitis.
5. Discuss testing that may need to be performed to suggest or confirm the etiologic agent (patch testing).
6. Provide patient education on contact dermatitis and treatment:

   - What is contact dermatitis and how does it develop?
   - List the various types of contact dermatitis.
   - What drug therapies are available for treatment?
   - What are the possible adverse effects of drug therapy?
   - What are symptoms that warrant physician referral?
   - Explain the importance of treatment compliance.
   - Educate the patient about the recognition of agents that may cause contact dermatitis.

DIAPER DERMATITIS

Diaper dermatitis, more commonly known as diaper rash, is a form of irritant contact dermatitis that affects the buttocks, upper thighs, lower abdomen, and genitalia of an estimated 7% to 35% of all infants.[34,35] Onset of occurrence is usually between 3 weeks and 2 years of age, with the most cases reported between 9 and 12 months of age.[36] More than 12 million adults who use diapers for incontinence also have an increased risk of developing diaper dermatitis.[35]

PATHOPHYSIOLOGY

❻ *Although many factors contribute to the etiology of diaper rash, it is most likely the result of prolonged contact of the skin with urine and feces in the diaper.* If a diaper is not changed soon after urination or defecation, the protective layer of the



Clinical Presentation of Diaper Dermatitis

Typical Symptoms

- Erythema is the most common symptom presenting with diaper rash. The rash may begin as light to medium pink with poorly defined edges, but when further developed may become dark red and raised lesions with distinct edges.
- Rashes generally appear in the folds of the skin around the diaper area, thighs, genitals, and buttocks.
- Other typical symptoms include irritation and pruritus.

Atypical Symptoms

Patients presenting with the following symptoms may indicate the need for more aggressive antibiotic or antifungal therapy and should be referred to a primary care physician for further evaluation:

- Rashes not responding to typical creams and concurrent nonpharmacologic treatment
- Rashes extending beyond the diaper region (e.g., upper abdomen or back)
- Formation of papules, bullae, or ulceration
- Excessive oozing
- Presence of genital discharge
- Concurrent fever
- Rashes appearing when diapers have not been used or rashes that fail to improve upon discontinuing diaper usage for extended periods of time (several days or more)
- Bleeding or open skin

TABLE 62–7. Oral Antihistamines Used for Pruritus[15]

Drug	Pediatric Dosage	Adult Dosage
Diphenhydramine (Benadryl®)	*Not recommended for use in infants or neonates* 2–6 years old: 6.25–12.5 mg every 4–6 hours as needed 6–12 years old: 12.5–25 mg every 4–6 hours as needed	25–50 mg every 6–8 hours as needed
Hydroxyzine (Atarax®)	0.6 mg/kg per dose every 6 hours as needed	25 mg every 6–8 hours as needed

skin can break down and make the area more susceptible to irritation and infection from the contents of the diaper.[37] While most mild cases of diaper rash present as erythema, moderate to severe cases can result in the formation of papules, vesicles, and even ulceration. If these cases are not effectively treated, the likelihood of secondary fungal or bacterial infections developing is greatly increased.[34]

TREATMENT

Desired Outcomes and Goals

❼ *The primary goal in the treatment of diaper rash is prevention and is most often accomplished through frequent diaper changes.* ❽ *When a diaper rash is already present, repairing the damaged skin, relieving discomfort, and preventing secondary infections from occurring are important factors to consider when developing an effective treatment regimen.*[37]

Nonpharmacologic Therapy

Most mild cases of diaper rash can be resolved with the use of nonpharmacologic therapies. Keeping the diaper area clean and dry by changing diapers as soon as practically possible is highly effective for treatment and prevention.[34,35] Other nondrug options include:[26,34]

- Washing the area with lukewarm water and mild soap and allowing to completely dry before applying a new diaper
- Keeping diapers loose and well ventilated
- Avoiding plastic pants over diapers
- Allowing infants to take naps on an open diaper or absorbent pad to promote drying and healing

Pharmacologic Therapy

Protectants

Protectants form an occlusive barrier between the skin and moisture from the diaper. Cream and ointment preparations are effective in providing a sufficient barrier in mild, irritant, non-infected diaper rashes. For more severe cases, a paste is the topical agent of choice. Pastes are thicker and often contain additional ingredients (e.g., petrolatum and moisturizers) to help decrease discomfort and promote healing.[36] Zinc oxide is one of the most commonly used topical protectants. In addition to forming an effective barrier against moisture, it has astringent and antiseptic properties that provide added symptom relief.[34]

Protectants are generally applied to the affected area after every diaper change and can be discontinued when the rash resolves. Other available protectants that can be used alone or in combination for the safe and effective treatment of diaper rash include white petrolatum, vitamins A and D, lanolin, and topical cornstarch. Many agents contain a combination of occlusive and protective agents such as Triple Paste® and Calmoseptine®.

Topical Steroids

Because of the increased permeability of their skin, infants are at risk for excessive absorption and toxicity from the use of topical steroids. Although these agents are effective in decreasing inflammation and relieving pruritus, steroid use in infants for the treatment of diaper dermatitis should be limited to only the low-potency preparations.[38]

A thin layer of hydrocortisone cream (0.25% to 1%) applied twice a day for no more than 2 weeks is an appropriate treatment regimen. The use of higher-potency steroids or use extending beyond 2 weeks should be at the discretion of a physician only.

Antifungals

Diaper rashes lasting longer than 48 to 72 hours are at increased risk for the development of fungal infections. These complications are most frequently caused by *Candida albicans* and require treatment with a topical antifungal[35,36] (Fig. 62–6).

Adverse events with the use of topical antifungals are generally limited to local irritation at the site of application.

Nystatin, clotrimazole, and miconazole creams or ointments applied two to four times daily with diaper changes have all shown to be effective in the treatment of candidal diaper rash. Although some of these products are available over the counter, parents and caregivers should be advised to initiate

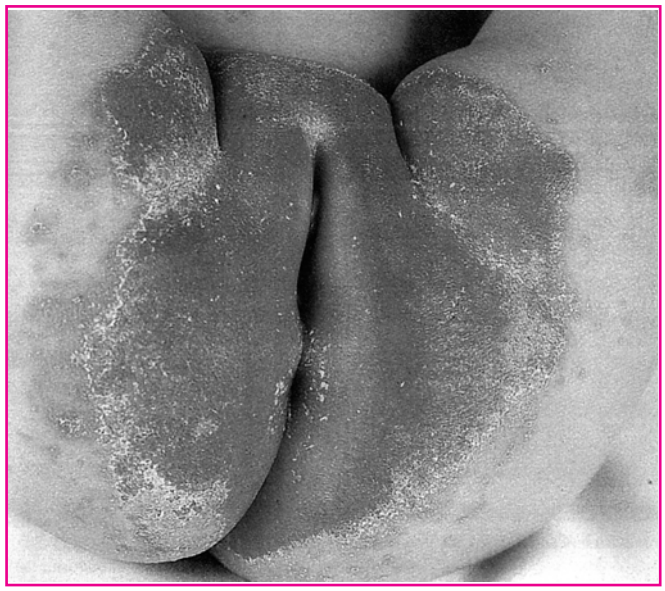


FIGURE 62–6. Candidiasis: diaper dermatitis. Confluent erosions, marginal scaling, and "satellite pustules" in the area covered by a diaper in an infant. (From Wolff K, Johnson RA. Cutaneous fungal infections. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology. 5th ed. New York: McGraw-Hill, 2005: 721.)

treatment with antifungal agents only after physician recommendation.

Antibacterials

If conventional treatment fails, unresolved diaper rash can also lead to secondary bacterial infections. *Staphylococcus aureus* and *streptococci* are the most likely pathogens responsible for these infections and require treatment with systemic antibiotics.[35–37] While topical protectants may be used as an adjunct in treatment, suspected bacterial infections should always be referred to a physician for accurate diagnosis and the selection of an appropriate antibacterial regimen.[34] Figure 62–7 shows a useful algorithm for the effective treatment of diaper dermatitis.

OUTCOME EVALUATION

Most diaper rashes can be effectively treated in less than 1 week. If symptoms do not resolve or begin to worsen, advise caregivers to seek medical attention to determine the presence of secondary fungal or bacterial infections. In addition, provide educational information on proper diaper hygiene techniques in order to prevent the development of future diaper rashes.

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

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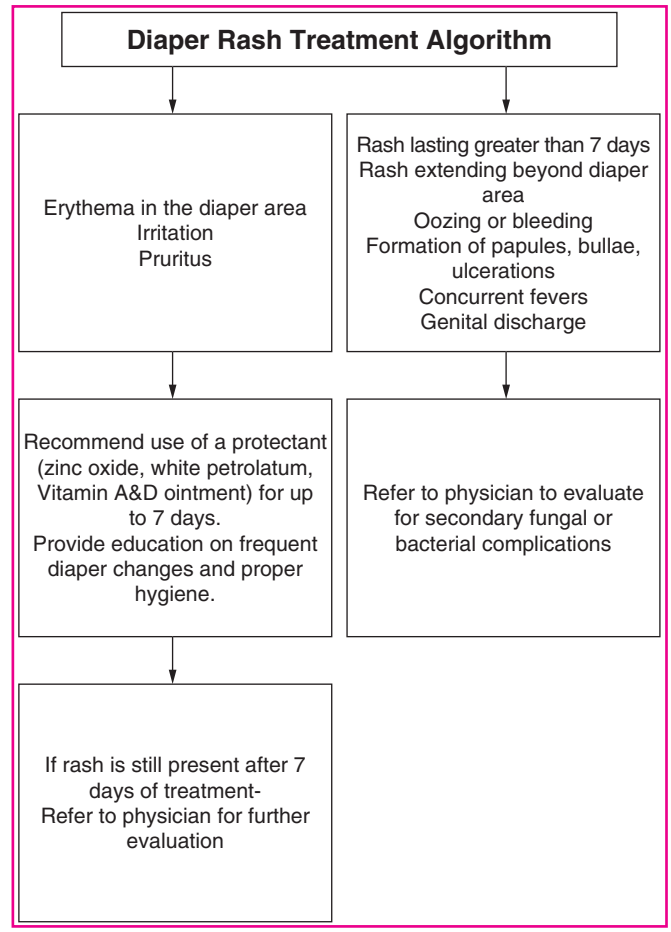


FIGURE 62–7. Diaper dermatitis treatment algorithm.



Patient Encounter

A gentleman presents to a community pharmacy with his 16-month-old daughter who recently developed a rash in her diaper area. He states that besides trying to keep the area clean and dry and changing her diapers more frequently than usual, he has tried to treat it with zinc oxide for the past 2 days. He says the rash is bright red, has persisted for 3 or 4 days and seems to be spreading. Although there is no blistering or oozing, he thinks the rash must be painful because his daughter cries with every diaper change.

- Identify the risk factors present that support the diagnosis of diaper rash.
- Elicit additional information to aid in your assessment of this patient.
- Based on the information obtained, develop a treatment plan for this patient. The plan should include the goals of therapy, nonpharmacologic and pharmacologic treatment options, follow-up instructions, and prevention education.



Patient Care and Monitoring

1. Assess rash symptoms. Determine the level of severity; is there a possibility of a secondary fungal or bacterial infection?
2. Identify signs and symptoms that require immediate physician referral.
3. Inquire about the patient's history, including any similar rashes in the past.
4. Educate the caregiver on the importance of frequent diaper changes and proper hygiene.
5. Obtain the patient's allergy status.
6. Discuss labs that may be necessary if a secondary infection is suspected (e.g., cultures or biopsies).
7. Develop a treatment regimen for the patient, including a plan for assessing improvement of the condition.
8. Provide patient education about diaper rash etiology, treatment, and prevention:
   - What is diaper rash and how does it develop? What exacerbates diaper rash?
   - Symptoms to report to a physician (blistering, oozing, bleeding, changes in the rash, or no improvement in symptoms within 2 to 3 days).
   - Available treatment options, including proper usage instructions and potential side effects.
   - Importance of treatment compliance.
   - Prevention measures.

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63 Anemia

Edward C. Li and James M. Hoffman



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Identify common causes of anemia.
2. Describe common signs and symptoms of anemia.
3. Discuss the appropriate diagnostic evaluation to determine anemia type and guide therapeutic decisions.
4. State the desired therapeutic outcomes for patients with anemia.
5. Compare and contrast the various oral and parenteral iron preparations.
6. Explain the optimal use of folic acid and vitamin B_{12} in patients with macrocytic anemia.
7. Evaluate the proper use of epoetin and darbepoetin in anemia patients with cancer and kidney disease.
8. Recommend a specific treatment regimen for anemia considering the underlying cause of anemia and patient-specific variables.
9. Develop a plan to monitor the outcomes of anemia pharmacotherapy.

Key Concepts

❶ Anemia is a reduction below normal in the concentration of hemoglobin in the body that results in a reduction of the oxygen-carrying capacity of the blood.
❷ Common signs and symptoms of anemia include fatigue, lethargy, dizziness, shortness of breath, headache, edema, and tachycardia.
❸ A standard initial laboratory evaluation for anemia includes a complete blood count (evaluation of the serum hemoglobin and hematocrit concentration, white blood cell count, platelets), measurement of the red blood cell count and size, and review of peripheral smear.
❹ The goal of anemia therapy is to increase hemoglobin, which will improve red cell oxygen-carrying capacity, alleviate symptoms, and prevent anemia complications.
❺ The underlying cause of anemia (e.g., blood loss; iron, folic acid, or B_{12} deficiency; or chronic disease) must be determined and used to guide therapy.
❻ In patients with iron-deficiency anemia, appropriate oral iron therapy that delivers sufficient elemental iron should be administered before giving parenteral iron.
❼ Anemia from vitamin B_{12} or folic acid deficiency is treated effectively by replacing the missing nutrient.
❽ Therapy with epoetin or darbepoetin can increase hemoglobin, decrease transfusion requirements, and improve quality of life in cancer and kidney disease patients with anemia.
❾ After treatment, patients should be monitored for symptom resolution, hemoglobin concentration, and adverse effects.

❶ ***Anemia*** *is a reduction below normal in the concentration of hemoglobin in the body that results in a reduction of the oxygen-carrying capacity of the blood.* Some patients with anemia may be asymptomatic initially, but eventually, the lack of oxygen to the tissues will result in fatigue, lethargy, shortness of breath, headache, edema, and tachycardia. Common causes of anemia include blood loss, decreased production of red blood cells (RBCs), increased destruction of RBCs, or some combination of these factors. Determination of the underlying cause of anemia is essential for successful management. Appropriate treatment of anemia will result in an increase in **hemoglobin,** with a corresponding increase in oxygen-carrying capacity and reduction in symptoms.

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Patient Encounter, Part 1

A 74-year-old Caucasian woman with a past medical history significant for hypertension and type II diabetes mellitus presents to her primary care physician complaining of shortness of breath and fatigue for the past few days. She denies any recent bleeding manifestations, including bright red blood per rectum, hemoptysis, melena, or epistaxis. She denies any fevers, chills, nausea, vomiting, or recent weight loss. A complete blood count (CBC) was taken and revealed hemoglobin of 9.3 g/dL (93 g/L or 5.8 mmol/L).

- Is this patient anemic? If so, what are possible causes of anemia?
- What additional laboratory assessments are required to make an appropriate therapeutic plan?
- How would the requested laboratory parameter(s) aid your decision making?

EPIDEMIOLOGY AND ETIOLOGY

Anemia is a common condition, and the prevalence of anemia varies widely based on age, gender, race/ethnicity, and comorbid conditions. A study of anemia prevalence in a nationally representative sample of community-dwelling individuals describes how anemia differs across different populations.[1] The prevalence of anemia in children (ages 1–16 years) was 6% to 9%, but the prevalence of anemia increases to approximately 11% in adults over age 65 years and to at least 20% in adults 85 years of age and older. Anemia is generally more common in women, particularly during their reproductive years (ages 17–49 years), when anemia occurs in over 12%, but in less than 2% of men. The same study showed that in the population over age 65, non-Hispanic whites and Mexican Americans had similar prevalence of anemia (9.0% and 10.4%, respectively), but with a prevalence of 27.8%, anemia was significantly more common in non-Hispanic blacks.

Comorbid conditions can increase the risk of anemia substantially. Anemia is especially common in cancer patients receiving chemotherapy and patients with chronic kidney disease (CKD). The incidence of anemia in cancer patients varies based on tumor type and the level of myelosuppression the chemotherapy regimen causes. For instance, serious anemia [hemoglobin 7.9 g/dL or less (79 g/L or 4.9 mmol/L)] occurs in at least 75% of patients who receive a common chemotherapy regimen for lymphoma, but serious anemia may occur in only approximately 10% of patients who receive common chemotherapy regimens for breast cancer.[2] Overall, retrospective reviews demonstrate that with an incidence of 50% to 60%, chemotherapy-induced anemia is most common in patients with lymphomas, lung tumors, and ovarian tumors. Anemia is very common in patients with CKD. For example, one study showed that 60% of patients with serious kidney disease have anemia.[3]

The causes of anemia can be divided into three main categories: decreased production, increased destruction, and blood loss. Drug therapy is the mainstay of treatment for anemias caused by reduced production of erythrocytes and will be the focus of this chapter.

A decrease in erythrocyte production can be multifactorial. A deficiency in nutrients (such as iron, vitamin B_{12}, and folic acid) is a common cause that often is easily treatable. In addition, patients with cancer and CKD are at risk for developing a hypoproductive anemia. Furthermore, patients with chronic immune-related diseases (such as rheumatoid arthritis and systemic lupus erythematosus) can develop anemia as a complication of their disease. Anemia related to these chronic inflammatory conditions is typically termed *anemia of chronic disease.*

PATHOPHYSIOLOGY

Erythropoiesis

Erythropoiesis is a process that starts with a pluripotent stem cell in the bone marrow that eventually differentiates into an erythroid colony-forming unit (CFU-E)[4] (Fig. 63–1). The development of these cells depends on stimulation from the appropriate growth factors, primarily erythropoietin. Other cytokines involved include granulocyte-monocyte colony-stimulating factor (GM-CSF) and interleukin 3 (IL-3). Eventually, the CFU-Es differentiate into **reticulocytes** and cross from the bone marrow into the peripheral blood. Finally, these reticulocytes mature into erythrocytes after 1 to 2 days in the bloodstream. Throughout this process, the cells gradually accumulate more hemoglobin and lose their nuclei.[4]

Hypoproliferative or Decreased-Production Anemias

Nutritional

Deficiencies in nutrients such as folic acid and vitamin B_{12} may hinder this process of erythrocyte maturation.[4,5] Folic acid and vitamin B_{12} are important nutrients required for the formation of DNA. In a setting where these nutrients are decreased, DNA synthesis is inhibited, and consequently, erythrocyte maturation also is inhibited.[4,5] Poor diet can be a contributor to the deficiencies in these

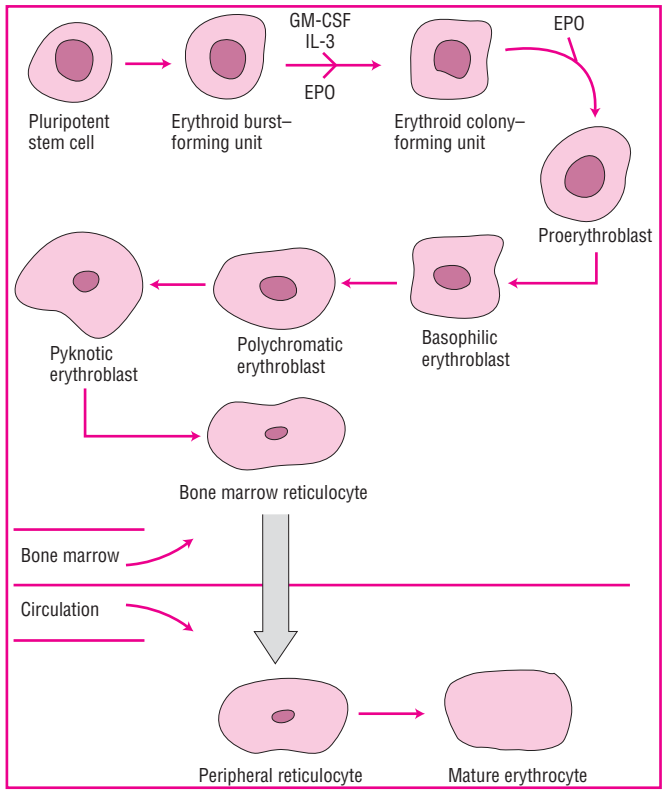


FIGURE 63–1. The process of erythropoiesis.

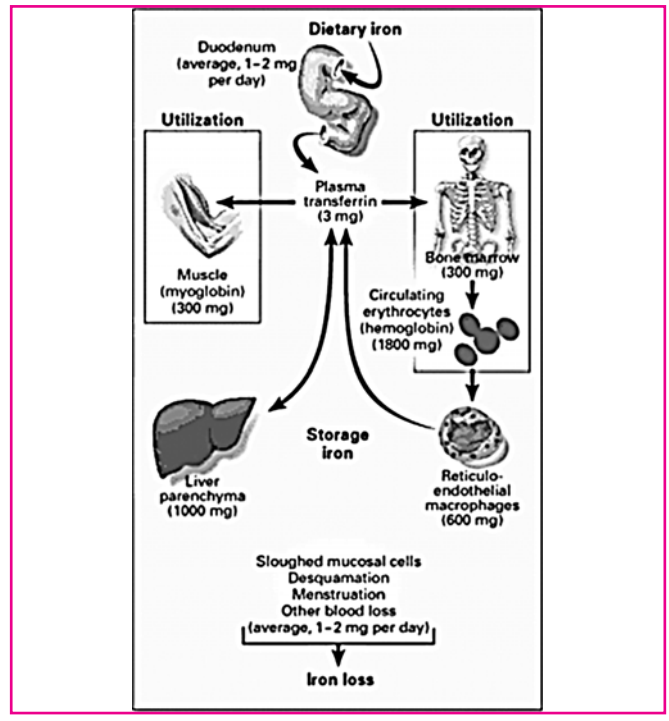


FIGURE 63–2. The distribution of iron use in adults. (From Andrews NC. Disorders of iron metabolism. *New Engl J Med* 1999; 341(26):1986–1995. Used by permission from NEJM. Copyright © 1999 Massachusetts Medical Society. All rights reserved.)

nutrients. Additionally, patients with pernicious anemia are not able to absorb vitamin B_{12} via the gastrointestinal tract because they lack intrinsic factor, a key glycoprotein that binds to vitamin B_{12} and facilitates its absorption in the ileum.[6]

Iron is another vital nutrient in the development of functioning erythrocytes; it is essential for the formation of hemoglobin. Lack of iron leads to a decrease in hemoglobin synthesis and ultimately red blood cells. Normal homeostasis of iron transport and metabolism is depicted in Fig. 63–2.[7] Approximately 1 to 2 mg of iron is absorbed through the duodenum each day, and the same amount is lost via blood loss, desquamation of mucosal cells, or menstruation.

Since there is no true "excretion" of iron from the body, iron-deficiency anemia occurs mostly because of inadequate absorption of iron or excess blood loss. Inadequate absorption may occur in patients who have congenital or acquired intestinal diseases, such as inflammatory bowel disease, celiac disease, or bowel resection. **Achlorhydria** and diets poor in iron also may contribute to poor absorption of iron. In contrast, iron deficiency also may occur in patients who exhibit a higher rate of iron loss from the body. This is manifested in blood loss, either from the gastrointestinal system, menstruation, cancer, or trauma.[7]

Hypoproliferative Marrow

Patients with chronic diseases exhibit a different pathophysiologic mechanism of disease. For example, patients with cancer may suffer from anemia because of chemotherapy and/or the tumor effects itself. Chemotherapy may cause destruction of highly proliferating stem cells, thereby decreasing the production of mature erythrocytes.[8] In addition, tumors can cause anemia via hemorrhage, replacing normal bone marrow with malignant cells, and releasing cytokines that lead to decreased erythropoietin production. Autoimmune hemolysis is also possible.[8]

Decreased Erythropoietin Production or Response

Patients with CKD suffer from a decrease in erythropoietin production because erythropoietin is produced mainly in the kidneys.[4,5] Finally, in patients with anemia of chronic disease, there is a blunted erythropoietin production as well as a diminished response to erythropoietin.[9] Anemia of chronic disease also affects iron homeostasis, causing iron sequestration into storage sites and decreasing the amount available to the rest of the body.[9]

CLINICAL PRESENTATION AND DIAGNOSIS



Clinical Presentation of Anemia

Signs and Symptoms

❷ *Generally, the signs and symptoms of anemia are nonspecific, and may include*:

- Fatigue, lethargy, dizziness
- Shortness of breath
- Headache
- Edema
- Tachycardia

Other findings that may be present in some patients include:

- Dry skin, chapped lips
- Nail brittleness
- Hunger for ice, starch, or clay (termed *pica*)

Past Medical History

Inquire about the following conditions:

- History of blood loss, such as hemorrhoids, melena, or menorrhagia (iron-deficiency anemia)
- Malnourished or recent weight loss (vitamin B_{12} or folate deficiency)
- Alcoholism (folate deficiency)
- Cancer or chronic kidney diseases
- Chronic autoimmune disorders or infections, such as human immunodeficiency virus (HIV) infection or rheumatoid arthritis (anemia of chronic disease)

Physical Examination

These findings aid the clinician in determining the severity of the anemia:

- Orthostatic hypotension and tachycardia secondary to volume depletion.
- Mental status changes and confusion
- Cutaneous changes such as pallor, jaundice, and nail brittleness

Laboratory Evaluation

Table 63–1 describes common tests used to determine the etiology of anemia. A diagnostic and treatment algorithm for anemia is outlined in Fig. 63–3.

1. ❸ *A complete blood count (CBC) is a necessary first step in evaluating a patient with anemia. If the hemoglobin and hematocrit are less that the normal range, the patient is anemic. Subsequent evaluations of red blood cell indices and the peripheral smear often are necessary to determine the etiology (and ultimately, the treatment) of the anemia.*
2. Evaluating the mean corpuscular volume (MCV) is the next step in an anemia work-up. It is classified as microcytic, normocytic, or macrocytic if the MCV is below, within, or above the normal range of 80 to 96 fL/cell, respectively.

Microcytic Anemia and Iron Evaluation

Iron studies (see Table 63–1) should be evaluated in the setting of a low MCV. These include

- Serum iron
- Serum ferritin—the best indirect determinant of body iron stores. It is commonly decreased in patients with iron-deficiency anemia.
- **Total iron-binding capacity (TIBC)—**quantifies the iron-binding capacity of transferrin and is increased in iron-deficiency anemia
- **Transferrin saturation** (serum iron/TIBC)—indicates the amount of transferrin that is bound with iron; it is lower in iron-deficiency anemia.

Macrocytic Anemia

- Evaluate folic acid and vitamin B_{12} levels in the setting of an elevated MCV.
- Further investigation by administering radiolabeled B_{12} (i.e., Schilling test) to determine if lack of intrinsic factor.
- Consider obtaining homocysteine and methylmalonic acid levels.

Normocytic Anemia

- Evaluate reticulocytes and CBC.
- High reticulocyte counts may indicate red blood cells loss via acute blood loss, hemolysis, or splenic sequestration.
- Low reticulocyte counts may indicate a diseased bone marrow (e.g., aplastic anemia, myelodysplasia, or leukemia), especially if the white blood cells and platelets are low.
- High WBC/platelets may be from anemia of chronic disease, malignancy, or chronic kidney disease.



Patient Encounter, Part 2

Additional laboratory parameters are ordered, and the following is observed:

CBC

- *WBC:* 5.50 × 10^3/μL (5.50 × 10^9/L)
- *Hgb:* 9.3 g/dL (93 g/L or 5.77 mmol/L)
- *Hct:* 27.8% (0.278)
- *Plt:* 170 × 10^3/μL (170 × 10^9/L)

Red blood cell indices

- *MCV:* 78 fL/cell
- *MCH:* 26 pg/cell
- *MCHC:* 33.5g/dL (335 g/L)

Others

- *RBC count:* 3 M/μL (3 × 10^{12}/L)
- *RDW:* 15% (0.15)
- *Retic%:* 3% (0.03)

Iron studies

- *Serum iron:* 45 mcg/dL (8.1 μmol/L)
- *Serum ferritin:* 7 mcg/L (15.7 pmol/L)
- *TIBC:* 462 mcg/dL (82.7 μmol/L)
- *Ferritin saturation:* 10% (0.10)

B_{12} and folate

- *Serum folate:* 20 mcg/dL (45 nmol/L)
- *Serum B_{12}:* 675 pg/mL (498 pmol/L)

- Is this a macrocytic or microcytic anemia?
- Specifically, what is the etiology of the anemia?
- What therapy should the patient receive?

TABLE 63–1. Pertinent Laboratory Tests in the Evaluation of Anemia

Test Name	Normal Range	Description/Significance
Complete Blood Count		
Hemoglobin (Hgb)	Males: 14–17.5 g/dL (140–175 g/L or 8.69–10.9 mmol/L) Females: 12.3–15.3 g/dL (123–153 g/L or 7.63–9.5 mmol/L)	Amount of hemoglobin in the blood; signifies oxygen-carrying capacity of the blood and determines if a patient is anemic.
Hematocrit (Hct)	Males: 42–50% (0.42–0.50) Females: 36–45% (0.36–0.45)	The percent of blood that the erythrocytes encompass; also indicates anemia; the hemoglobin is measured, and the hematocrit is calculated.
Red blood cell count (RBC)	Males: 4.5–5.9 × 10^6 cells/mL (4.5–5.9 × 10^{12} cells/L) Females: 4.1–5.1 × 10^6 cells/mL (4.1–5.1 × 10^{12} cells/L)	The number of erythrocytes in a volume of blood; also indicates anemia, but seldom used.
Red Blood Cell Indices		
Mean cell volume (MCV)	80–96 fL/cell	A widely used laboratory value to measure RBC "size"; higher values indicate macrocytosis and lower values indicate microcytosis.
Mean cell hemoglobin (MCH)	27–33 pg/cell	Amount of Hgb per RBC; may be decreased in iron deficiency anemia.
Mean cell hemoglobin concentration (MCHC)	33.4–35.5 g/dL (334–355 g/L)	Hemoglobin divided by the hematocrit; also low in iron-deficiency anemia.
Iron Studies		
Serum iron		
Males:	45–160 mcg/dL (8.1–31.3 µmol/L)	Measures amount of iron bound to transferrin; low in iron-deficiency anemia.
Females:	30–160 mcg/dL (5.4–31.3 µmol/L)	
Serum ferritin	Less than 10–20 mcg/L (22–44 pmol/L)	Ferritin is the protein-iron complex found in macrophages used for iron storage; low in iron-deficiency anemia.
Total iron-binding capacity (TIBC)	220–420 mcg/dL (39.4–75.2 µmol/L)	Measures the capacity of transferrin to bind iron; high in iron-deficiency anemia.
Transferrin saturation (TSAT)	30–50% (0.30–0.50)	Transferrin saturation = (serum iron/TIBC) × 100; a saturation of less than 15% is common in iron-deficiency anemia.
Other Tests		
Red blood cell distribution width (RDW)	11.5–14.5% (0.115–0.145)	A higher value means the presence of many different sizes of RBCs; the MCV is therefore less reliable.
Reticulocyte count		
Males:	0.5–15% of RBCs (0.005–0.025)	Should be elevated in patients who are responding to treatment.
Females:	0.5–2.5% of RBCs (0.005–0.025)	
Folic acid (plasma)	3.1–12.4 ng/mL or mcg/L (7–28 nmol/L)	Used to determine folic acid deficiency.
Folic acid (RBC)	125–600 ng/mL (283–1360 nmol/L)	Used to determine folic acid deficiency.
Vitamin B_{12}	180–600 pg/mL (133–738 pmol/L)	Used to determine vitamin B_{12} deficiency.
Erythropoietin level	2–25 mIU/mL (2–25 IU/L)	Patients may benefit from erythropoietin therapy if they are anemic and erythropoietin levels are normal or mildly elevated.

TREATMENT

Desired Outcomes

❹ *The goal of anemia therapy is to increase the hemoglobin level, which will improve red cell oxygen-carrying capacity, alleviate symptoms, and prevent anemia complications.* Normal hemoglobin values are 14 to 17.5 g/dL (140–175 g/L or 8.69–10.9 mmol/L) for males and 12.3 to 15.3 g/dL (123–153 g/L or 7.63–9.5 mmol/L) for females. It is important to note that continuation of a patient's therapy should be assessed primarily resolution of clinical signs and symptoms. Patients who experience a resolution in their symptoms such as shortness of breath, tachycardia, fatigue, dizziness, and edema may not require aggressive therapy to maintain their hemoglobin values within normal limits. Ultimately, prevention of complications owing to anemia such as hypoxia and cardiovascular sequelae can be avoided if hemoglobin levels are greater than 7 g/dL (70 g/L or 4.34 mmol/L).[10]

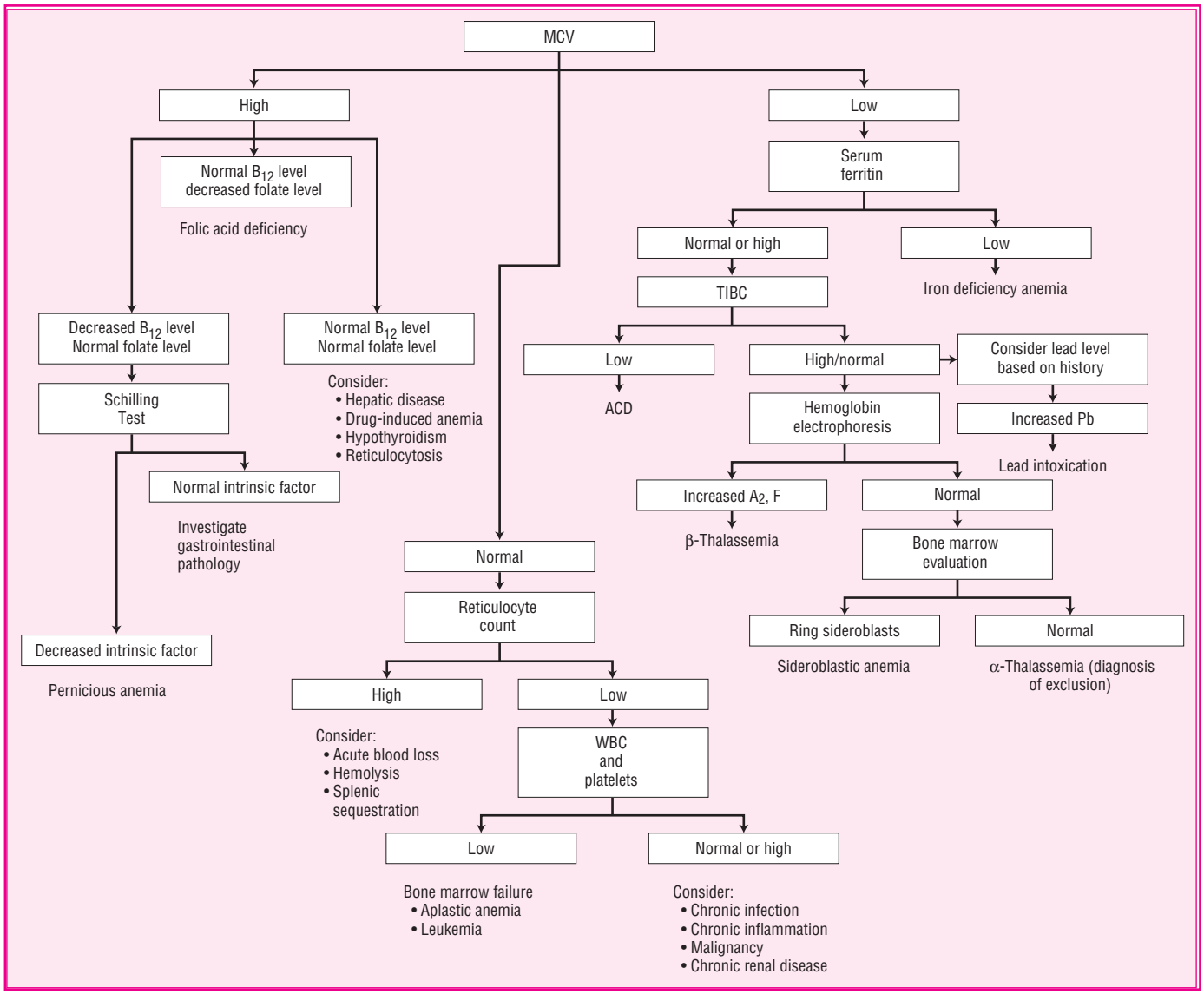


FIGURE 63–3. The anemia evaluation process. MCV, mean corpuscular volume; Pb, lead; TIBC, total iron binding capacity; ACD, anemia of chronic disease.

General Approach to the Anemic Patient

❺ *The underlying cause of anemia (e.g., blood loss; iron, folic acid, or vitamin B_{12} deficiency; or chronic disease) must be determined and used to guide therapy.* As discussed previously, patients should be evaluated initially based on laboratory parameters to determine the etiology of the anemia (see Fig. 63–3). Subsequently, the appropriate pharmacologic treatment should be initiated based on the cause of anemia.

Nonpharmacologic Therapy

The most important nonpharmacologic treatment of anemia is the transfusion of red blood cells. However, because of the risk of infection, immunosuppression, and microcirculatory complications and the high cost of the procedure, the threshold for transfusion has been debated.[11] Generally, only patients requiring immediate correction receive blood transfusions. Determining which patient requires immediate correction is left to the health care provider. Usually, symptomatic patients who present with a hemoglobin concentration of 7 to 8 g/dL (70–80 g/L or 4.34–4.96 mmol/L) are candidates for transfusion.[12]

Other than transfusion, nonpharmacologic therapy plays a limited role in the management of anemia. Certainly, some causes of anemia can be attributed to diets poor in iron, folic acid, or vitamin B_{12}. However, in the United States, nutrient-poor diets are rarely the sole cause of anemia in a patient. Therefore, ingesting a diet that is rich in iron, folic acid, or vitamin B_{12} should be encouraged but should not be the only

TABLE 63–2. Food Sources of Iron, Folic Acid, or Vitamin B_{12}[5]

Nutrient	Food Sources
Iron	Red meat, organ meats, wheat germ, egg yolks, oysters
Folic acid	Green vegetables, liver, yeast, fruits
Vitamin B_{12}	Animal by-products, legumes

modality of treatment. Food sources of iron, folic acid, and vitamin B_{12} are listed in Table 63–2.[5]

Pharmacologic Therapy

Iron-Deficiency Anemia

❻ *The initial treatment of iron-deficiency anemia is oral iron therapy with 200 mg of elemental iron daily for those who are able to tolerate the oral route.* In order to attain this amount of elemental iron daily, many different iron products and salt forms are available. Table 63–3 lists the various salt forms of oral iron available, the amount of elemental iron in each product, and the approximate daily dose of the salt to attain 200 mg of elemental iron daily.

Iron supplementation resolves anemia by replacing iron stores in the body that are necessary for red blood cell production and maturation. If treated properly, a response (via the presence of reticulocytosis) should be seen in 7 to 10 days, and hemoglobin values should rise by about 1 g/dL (10 g/L or 0.62 mmol/L) per week. Patients should be reassessed if hemoglobin does not increase by 2 g/dL (20 g/L or 1.24 mmol/L) in 3 weeks.

Dosing for iron should be divided equally into two to three doses daily. An empty stomach (1 hour before or 2 hours after a meal) is preferred for maximal absorption. After absorption, iron binds to transferrin in the plasma and is transported to the muscles (for myoglobin), liver (for storage), or bone marrow (for red cell production). Iron is not actively excreted from the body but is "lost" through other measures already described.[7] Some studies suggest that iron absorption may be increased by adding ascorbic acid (vitamin C) to the drug regimen.[13] However, administration of iron on an empty stomach and with ascorbic acid may increase the incidence of gastrointestinal (GI) side effects, such as abdominal pain, nausea, and heartburn. Patients who cannot tolerate their iron on an empty stomach may be told to take it with food.

Common toxicities associated with oral iron products include abdominal pain, nausea, and heartburn. Constipation and the presence of dark stools are reported often. Drug interactions may occur with iron products, predominantly owing to iron-drug binding, resulting in decreased absorption of the interacting drug. Examples include fluoroquinolones, tetracyclines, and phenytoin. To avoid this interaction, doses of iron and the interacting drug should be separated by 2 to 4 hours.

Parenteral iron therapy may be appropriate in cases where patients are unable to tolerate the oral formulation because of toxicities or compliance. In addition, those who have documented iron-deficiency anemia and have not responded to



Patient Encounter, Part 3

The patient is diagnosed with iron-deficiency anemia and is started on ferrous sulfate 325 mg orally three times daily to be taken on an empty stomach. Follow-up CBC 1 month later reveals a Hgb of 10 g/dL (100 g/L or 6.2 mmol/L), previously 9.3 g/dL (93 g/L or 5.77 mmol/L). The patient complains of shortness of breath on exertion and constipation. She also admits to taking only one tablet a day because of nausea.

- What hemoglobin level would constitute a therapeutic response in this patient?
- How can nausea secondary to ferrous sulfate be reduced in this patient?
- What changes to this patient's iron therapy do you recommend?

TABLE 63–3. Iron Products (IV and PO) and Elemental Iron Content

Salt Form	Brand Name(s)	Elemental Iron Content per Dose Form
Oral Formulations		
Ferrous sulfate	Feosol	65 mg/325-mg tablet
		60 mg/300-mg tablet
Ferrous sulfate, anhydrous	N/A	65 mg/200-mg tablet
Ferrous gluconate	Fergon	39 mg/325-mg tablet
		37 mg/300-mg tablet
Ferrous fumarate	Feostat	33 mg/100-mg tablet
Polysaccharide-iron complex	Niferex	150 mg/capsule
		50 mg/tablet
Parenteral Formulations		
Iron dextran	InFED	50 mg/mL
Iron sucrose	Venofer	20 mg/mL
Sodium ferric gluconate	Ferrlecit	62.5 mg/5 mL

oral iron therapy (e.g., because of malabsorption) are also candidates for parenteral iron therapy.

Parenteral iron therapy currently is available in three different formulations, which are listed in Table 63–3. Iron dextran was the first parenteral iron formulation to be approved, followed by ferric gluconate, and then iron sucrose. Although these newer agents are only approved by the Food and Drug Administration (FDA) to treat anemia associated with CKD in patients receiving erythropoietin products, they are effective in treating iron-deficiency anemia as well. Iron dextran is FDA approved for treating documented iron deficiency in patients who are unable to tolerate the oral formulation.

The dose of iron dextran can be calculated by the following equation: dose (mL) = 0.0442 (desired Hgb – observed Hgb) × body weight + (0.26 × body weight). The body weight that should be used is lean body weigh for adults and children weighing more than 15 kg and actual body weight for children weighing 5 to 15 kg. The dose in milligrams can be calculated based on a standard concentration of 50 mg elemental iron per milliliter.[14] The prescribing information recommends administering iron dextran in 100-mg aliquots daily until the total dose is achieved. However, anecdotal evidence reports that the total calculated dose can be administered safely over 4 to 6 hours in one day. It is important to note that a test dose (0.5 mL over at least 30 seconds) must be administered to patients who are about to receive their first dose of iron dextran because of the risk of anaphylaxis. Patients should be monitored for signs of anaphylaxis for at least 1 hour after the test dose before administering the total dose. Other adverse effects include arthralgias, arrhythmias, hypotension, flushing, and pruritus.

The use of newer parenteral iron products (e.g., iron sucrose and ferric gluconate) for treating iron-deficiency anemia is controversial; they are FDA approved for the treatment of anemia associated with CKD. It is appealing to use these agents in the setting of iron-deficiency anemia because they are considered "safer" owing to a decreased risk of anaphylaxis. However, the high cost and lack of reimbursement for these agents may preclude their routine use in iron-deficiency anemia patients without kidney disorders.[15]



Patient Encounter, Part 4

Because the patient is not able to tolerate oral iron therapy (constipation and nausea), changing to intravenous iron therapy is appropriate.

- What formulation of intravenous iron therapy should the patient receive?
- Calculate this patient's dose of parenteral iron.
- What adverse effects are associated with parenteral iron?

Vitamin B_{12} and Folic Acid anemia

❼ *Anemia from vitamin B_{12} or folic acid deficiency is treated effectively by replacing the missing nutrient.* Both folic acid and vitamin B_{12} are essential for erythrocyte production and maturation. Replacing these factors allows for normal DNA synthesis and, consequently, normal erythropoiesis.

Vitamin B_{12} (cyanocobalmin) administered both orally and parenterally is equally effective in treating anemia from vitamin B_{12} deficiency. However, use of parenteral cyanacobalamin is the most common method of vitamin B_{12} replacement because it may be more reliable and practical. Subcutaneous or intramuscular administration is appropriate. Vitamin B_{12} is absorbed completely following parenteral administration, whereas oral vitamin B_{12} is absorbed poorly via the GI tract. Furthermore, use of parenteral vitamin B_{12} to treat megaloblastic anemia may circumvent the need to perform a Schilling test to diagnose lack of intrinsic factor.

A typical cyanocobalmin dosing regimen is 800 to 1000 mcg/day for 1 to 2 weeks, followed by 100 to 1000 mcg/day every week until the Hgb/Hct normalizes and maintenance of 100 to 1000 mcg monthly for life. However, a number of dosing regimens exist. In addition, a number of oral vitamin B_{12} preparations are available, including many over-the-counter formulations. A common oral dosing regimen is from 1000 to 2000 mcg/day. If parenteral cyanocobalmin is used initially, oral vitamin B_{12} can be useful as maintenance therapy. Typically, the response to therapy is quick. Neurologic symptoms and megaloblastic cells disappear within a few days, and hemoglobin levels increase after a week of therapy.

Vitamin B_{12} generally is well tolerated and exhibits minimal adverse effects. Injection-site pain, pruritus, rash, and diarrhea have been reported. Drug interactions have been observed with omeprazole and ascorbic acid that decrease oral absorption.

When treating folic acid deficiency, an initial daily dose of 1 mg/day by mouth typically is effective. Absorption of folic acid generally is rapid and complete. However, patients with malabsorption syndromes may require larger doses (up to 5 mg/day). Similar to vitamin B_{12} deficiency, resolution of symptoms and reticulocytosis is prompt, occurring within days of commencing therapy. Hgb will start to rise after 2 weeks of therapy and may take from 2 to 4 months to resolve the deficiency completely. Afterwards, if the underlying deficiency is corrected, folic acid replacement can be discontinued. However, in cases where folic acid is consumed rapidly or absorbed poorly, chronic replacement may be required.

Folic acid is also well tolerated. Some nonspecific adverse effects include allergic reactions, flushing, malaise, and rash. Folic acid has been reported to decrease phenytoin levels by inducing its metabolism.

Anemia of Chronic Disease

Anemia of chronic disease is a term given those with underlying conditions that contribute to or cause anemia in a patient. These chronic diseases can include cancer, chronic

kidney diseases, and other inflammatory disorders. ❽ *In* patients with anemia owing to cancer and chronic kidney disease, therapy with epoetin or darbepoetin can increase hemoglobin, decrease transfusion requirements, and improve quality of life.

Chemotherapy induced Anemia

Studies have shown that in patients with chemotherapy-related anemia, therapy with erythropoietin products (epoetin-alfa and darbepoetin) can increase hemoglobin, decrease transfusion requirements, and improve quality of life.[12] Epoetin is recombinant human erythropoietin, and darbepoetin is structurally similar to endogenous erythropoietin. Both bind to the same receptor to stimulate red blood cell production. Darbepoetin differs from epoetin in that it is a glycosylated form and exhibits a longer half-life in the body. The half-lives of a single subcutaneous injection of epoetin or darbepoetin in patients are roughly 27 and 43 hours, respectively.

The National Comprehensive Cancer Network (NCCN) recommends an anemia work-up for patients with hemoglobin of less than 11 g/dL (110 g/L or 6.8 mmol/L). Patients who are symptomatic or asymptomatic with significant risk factors (e.g., extensive transfusion history, myelosuppressive chemotherapy, etc) may qualify for treatment with erythropoietic agents such as epoetin-alfa or darbepoetin. Data do not support the use of one agent over another; they are both equally effective in treating this type of anemia.[12] Table 63–4 provides dosing recommendations for chemotherapy-related anemia.

The response to erythropoietin products must be monitored closely to prevent adverse effects associated with these agents. The common adverse effects experienced include hypertension and thrombosis. Concomitant drugs with the same adverse-effect profile may increase a patient's risk for these complications. Also, the patient's overall survival may be decreased if the hemoglobin level is titrated to above the recommended 11 to 12 g/dL (110–120 g/L or 6.82–7.44 mmol/L) value. Therefore, it is important to follow the dosing and titration scheme recommended by the NCCN and summarized in Fig. 63–4. Patients should have their hemoglobin evaluated at least every 2 weeks. If in that time period the hemoglobin value rises 1 g/dL (10 g/L or 0.62 mmol/L) or greater, then the dose should be reduced by 25%. In addition, the dose of an erythropoietin agent should be held in patients who have a hemoglobin value equal to or greater than 12 g/dL (120 g/L or 7.44 mmol/L) as a result of treatment. Therapy can be reinitiated once the hemoglobin falls to less than 12 g/dL (120 g/L or 7.44 mmol/L), but the dose should be reduced by 25%.

Patients who do not exhibit at least a 1 g/dL (10 g/L or 0.62 mmol/L) increase in their hemoglobin level after 6 weeks of treatment should have their doses increased by 50%. In addition, if their hemoglobin has not increased by this amount after 12 weeks of therapy, then the drug should be discontinued, and further work-up is required.

Cancer patients also may have concurrent iron deficiency secondary to erythropoietin use ("functional" iron deficiency) or to cancer. Therefore, it is imperative that these patients have iron studies done to assess adequate iron stores needed to drive hematopoiesis. If the patient is determined to have suboptimal iron stores or is iron deficient, then replacement either orally or intravenously may be necessary, in addition to the use of erythropoietin products. The use of iron in these patients is the same as discussed previously under "Iron-Deficiency Anemia."

Chronic Kidney Disease (CKD)

Patients with CKD progress through five stages of disease based on the glomerular filtration rate (GFR).[16] Anemia is a common development in patients with CKD, and anemia evaluation and treatment should be initiated in patients with stage 3 CKD patients (GFR less than 60 mg/dL). Early treatment of anemia in patients with CKD has been associated with slower disease progression and a lower risk of death once patients receive dialysis.[17,18] Therefore, it is essential to evaluate and treat anemia in patients before they progress to stage 5 CKD, which is a GFR of less than 15 mg/dL or dialysis.

To rule out other causes of anemia, a thorough anemia evaluation should be completed in patients with CKD.[19] CKD

TABLE 63–4. Erythropoietin Products and Their Usual Doses for Anemia from Cancer/Chemotherapy and CKD

	Epoetin-alfa (Epogen, Procrit)	Darbepoetin-alfa (Aranesp)
Cancer/chemotherapy dosing regimens	150 units/kg subcutaneously three times per week 40,000 units subcutaneously once every week	2.25 mcg/kg subcutaneously once every week 3 mcg/kg subcutaneously once every 2 weeks; may increase to 5 mcg/kg 200 mcg subcutaneous fixed dose every 2 weeks, may increase to 300 mcg 300–500 mcg every 3 weeks
CKD dosing regimens[a]	50–100 units/kg subcutaneously three times per week	0.45 mcg/kg subcutaneously once every week 0.75 mcg/kg subcutaneously once every two weeks

[a]According to National Kidney Foundation guidelines for the use epoetin in patients with anemia owing to kidney disease, the subcutaneous route is preferred. However, the intravenous route is used commonly in clinical practice.

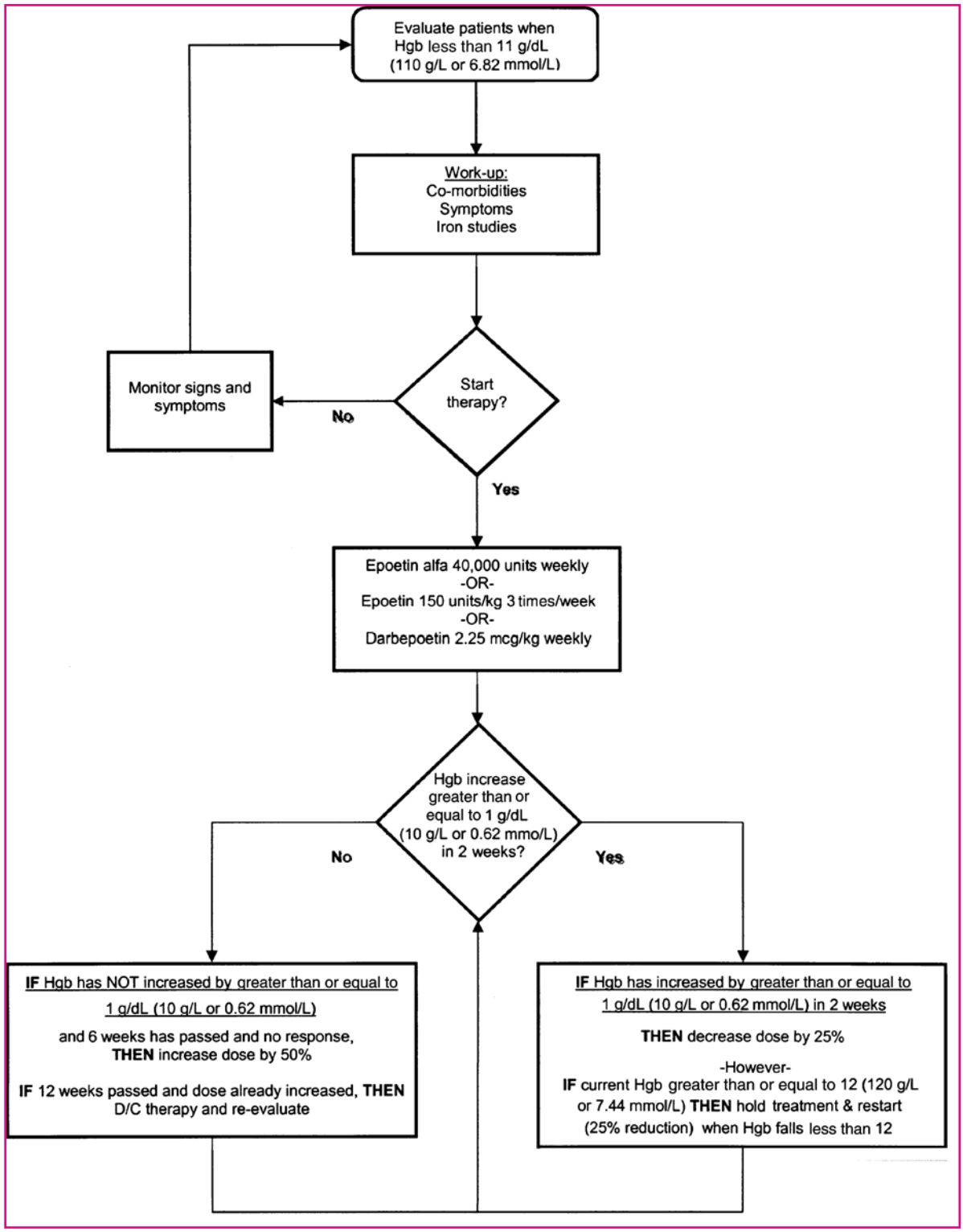


FIGURE 63–4. Summary of treatment guidelines for anemia from cancer/chemotherapy.

anemia typically is a normocytic, normochromic anemia that is due to erythropoietin (EPO) deficiency. Therefore, therapy with epoetin and darbepoetin is effective in treating CKD anemia. The target hemoglobin value in patients with CKD is similar to the target for patients undergoing chemotherapy of 11 to 12 g/dL (110–120 g/L or 6.82–7.44 mmol/L), but the epoetin and darbepoetin doses required for CKD anemia typically are lower than the doses for anemia from cancer/chemotherapy, and subcutaneous administration is the preferred route of administration (Table 63–4). According to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) guidelines, epoetin doses should be increased by 50% if patients do not have an adequate response (less than 2% increase in Hct) after 2 to 4 weeks of therapy and decreased by 25% if the absolute increase in hemoglobin is greater than 3 g/dL (30 g/L or 1.9 mmol/L) or the target hemoglobin is surpassed.

Although EPO deficiency is the primary cause of CKD anemia, iron deficiency is often present, and it is essential to assess and monitor the CKD patient's iron status (NKF-K/DOQI guidelines). Iron stores in patients with CKD should be maintained so that transferrin saturation (TSAT) is greater than 20% and serum ferritin is greater than 100 ng/mL (100 mcg/L or 225 pmol/L). If iron stores are not maintained appropriately, epoetin or darbepoetin will not be effective, and most CKD patients will require iron supplementation. Oral iron therapy can be used, but it is often ineffective, particularly in CKD patients on dialysis. Therefore, intravenous iron therapy is used extensively in these patients. Details of the pharmacology, pharmacokinetics, adverse effects, interactions, dose, and administration of erythropoietin and iron products have been discussed previously.

Other Chronic Diseases

Besides anemia associated with cancer and CKD, anemia of chronic disease can result from inflammatory processes and occurs commonly in autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus. In treating these types of anemia of chronic disease, the most important principle is treating the underlying disease. These patients also may have iron deficiency and should be treated in the manner already discussed. Erythropoietin therapy such as epoetin-alfa therapy at a dose of 150 units/kg three times a week also may be used in these patients.

OUTCOME EVALUATION

❾ *After treatment, patients should be monitored for symptom and laboratory value resolution, hemoglobin concentration, and adverse effects.* The goal of anemia therapy is to correct the underlying source of the anemia, normalize the hemoglobin, and alleviate associated symptoms.

- Monitor the CBC to ensure the correct Hgb titration:
- A 1 g/dL (10 g/L or 0.62 mmol/L) per week titration is desirable in patients with iron-deficiency anemia. Reevaluate patients with an increase of less than 2 g/dL (20 g/L or 1.24 mmol/L) in 3 weeks.
- In patients with folic acid deficiency, methylmalonic acid may be normal, and homocysteine may be high. Monitor hemoglobin periodically, and reevaluate patients who fail to normalize hemoglobin levels after 2 months of therapy.
- In patients with vitamin B_{12} deficiency, methylmalonic acid and homocysteine levels may be high. Monitor for resolution of neurologic symptoms (i.e., confusion and paresthesias), if applicable, and Hgb levels periodically until the levels normalize.
- Do not exceed more than 1 g/dL (10 g/L or 0.62 mmol/L) every 2 weeks when using erythropoietin products to increase hemoglobin. Otherwise, decrease the dose of the erythropoietin product.
- Do not exceed Hgb of greater than 13 g/dL (130 g/L or 8.1 mmol/L) because of an increased risk of death and thrombosis in cancer patients.
- Monitor other laboratory tests, such as MCV, iron studies, and presence of reticulocytosis.



Patient Care and Monitoring

1. Identify and treat the underlying cause of anemia.
2. Determine if immediate correction of anemia is required with a transfusion or if chronic therapy can be initiated.
3. Monitor symptoms such as fatigue, shortness of breath, lethargy, headache, edema, and tachycardia for resolution.
4. Monitor the complete blood count monthly.
5. When initiating erythropoietin products, assess the patient's iron status.
6. Monitor side effects of therapy, such as
   - *Oral iron:* nausea, vomiting, abdominal pain, heartburn, constipation, and dark stools
   - *Parenteral iron:* anaphylaxis (test dose required for iron dextran and observe for 1 hour after), injection-site pain/irritation, arthralgias, myalgias, flushing, malaise, and fever
   - *Folic acid:* bad taste and nausea, rash, and allergic reactions
   - *Vitamin B_{12}*: hyperuricemia, hypokalemia, and sodium retention (rare)
   - *Erythropoietin products:* hypertension (monitor blood pressure), thrombosis (e.g., DVT/PE, MI, CVA, and TIA), arthralgias, and headache

ABBREVIATIONS

CBC:	complete blood count
CKD:	chronic kidney disease
EPO:	erythropoietin
GFR:	glomerular filtration rate
Hgb:	hemoglobin
Hct:	hematocrit
IDA:	iron-deficiency anemia
MCV:	mean corpuscular volume
MCH:	mean corpuscular hemoglobin
NCCN:	National Comprehensive Cancer Network
NKF-K/DOQI:	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
RBC:	red blood cell
TIBC:	total iron-binding capacity
TSAT:	transferrin saturation

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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64 Coagulation Disorders

Alma Hamidovic



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Describe the basics of the regulation of hemostasis and thrombosis.
2. Determine which factor-replacement preparation is appropriate in a clinical situation.
3. Calculate an appropriate factor-concentrate dose for a product, given the percentage correction desired.
4. List the complications from hemophilia bleeding episodes.
5. Devise a treatment plan for a patient with a specific variant of von Willebrand's disease.
6. Identify which laboratory tests may aid in the diagnosis of disseminated intravascular coagulation (DIC).
7. Recommend treatment approach for the initial treatment of immune thrombocytopenic purpura (ITP).
8. Identify basic clinical features of thrombotic thrombocytopenic purpura (TTP).
9. List etiologies for neonatal vitamin K deficiency.

Key Concepts

❶ Intravenous factor replacement with recombinant or plasma-derived products to treat or prevent bleeding is the primary treatment of hemophilia.

❷ Type 1 patients unresponsive to desmopressin, patients with types 2 and 3 von Willebrand's disease, and major surgery patients require replacement therapy with plasma-derived intermediate- and high-purity factor VIII virus–inactivated factor VIII concentrates containing von Willebrand factor.

❸ The primary treatment of recessively inherited coagulation disorders is single-donor fresh-frozen plasma (FFP) that contains all coagulation factors.

❹ The cornerstone of the management of disseminated intravascular coagulation (DIC) is aggressive treatment of the underlying primary illness. Supportive measures may be used as necessary; however, owing to the heterogeneity of the DIC etiology, treatment should be guided by predominant symptoms (bleeding or clotting).

❺ Almost all neonates are vitamin K–deficient as a result of (1) insignificant transplacental vitamin K crossover, (2) lack of colonization of the colon by vitamin K–producing bacteria, and (3) inadequate dietary vitamin K intake.

❻ The treatment of immune thrombocytopenic purpura (ITP) is determined by the symptom severity. In some cases, no therapy is needed.

COMPONENTS OF THE HEMOSTATIC SYSTEM

Following endothelial injury, vessel-wall response involves vasoconstriction, platelet plug formation, coagulation, and fibrinolysis regulation. In normal circumstances, platelets circulate in the blood in an inactive form. After injury, platelets undergo activation, which consists of (1) adhesion to the subendothelium, (2) secretion of granules containing chemical mediators (e.g., adenosine diphosphate, thromboxane A_2, thrombin, etc.), and (3) aggregation. Chemical factors released from the injured tissue and platelets stimulate the coagulation cascade and thrombin formation. In turn, thrombin catalyzes the conversion of fibrinogen to fibrin and its subsequent incorporation into plug.

The coagulation system that generates thrombin consists of intrinsic and extrinsic pathways. Both pathways are composed of a series of enzymatic reactions eventually producing thrombin, fibrin, and a stable clot. In parallel with the coagulation, the fibrinolytic system is activated locally. Plasminogen is converted to plasmin, which dissolves the fibrin mesh[1] (Fig. 64–1).

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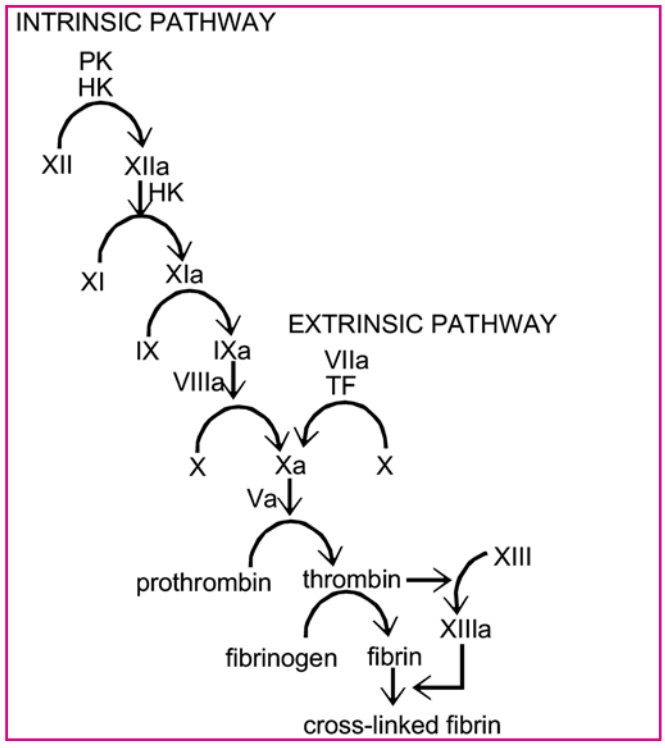


FIGURE 64–1. Cascade model of coagulation demonstrates activiation via the intrinsic or extrinsic pathway. This model shows successive activiation of coagulation factors proceeding from the top to the bottom where thrombin and fibrin are generated. PK, prekallikrein; HK, high-molecular-weight kininogen; TF, tissue factor. (Reproduced from Roberts HR et al. Molecular biology and biochemistry of the coagulation factors and pathways of hemostasis. In: Beutler et al, (eds.) Williams Hematology. 6th ed. New York: McGraw-Hill; 2001: 1409–1434.)



Clinical Presentation and Diagnosis

Hemophilia A and hemophilia B are clinically indistinguishable.

Symptoms

- Ecchymoses
- Hemathrosis* (especially knee, elbow and ankle)
  - Joint pain swelling and erythema
  - Cutaneous warmth
  - Decreased range of motion
- Muscle hemorrhage
  - Swelling
  - Pain with motion of affected muscle
  - Signs of nerve compression
  - Potential life-threatening blood loss, especially with thigh bleeding
  - Mouth bleeding with dental extractions or trauma
  - Genitourinary bleeding
  - Hematuria
  - Intracranial hemorrhage (spontaneous or following trauma), with headache, vomiting, change in mental status, and focal neurologic signs
  - Excessive bleeding with surgery

Hemophilia Is Categorized by Factor Level

Severe: less than 0.01 units/mL (less than 1 IU/dL)
Moderate: 0.01 to 0.05 units/mL (1–5 IU/dL)
Mild: greater than 0.05 units/mL (greater than 5 IU/dL)

*Hallmark of hemophilia; recurrent inadequately managed hemarthrosis leads to chronic deformity and pain.

INHERITED COAGULATION DISORDERS: HEMOPHILIA

Etiology and Epidemiology

Hemophilia A and B are coagulation disorders that result from defects in the genes encoding for plasma coagulation proteins. Hemophilia A (classic hemophilia) is caused by the deficiency of factor VIII, and hemophilia B (Christmas disease) is caused by the deficiency of factor IX. The incidences of hemophilia A and B are estimated at 1 in 5000 and 1 in 30,000 male births, respectively. Both types of hemophilia are evenly distributed across all ethnic and racial groups.[1]

Pathophysiology

The pathophysiology of hemophilia is based on the factor VIII or IX deficiency resulting in inadequate thrombin generation and an impaired intrinsic-pathway coagulation cascade (see Fig 64–1). Factor VIII and IX genes are located on the X chromosome. The hemophilias are recessive X-linked diseases. Generally, affected males carrying either defective allele on their X chromosome do not transmit the gene to their sons. However, their daughters are obligate carriers. Over 800 point mutations, deletions, and inversions have been identified throughout the factor VIII and IX genes. Consequently, hemophilia is not a result of a single genetic mutation. However, inversion at intron 22 of the factor VIII gene accounts for 45% of severe hemophilia A cases. Owing to the high incidence, this mutation is used for carrier and prenatal testing.[2]

Complications of Hemophilia

The severity of bleeding associated with hemophilia correlates with the degree of factor VIII or factor IX deficiency as measured against the normal plasma standard. Table 64–1 summarizes the age at onset and laboratory and clinical manifestations of hemophilia.[3]

TABLE 64–1. Laboratory and Clinical Manifestations of Hemophilia

	Severe (less than 0.01 units/mL)	Moderate (0.01–0.05 units/mL)	Mild (less than 0.05 units/mL)
Age at onset	Less than or equal to 1 year	1–2 years	2 years–adult
Neonatal symptoms			
PCB:	Usually	Usually	Rare
ICH:	Occasionally	Uncommonly	Rare
Muscle/joint hemorrhage	Spontaneous	Minor trauma	Minor trauma
CNS hemorrhage	High risk	Moderate risk	Rare
Postsurgical hemorrhage (without prophylaxis)	Frank bleeding, severe	Wound bleeding, common	Wound bleeding, with factor less than 0.3 units/mL
Oral hemorrhage following trauma, tooth extraction	Usual	Common	Often

Normal range of factor VIII/IX activity level is 0.5–1.5 units/mL (50%–150%). 1 unit/mL corresponds to 100% of the factor found in 1 mL of normal plasma. CNS, central nervous system; ICH, intracranial hemorrhage; PCB, postcircumceisional bleeding.

Treatment

Desired Outcomes

The life expectancy of hemophiliacs was only 8 to 11 years in the 1920s and 1930s. With the development of effective treatment strategies, life expectancy is currently about 65 years, or nearly that of the normal population.

The short-term goals of hemophilia treatment are to:

- Decrease the number of bleeding episodes per year or bleeding frequency
- Normalize or improve clotting factor concentrate levels

The long-term goals of hemophilia treatment are to:

- Maintain clinical joint function.
- Normalize orthopedic joint score.
- Normalize radiologic joint score.
- Maintain quality-of-life measurements.

General Approach to Treatment

❶ *Intravenous factor replacement with recombinant or plasma-derived products to treat or prevent bleeding is the primary treatment hemophilia. Primary prophylaxis* is defined as the regular administration of factor concentrates with the intention of preventing joint bleeds.[4] The rationale for primary prophylaxis is that individuals with factor levels of greater than 0.02 unit/mL (2 IU/dL) rarely suffer from spontaneous bleeds and arthropathy. Therefore, to maintain a trough level above this might convert "severe" hemophilia to "moderate" disease, with the abolition of joint bleeds and the associated arthropathy.[5]

Primary prophylaxis is expensive, but historical cohorts show progressively better outcomes (e.g., joint function and radiologic appearances) with more treatment, and prophylaxis thus is recommended as optimal therapy by the WFH, the World Health Organization (WHO), the U.K. Haemophilia Centre Doctors' Organization, and the National Hemophilia Foundation of the United States. However, a recent Cochrane Review attempting to search for evidence of the benefit of prophylaxis concluded that there were too few trials (only four) to prove benefit.[6]

Nonpharmacologic Therapy

Surgery

Open surgical arthroscopic synovectomy reduces replacement-therapy-resistant disease and repetitive hemarthresis of a single joint. This procedure removes inflamed tissue and joint blood vessels.

Orthotics

Joint prostheses do not deal with the deformities directly. Orthotics in hemophilia serve as an important supportive measure before or after surgery.

Pharmacologic Therapy

Hemophilia A

Primary therapy is based on disease severity and type of hemorrhage.[7] Most patients with mild to moderate disease and a minor bleeding episode can be treated with 1-desamino-8-D-arginine vasopressin [desmopressin acetate (DDAVP)], a synthetic analog of the antidiuretic hormone vasopressin. DDAVP causes release of von Willebrand factor (vWF) and factor VIII from endogenous storage sites. This formulation increases plasma factor VIII levels by three- to fivefold within 30 minutes. The recommended dose is 0.3 mcg/kg intravenously (in 50 mL normal saline infused over 15 to 30 minutes) or subcutaneously or 300 mcg intranasally via concentrated nasal spray every 12 hours. Peak effect with intranasal administration occurs 60 to 90 minutes after administration, which is somewhat later than with intravenous administration. Desmopressin infusion may be administered daily for up to 2 to 3 days. Tachyphylaxis, an attenuated response with repeated administration, may occur after several doses.[8]

Factor VIII Replacement Patients with severe hemophilia may receive primary (before the first major bleed) or secondary (after the first major bleed) prophylaxis, and all hemophiliacs with a major bleed require factor VIII replacement. The therapy may include recombinant (produced via transfection of mammalian cells with the human factor VIII gene) or plasma-derived (concentrate from pooled plasma) factor VIII (Table 64–2). The choice of product and dose are based on the overall clinical scenario because there is no difference in efficacy among various preparations. Newer-generation plasma-derived coagulation factor concentrates are considerably safer owing to advancements in viral testing and inactivation technology. Typically, recombinant factor VIII concentrates are recommended for (1) previously untreated patients, (2) human immunodeficiency virus (HIV)– and hepatitis C virus (HCV) seronegative patients, and (3) mild to moderate hemophiliacs after surgery or trauma when DDAVP is not sufficient.[9]

The severity of hemorrhage and its location are major determinants of percent correction to target, as well as duration of therapy (Table 64–3). Minor bleeding may be treated with a goal of 25% to 30% of normal (0.25–0.30 unit/mL, or 20–30 IU/dL), whereas serious or life-threatening bleeding requires at least 50% of normal activity. Factor VIII is a large molecule that remains in the intravascular space, and estimated volume of distribution, therefore, is approximately 50 mL/kg. Generally, factor VIII levels increase 2% (0.02 unit/mL, or 2 IU/dL) for every 1 unit/kg of factor VIII concentrate infused. The half-life of factor VIII ranges from 8 to 15 hours. Thus, a 1750 units/kg factor VIII bolus would be expected to provide an incremental rise of approximately 50% (0.5 unit/mL, or 50 IU/dL) over baseline (1750 units/70 kg × 0.02 unit/mL). Half the initial dose is given every half-life (every 8–15 hours) to maintain the desired factor VIII level.[10] Although intermittent bolus infusions of factor concentrates have been used successfully, continuous-infusion protocols are being instituted successfully to decrease the overall cost of therapy.

Hemophilia B

Factor IX Replacement Hemophilia B therapy may include recombinant (produced via transfection of mammalian cells with the human factor IX gene) or plasma-derived (concentrate from pooled plasma) factor IX (see Table 64–2). Guidelines for choosing the factor-concentrate formulation for hemophilia B are similar to the guidelines for hemophilia A. However, older-generation factor IX concentrates containing other vitamin K–dependent proteins (e.g., factors II, VII, and IX), called *prothrombin complex concentrates* (PCCs), have been associated with thrombogenic side effects. Consequently, these products are not first-line treatment for hemophilia B.[11]

TABLE 64–2. Factor Concentrates

Brand Name	Product Type	Viral Inactivation or Exclusion Method	Other Contents
Factor VIII concentrates			
Alphanate	Plasma	Solvent detergent, dry heat	Albumin, heparin, vWF
Hemophil M	Plasma	Solvent detergent, monoclonal antibody	Albumin
Humate-P	Plasma	Pasteurization	Albumin, vWF
Koãte-DVI	Plasma	Solvent detergent, dry heat	Albumin, heparin, vWF
Monarc-M	Plasma	Solvent detergent, monoclonal antibody	Albumin
Monoclate P	Plasma	Pasteurization, monoclonal antibody	Albumin
Advate	Recombinant	None	
Bioclate	Recombinant	None	Albumin
Helixate FS	Recombinant	Solvent detergent	Albumin (fermentation only); sucrose
Kogenate	Recombinant	Monoclonal antibody	Albumin
Kogenate FS	Recombinant	Solvent detergent, monoclonal antibody	Albumin (fermentation only); sucrose
Recombinate	Recombinant	Monoclonal antibody	Albumin
ReFacto	Recombinant B domain deleted	None	Albumin (fermentation only); sucrose
Factor IX concentrates			
AlphaNine SD	Plasma	Solvent detergent, filtered	Heparin
Mononine	Plasma	Monoclonal antibody, ultrafiltration	Heparin
Benefix	Recombinant	None	
APCC			
Autoplex T	Plasma	Dry heat	Heparin, IIa, VIIa, trace VIIIa, IXa, Xa
Feiba VH Immuno	Plasma	Vapor heat	IIa, VIIa, VIIIa, IXa, Xa
PCC			
Bebulin VH	Plasma	Vapor heat	Heparin, II, IX, X
Profilnine SD	Plasma	Solvent detergent	II, VII, IX, X
Proplex T	Plasma	Dry heat	Heparin, II, VII, IX, X
Other			
NovoSeven	Recombinant VII	None	
Hyate:C	Porcine VIII	Freeze-dried	Citrate

APCC, activated prothrombin complex concentrate; PCC, prothrombin complex concentrate; vWF, von Willebrand factor.

TABLE 64–3. Guidelines for Replacement Dosing with Factor VIII and Factor IX

Type of Hemorrhage	Desired Plasma Factor VIII Level (% of Normal)	Desired Plasma Factor XI Level (% of Normal)	Duration of Therapy (Days)
CNS, intracranial, retropharyngeal, retroperitoneal, surgical prophylaxis	80%–100%	80%–100%	Factor VIII: q8–12 hours over 10–14 days Factor IX: q12 hours over 10–14 days
Mild hemarthrosis, musosal (e.g., epistaxis, nosebleed), superficial hematoma	30%	20%–30%	Factor VIII: q8–12 hours over 1–2 days Factor IX: q12–24 hours over 1–2 days

Because it is a small protein, the factor IX molecule passes into the intravascular and the extravascular spaces. Therefore, the volume of distribution of recombinant factor IX is twice that of factor VIII. Consequently, 1 unit of factor IX administered per kilogram of body weight yields a 1% rise in the plasma factor IX level (0.01 unit/mL, or 1 IU/dL). Thus 1750 units of factor IX provides an incremental increase of 50% of normal (0.5 unit/mL, or 50 IU/dL), that is, 1750 units/70 kg × 0.01 unit/mL (1 IU/dL).[12] Additionally, the recovery rate with recombinant factor IX is 20% lower than that with the plasma-derived products. Therefore, initial and subsequent maintenance doses should be adjusted accordingly.

Treatment of Patients with Factor VIII or IX Inhibitors

Factor VIII and IX inhibitors are antibodies that develop in 20% and 12% of hemophilia A and hemophilia B patients, respectively, in response to replacement therapy. These antibodies bind to and neutralize the activity of infused factor concentrates. Although the inhibitors do not increase hemorrhage frequency, their existence challenges the treatment of bleeding episodes. Titers of inhibitors are measured and reported in Bethesda units (BU), and this measurement is used to guide therapy (Fig. 64–2). The therapeutic options for patients with factor inhibitors include recombinant factor VIIa (rFVIIa), prothrombin complex concentrates (PCCs), porcine factor VIII, and gene therapy.[13]

Factor VIIa (rFVIIa) is a bypassing agent designed to generate thrombin only at tissue injury sites, where it binds tissue factor and, in this manner, minimizes the risk of systemic thrombotic events. rFVIIa is used effectively in surgeries and spontaneous bleeds.[14]

PCCs contain the vitamin K–dependent factors II, VII, IX, and X. These agents represent another attempt to bypass the factor at which the antibody is directed (see Fig. 64–2). However, PCCs carry the risk of serious thrombotic complications. Porcine factor VIII is most useful when the inhibitor titer is less than 50 BU (see Fig. 64–2 for dose and frequency). Owing to its similarity to human factor VIII, porcine factor VIII participates in the coagulation cascade. However, most inhibitors have very weak neutralizing activity against it. Porcine factor VIII is a third-line agent (only after factor VIIa and a PCC have failed) owing to a 15% incidence of cross-reactivity.[15]

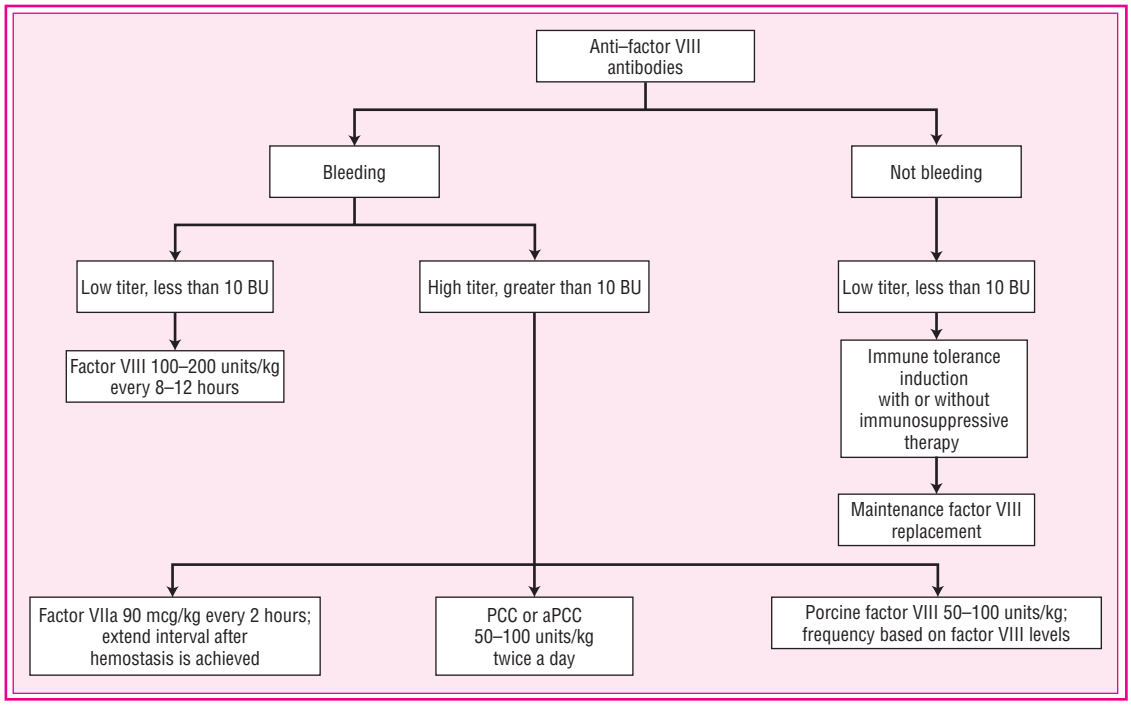


FIGURE 64–2. Treatment algorithm for the management of patients with hemophilia A and factor VIII antibodies. BU, Bethesda unit; PCC, prothrombin complex concentrate; aPCC, activated prothrombin complex concentrate.

Outcome Evaluation

The main goal of hemophilia treatment is to prevent bleeding episodes and their long-term complications. Clinicians should evaluate patients every 6 to 12 months for the following:

- Musculoskeletal status, including joint range of motion and radiologic assessment as indicated
- Number and type of bleeding episodes to assess adequacy of prophylactic treatment and home therapy
- Use of clotting-factor concentrates to check for the development of inhibitors, especially in patients with severe disease and poor treatment responders

VON WILLEBRAND DISEASE

Epidemiology and Etiology

Von Willebrand disease (vWD) is the most common inherited bleeding disorder caused by a deficiency or dysfunction of von Willebrand factor. The disease prevalence is estimated at 30 to 100 cases per million. In contrast to hemophilia, vWD is inherited as an autosomal dominant disorder (although autosomal recessive cases exist), ensuing equal frequency in male and females.[16]

Pathophysiology

Von Willebrand factor (VWF) is a large multimeric glycoprotein with two main functions in hemostasis: to aid the platelet adhesion to injured blood vessel walls and to carry and stabilize factor VIII in plasma. Table 64–4 represents three main vWD phenotypes, their frequency, and genetic transmission.[17]

Treatment

Desired Outcomes

Unlike hemophilia, the bleeding tendency in vWD is less frequent and generally less severe. Consequently, chronic prophylaxis usually is unwarranted. The goal of two mainstay therapeutic options in vWD is:

- To stop spontaneous bleeding as necessary
- To prevent surgical and postpartum bleeding

Nonpharmacologic Therapy

Local measures, including pressure and ice, may be used to control superficial bleeding.

Pharmacologic Therapy

Systemic therapy is used to prevent bleeding associated with surgery, childbirth, and dental extractions and to treat bleeding



Clinical Presentation and Diagnosis

Clinical manifestations vary depending on the sub-type. Patients with mild disease may be asymptomatic into adulthood.

Symptoms

- Bruising
- Mucocutaneous bleeding
  - Epistaxis
  - Oral cavity bleeding
  - Menorrhagia
  - GI bleeding
- Joint and deep tissue bleeding
- Postoperative bleeding

Laboratory Testing

- Normal PT
- Prolonged aPTT
- Platelet count
- Normal von Wilderbrand factor antigen and activity (vWF:Ag)
- Factor VIII coagulation assay (FVIII:C)
- Ristocetin cofactor activity (vWF:RCo)
- vWF multimer analysis (gel electrophoresis)

TABLE 64–4. Classification of von Willebrand Disease

Phenotype	Mechanism of Disease	% Cases	Genetic Transmission
Type 1 vWD	Partial (mild to moderate) quantitative deficiency of vWF and factor VIII	70%–80%	Autosomal dominant
Type 2 vWD	Qualitative abnormalities of vWF	10%–30%	Autosomal dominant
2A	Decreased platelet-dependent vWF function owing to lack of larger multimers		
2B	Increased platelet-dependent vWF function owing to lack of larger multimers		
2M	Defective platelet-dependent vWF functions not associated with multimer defects		
2N	Defective vWF binding to factor VIII		
Type 3 vWD	Severe quantitative deficiency of vWF	1%–5%	Autosomal recessive

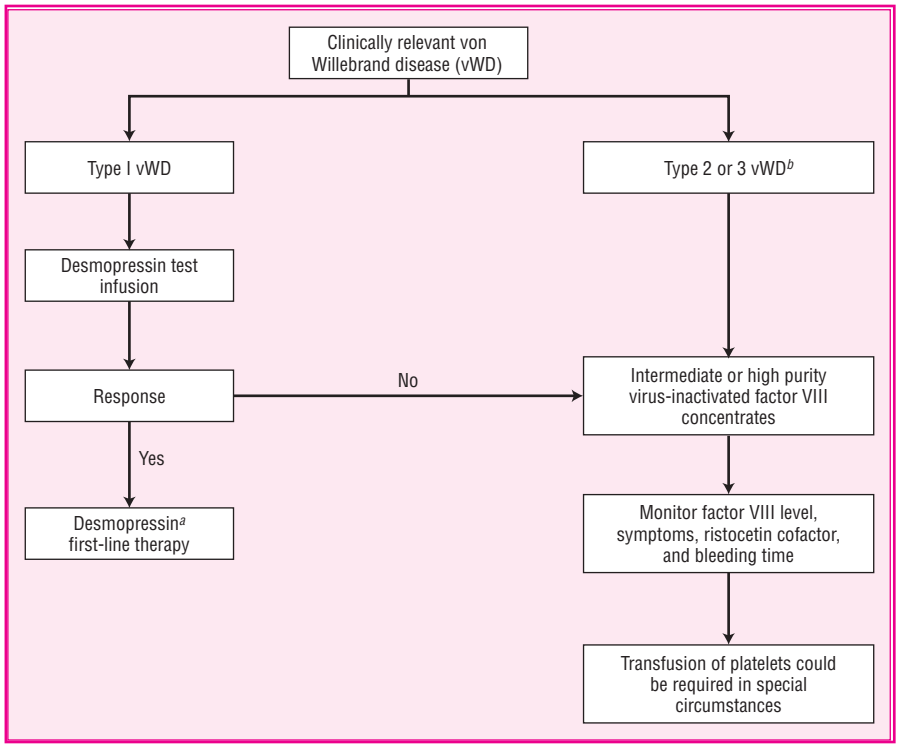


FIGURE 64–3. Guidelines for the treatment of von Willebrand disease. [a]Use factor VIII concentrate for life-threatening bleeding. [b]Some patients with type 2 or 3 von Willebrand disease may respond to desmopressin.

that cannot be controlled with local measures. The two systemic approaches involve using desmopressin, which stimulates the release of endogenous vWF, or administering products that contain vWF. The general approach to the treatment of vWD is depicted in Fig. 64–3.

Most patients with type 1 vWD (functionally normal vWF) and a minor bleeding episode can be treated successfully with desmopressin, which induces secretion of autologous factor VIII and vWF into plasma. The recommended dose is the same as that used to treat mild factor VIII deficiency (0.3 mcg/kg intravenously in 50 mL of normal saline infused over 15 to 30 minutes). This therapy generally is ineffective in type 2A patients who secrete qualitatively abnormal vWF and is controversial in type 2B patients because it may increase the risk of postinfusion thrombocytopenia. Type 3 vWD patients who lack releasable stores of vWF do not respond to DDAVP therapy.[18]

The individual responsiveness to desmopressin is consistent, and a test dose administered at the time of diagnosis or prior to therapy is the best predictor of response. Generally, DDAVP is more effective in vWD than in hemophilia patients, with an average 30% to 50% increase in vWF and factor VIII levels. In patients with an adequate response, desmopressin is first-line therapy because it allows for once-daily administration (elevates plasma levels for 8–10 hours), does not pose a threat in terms of viral transmission, and the cost is substantially less than that of the plasma-derived products. Fibrinolysis inhibitors (50–60 mg/kg of aminocapriotic acid every 4–6 hours or trenexamic acid 10–15 mg/kg every 8–12 hours) and OCs are used successfully in the management of epistaxis and menorrhagia or as adjuvant treatments.

Replacement Therapy

❷ *Type 1 patients unresponsive to desmopressin, patients with types 2 and 3 vWD, and major surgery patients require replacement therapy with plasma-derived, intermediate- and high-purity factor VIII virus–inactivated factor VIII concentrates containing vWF*. The usual dosing guidelines and target levels of replacement-therapy concentrates for control of various types of hemorrhage are provided in Table 64–5. Ultra-high-purity (monoclonal) plasma-derived and recombinant factor VIII concentrates do not contain vWF and should not

TABLE 64–5. Replacement Therapy in von Willebrand Disease[a]

Condition	Therapy
Major surgery	Maintain factor VIII level greater than or equal to 50% for 1 week Prolonged treatment in type 3 patients (greater than 7 days)
Minor surgery	Maintain factor VIII level greater than or equal to 50% for 1–3 days Maintain factor VIII level greater than 20%–30% for an additional 4–7 days
Dental extraction	Single infusion to achieve factor VIII level greater than 50% Desmopressin prior to procedure for type I
Spontaneous or posttraumatic bleeding	Usually single infusion of 20–40 units/kg

[a]The yield of factor VIII after first infusion is similar to that observed in hemophilia A (about 2% increment over baseline amount for every 1 unit/kg of factor VIII infused).

TABLE 64–6. Clotting Factor Deficiency Characteristics

Factor Deficient	Inheritance Pattern	Estimated Incidence	Severity of Bleeding
II (prothrombin)	Autosomal dominant or recessive	Extremely rare	Mild to moderate
V	Autosomal recessive	1:1 million	Mild to moderate
VII	Autosomal recessive	1:500,000	Mild to severe
X	Autosomal recessive	1:500,000	Mild to severe
XI	Autosomal recessive	4% of Askenazi Jews, otherwise rare	Mild to moderate
XII	Unknown	Unknown	No bleeding
XIII	Autosomal recessive	Less than 1:1 million	Moderate to severe

be used in the treatment of vWD. Cryoprecipitate contains considerable amounts of both factor VIII and vWF. However, this product is not a first-line treatment option because it does not undergo viral inactivation.

Outcome Evaluation

The main goal of vWF treatment is to prevent bleeding with surgery or dental procedures. Clinicians should evaluate patients every 6 to 12 months for the following:

- Number and type of bleeding episodes to assess the need for prophylactic treatment.
- Ensure that the factor VII level is greater than or equal to 50% for 1 week prior to major surgery, 1 to 3 days prior to minor surgery, and just prior to a dental extraction.

OTHER CLOTTING FACTOR DEFICIENCIES

Etiology and Epidemiology

Recessively inherited coagulation disorders (RICDs) refer to relatively rare deficiencies in factor II, V, VII, and X–XIII resulting in either decreased clotting factor production or production of a dysfunctional molecule with reduced activity.[19] The clinical severity of bleeding varies and generally is poorly correlated with the factor blood levels. Table 64–6 illustrates these clotting factor deficiencies and some of their characteristics.

Pathophysiology

The other factor deficiencies are rare genetic disorders. Mutations in the gene for the respective clotting factors results in impaired functionality or production of the factor (Table 64–7).

TABLE 64–7. Treatment of Factor Deficiencies

Factor Deficient	Major Surgery	Spontaneous Bleeding
II	1. PCC: 20–30 units/kg 2. FFP: 15–20 mL/kg Target: Greater than 30% until healing complete	1. FFP: 15–20 mL/kg Target: Greater than 30% until healing complete
V	1. FFP: 15–20 mL/kg Target: Greater than 20% until healing complete	1. FFP: 15–20 mL/kg Target: Greater than 20% until bleeding stops
VII	1. rFVIIa: 15–30 mcg/kg q12 hours 2. Concentrate: 30–40 units/kg q12 hours Target: Greater than 20% until healing complete	1. rFVIIa: 15–30 mcg/kg q12 hours 2. Concentrate: 30–40 units/kg q12 hours Target: Greater than 20% until bleeding stops
X	1. PCC: 20–30 units/kg 2. FFP: 15–20 mL/kg Target: Greater than 20% until healing complete	1. PCC: 20–30 units/kg 2. FFP: 15–20 mL/kg Target: Greater than 20% until bleeding stops
XI	1. FFP: 15–20 mL/kg Target: Greater than 20% until healing complete	1. FFP: 15–20 mL/kg Target: Greater than 20% until bleeding stops
XIII	1. Concentrate: 10–20 units/kg 2. FFP: 15–20 mL/kg 3. Cryoprecipitate (1 bag per 10 kg) Target: Greater than 5% until healing is complete	1. Concentrate: 10–20 units/kg 2. FFP: 15–20 mL/kg 3. Cryoprecipitate (1 bag per 10 kg) Target: Greater than 5% until healing is complete

FFP, fresh frozen plasma; PCC, prothrombin complex concentrates.

Clinical Presentation and Diagnosis

Deficient Factor	Main Clinical Symptoms	Laboratory Tests	Other Diagnostic Tests
II	Umbilical cord, joint, and mucosal tract bleeding	Prolonged prothrombin (PT) and activated partial thromboplastin time (aPTT)	Specific assay for prothrombin
V	Mucosal tract bleeding	Prolonged PT and aPTT Normal thrombin time	Specific factor V assay
VII	Mucosal tract, joint and normal aPTT	Prolonged PT	Specific factor VII assay
X	Umbilical cord, joint, and muscle bleeding	Prolonged PT and aPTT Normal thrombin time Prolonged Russel's viper venom	Specific factor X assay
XI	Posttraumatic bleeding	Prolonged aPTT Normal PT Normal thrombin time	Specific factor XI assay
XII	No bleeding	Prolonged aPTT Normal PT Normal thrombin time	Specific factor XII assay
XIII	Umbilical cord, intracranial, and joint bleeding; recurrent miscarriages, impaired wound healing	Normal PT, aPTT, thrombin time, bleeding time	Specific factor XIII assay

Treatment

Desired Outcomes

The main goal of recessively inherited coagulation disorder (RICD) treatment is to prevent and control spontaneous and surgery-related bleeding episodes. Specifically, therapeutic options improve hemostasis via replacement of deficient blood coagulation factors while minimizing the development of immune tolerance.[20]

Nonpharmacologic Therapy

Transfusional Therapies

❸ *The primary treatment of recessively inherited coagulation disorders is single-donor fresh-frozen plasma (FFP) that contains all coagulation factors.* Plasma concentrates of single coagulation factors are not available in the United States. Disadvantages of FFP include the risk of volume overload, especially when repeated infusions are administered in order to improve and maintain **hemostasis,** risk of infections, and risk of inhibitor development. Prothrombin complex concentrates (PCCs) licensed for the treatment of hemophilia B also contain significant levels of vitamin K–dependent factors and may be used off-label for treatment of RICD. Table 64–7 lists the recommended RICD treatment schedules in different clinical scenarios.

Pharmacologic Therapy

Less severe hemorrhages may be treated successfully with antifibrinolytic amino acids alone or in combination with factor replacement therapy. Tranexamic acid (20–25 mg/kg every 8 to 12 hours) and epsilon aminocaproic acid (50–60 mg/kg every 4–6 hours) may be administered intravenously or orally.

ACQUIRED COAGULATION DISORDERS: DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

Etiology and Epidemiology

Disseminated intravascular coagulation (DIC) is a systemic thrombohemorrhagic disorder characterized by an increased propensity for clot formation secondary to a wide variety of clinical conditions (Table 64–8). Central to the etiology of DIC is excessive and unregulated generation of thrombin, leading to an aggressive compensatory **fibrinolysis.** Therefore, clinical manifestations of DIC result from a loss of balance between the clot-promoting (leading to thrombosis) and the clot-lysing (leading to hemorrhage) systems. Although this balance may tip in either direction, presenting as bleeding or clotting, bleeding is most common and is observed in 70% to 90% patients.[21]

TABLE 64–8. Conditions Associated with Disseminated Intravascular Coagulation

Cardiovascular
- Acute myocardial infarction
- Angiopathy
- Aortic aneurysm
- Aortic balloon assist devices
- Giant hemangiomas
- Peripheral vascular disease
- Postcardiac arrest
- Prosthetic devices
- Raynaud's syndrome

Infectious
- Arbovirus
- *Aspergillus*
- *Candida albicans*
- Cytomegalovirus
- Ebola virus
- Gram-negative bacteria
- Gram-positive bacteria
- Herpesvirus
- Histoplasma
- Human immunodeficiency virus
- Influenza
- Kala-azar
- Malaria
- *Mycobacteria*
- *Mycoplasma*
- Paramyxoviruses
- Rocky Mountain spotted fever
- Rubella
- Typhoid
- Varicella
- Variola

Intravascular hemolysis
- Hemolytic transfusion reaction
- Hemolytic uremic syndrome
- Minor hemolysis
- Massive transfusion

Newborn
- Birth asphyxia
- Hypothermia
- Meconium or amniotic fluid aspiration
- Necrotizing enterocolitis
- Respiratory distress syndrome
- Shock

Obstetrics
- Abortion
- Amniotic fluid embolism

Obstetrics (Continued)
- Fatty liver of pregnancy
- Placental abruption
- Preeclampsia/eclampsia
- Retained fetus syndrome

Pulmonary
- syndrome
- syndrome
- Empyema
- Hyaline membrane disease
- Pulmonary embolism
- Pulmonary infarction

Tissue injury
- Burns
- Crush injuries
- Extensive surgery
- Head trauma
- Multiple trauma

Miscellaneous
- Acid-base imbalance
- Acute liver failure
- Amphetamines
- Anaphylaxis
- Autoimmune diseases
- Cholestasis
- Chronic inflammatory diseases
- Collagen vascular disease
- Craniotomy
- Extracorporeal circulation
- Extracorporeal membrane oxygenation
- Fat embolism
- Heat stroke
- Hemorrhagic telangiectasia
- Hepatitis
- Leukemia
- Lightening strikes
- Near drowning
- Organic solvent poisoning
- Paroxysmal nocturnal hemoglobinuria
- Peritoneovenous or pleurovenous shunts
- Polycythemia rubra vera
- Renal vascular disorders
- Severe anoxia
- Snake bite
- Solid tumors
- Transplant rejection

Pathophysiology

Once injured or activated by a toxic substance (e.g., bacterial toxins, placenta chemicals, snake venom, etc.), endothelial cells and monocytes respond by generating tissue factor on the cell surface. This, in turn, leads to the generation of tissue factor–factor VIIIa complexes, followed by unregulated and excessive generation of thrombin, fibrin, systemic **microthrombi** and consumption of coagulation factors, platelets, and regulators (e.g., antithrombin, protein C, and protein S). While bleeding into the subcutaneous tissues, skin, and mucous membranes takes place, microvascular thrombosis exacerbates tissue ischemia and organ damage.[22]



Clinical Presentation and Diagnosis

Clinical manifestations generally are associated with underlying primary illness, as described in Table 64–8.

Signs and Symptoms
- Thrombosis, hemorrhage, or both
- Hemorrhagic bullae
- Peripheral cyanosis
- Petechiae and purpura

Thrombus and End-Organ Dysfunction
- Skin: 70%
- Lungs: 50%
- Kidneys: 50%
- Liver: 35%
- Adrenal: 30%
- Heart: 20%

Laboratory Testing
- Increased D-dimer
- Thrombocytopenia
- Decreased fibrinogen
- Decreased antithrombin
- Decreased protein C and protein S
- Elevated fibrinopeptides A and B
- Increased prothrombin fragments 1 and 2
- Evidence of end-organ dysfunction or failure

Treatment

Desired Outcomes

❹ *The cornerstone of the management of DIC is aggressive treatment of the underlying primary illness. Supportive measures may be used as necessary, but owing to the heterogeneity of DIC etiology, treatment should be guided by predominant symptoms (bleeding or clotting).*[23]

- Replace missing blood components.
- Interrupt coagulation.
- Treat underlying disease.

Pharmacologic Therapy

Anticoagulants

While bleeding is the most frequently observed symptom of DIC, thrombotic events cause most of the mortality. Heparin is an effective anticoagulant with the potential to inhibit thrombin formation and function; however, its use is limited by the potential for bleeding. Clinical trials of heparin in DIC have not shown a consistent benefit. DIC patients most likely to benefit



Patient Encounter, Part 1

A 48-year-old woman was admitted to the intensive care unit with sepsis and hemodynamic instability. Three days earlier, she had undergone an abdominal surgery. After treatment with intravenous antibiotics and fluid administration, the patient was described as stable. Several hours later, the patient's nurse identified extravasation from the intravascular lines and abdominal drains.

- What information is suggestive of DIC?
- What additional information do you need to create a treatment plan for this patient?

from heparin are those with symptomatic thromboemboli, extensive fibrin deposition, persistent coagulation abnormalities despite replacement of hemostatic factors, and solid tumors. Heparin is contraindicated in DIC patients with serious or life-threatening bleeding, such as intracranial bleeding.[24]

Heparin may be given intravenously or subcutaneously, and there is no universally accepted dose. Full-dose heparin therapy in adults is a bolus of 5000 units, followed by a continuous infusion of 1000 units/hour. Since the aPTT is already elevated in individuals with DIC, monitoring full-dose heparin therapy may be difficult, and D-dimer and fibrinogen levels may be better markers of activity. Subcutaneous heparin at a dose of 80 to 100 units/kg every 4 to 6 hours and low-molecular-weight heparins are other, less studied options.[25]

Platelets and Fresh-Frozen Plasma

Treatment with platelet concentrates and plasma is indicated in patients who are bleeding or who require an invasive procedure. In a bleeding patient, the platelet count should be maintained above 50,000/mm^3 (50×10^3/μL or 50×10^9/L), and platelet concentrates should be given at a dose of 1 unit/10 kg of body weight. Fresh-frozen plasma contains all the coagulant factors as well as fibrinogen. Adding fibrinogen to the blood system in a situation where the level of antithrombin is already low may predispose to widespread microvascular thrombosis and aggravate end-organ damage. Non-fibrinogen-containing components are packed red cells, platelet concentrates, and nonclotting protein containing volume expanders such as albumin. If used, **fresh-frozen plasma** (FFP) is dosed at 10 to 15 mL/kg. Both platelet and plasma transfusions should be monitored, and platelet count as well as aPTT should be assessed.



Patient Encounter, Part 2

Meds
- Glyburide 10 mg once daily
- Hydrochlorothiazide 25 mg once daily
- Fluoxetine 20 mg once daily

Labs
- Platelet count: 30,000/mm^3 (30×10^3/μL or 30×10^9/L)
- aPTT: 46 s
- PT: 31 s
- Fibrinogen degradation product level: 380 to 540 g/L
- Plasma antithrombin level: 25%

- Given this additional information, what is your assessment of the patient's emergency?
- Identify your treatment goals for this patient.



Patient Encounter, Part 3: Creating a Care Plan

Based on the information presented, create a care plan for this patient's DIC.

Cryoprecipitate

If FFP cannot maintain fibrinogen concentration above 100 mg/dL (1 g/L) in a symptomatic patient, 1 to 4 units/10 kg of cryoprecipitate may be administered.

Outcome Evaluation

- With each therapeutic option, postinfusion increments (platelets, PT, aPTT, fibrinogen) should be checked within 30 to 60 minutes and every 6 hours thereafter, and the dose should be adjusted accordingly.
- Monitor the patient for relief of symptoms and signs of hemorrhage.

VITAMIN K DEFICIENCY OF THE NEWBORN

Etiology and Epidemiology

Vitamin K is a fat-soluble vitamin cofactor for the activation of factors II, VII, IX, and X in the liver. ❺ *Almost all neonates are vitamin K–deficient at as a result of (1) insignificant transplacental vitamin K crossover, (2) lack of colonization of the colon by vitamin K–producing bacteria, and (3) inadequate dietary vitamin K intake* (especially in breast-fed infants because human milk contains less vitamin K than infant formula or cow's milk). *Vitamin K–deficiency bleeding* (VKDB) refers to bleeding attributable to vitamin K deficiency within first 6 months of life. It occurs in three general time frames: early (0–24 hours), classic (1–7 days), and late (2–12 weeks). Early onset occurs rarely and usually is associated with maternal ingestion of anticonvulsants, rifampin, isoniazid, and warfarin. Classic vitamin K–dependent bleeding usually results from the lack of prophylactic vitamin K administration in



Clinical Presentation and Diagnosis

Symptoms
- Dark melena stools
- Bleeding from the umbilical stump
- Circumcision bleeding
- Bloody vomit
- Blood-stained urine
- Nose bleed
- Petechiae
- Venopuncture site bleed

Laboratory Testing
- Prolonged PT
- Prolonged aPTT
- Elevated abnormal (des-γ-carboxy) prothrombin (PIVKA) II
- Normal thrombin
- Normal platelet count
- Normal fibrinogen

brest-fed infants. The incidence of early and classic disease in the United States is variably reported from 0.25% to 1.7%. Late-onset VKDB is more severe clinically than early-onset or classic disease and has a high incidence (50% to 82%) of intracranial hemorrhage (ICH). The rate of late VKDB ranges from 4.4 to 7.2 per 100,000 births according to reports from Europe and Asia. In addition to breast-feeding, identified risk factors are cystic fibrosis, hepatitis, celiac disease, and α_1-antitrypin deficiency.[26]

Pathophysiology

The levels of vitamin K–dependent coagulation factors are physiologically low in neonates. Absence of vitamin K impairs γ-carboxylation, and the inactive precursors of factors II, VII, IX, and X accumulate in the plasma, unable to bind calcium and cell membranes. Consequently, the precursor levels may decline further, impairing coagulation and potentially leading to VKDB.

Treatment

Desired Outcomes

The main goal of treatment for vitamin K deficiency is prevention and control of VKDB. Specifically, therapeutic options may

- Reduce the incidence of VKDB via prophylaxis
- Improve hemostasis when VKDB occurs

Pharmacologic Therapy

Prophylactic Therapy

Administration of 100 mcg to 1 mg phytonadione intramuscularly at birth is the standard of care in the United States. A single dose corrects the deficiency state and usually does not need to be repeated in an otherwise healthy infant.

VKDB Therapy

Immediate administration of 100 mcg to 1 mg vitamin K subcutaneously or intravenously, followed by administration of FFP as necessary. Vitamin K administration via the intramuscular route may induce hematoma owing to coagulopathy, and intravenous administration should be slow because it has been associated with anaphylaxis. Prothrombin complex concentrate (PCC) at minimum dose of 50 units/kg should be given for life-threatening bleeding.[27,28]

Outcome Evaluation

- Monitor patient for cessation of bleeding.
- Monitor PT and aPTT.
- If evidence of intracranial bleeding is observed, consider transfer to a level III nursery.
- Monitor patient for toxicities such as hematomas and anaphylactic reactions.

PLATELET DISORDERS: IMMUNE THROMBOCYTOPENIC PURPURA

Etiology and Epidemiology

Immune thrombocytopenic purpura (ITP) is one of the most common causes of acquired thrombocytopenia. The estimated incidence is 100 cases per 1 million persons per year, about half of whom are children. ITP is an autoimmune disorder caused by the binding of antibodies (usually IgG) to platelet surface antigens resulting in shortened platelet life span. ITP can occur as an isolated condition or secondary to an underlying disorder. Childhood-onset and adult-onset ITP present very differently. Adult-onset ITP is generally chronic and affects women two to three times more often than men. By contrast, childhood-onset ITP is sudden and usually follows an infectious illness, and both sexes are equally affected. ITP occurs in 1 to 2 of every 1000 pregnancies. In pregnant women with preexisting ITP, both maternal and fetal complications may occur, requiring separate management.[29]

Pathophysiology

IgG autoantibody–coated platelets induce Fcγ receptor–mediated **phagocytosis** by mononuclear macrophages, predominantly in the spleen and liver. Thrombocytopenia develops as a consequence of megakaryocyte inability to increase platelet production and maintain a normal number of circulating platelets. Currently used treatments are directed at different aspects of the antibody production, platelet sensitization, and the clearance and production cycle.[30]



Clinical Presentation and Diagnosis

General

The typical patient is well with the exception of bleeding.

Symptoms

- **Petechiae**
- **Purpura**
- **Ecchymoses**
- Cutaneous bleeding
- Mucosal site bleeding
- Epistaxis
- Gingival bleeding
- Hematuria

Laboratory Testing

- Normal or slightly elevated thrombopoietin
- CBC
- Peripharal blood smear
- Direct antiglobulin test
- *Helicobacter pylori* testing
- Antibody to HIV

Treatment

Desired Outcomes

The main goal of ITP treatment is to maintain the platelet count (greater than 20,000–30,000/mm^3, 20–30 $\times$ 10^3/μL or 20–30 $\times$ 10^9/L) while awaiting spontaneous or treatment-induced remission.[31]

General Approach to Treatment

❻ *The treatment of ITP is determined by the symptom severity (Table 64–9). In some cases, no therapy is needed.* The initial treatment of children with ITP is controversial because more than 70% of cases resolve spontaneously irrespective of pharmacologic intervention. Currently, therapy is indicated in children with platelet counts less than 10,000 to 20,000/mm^3 (10–20 $\times$ 10^3/μL or 10–20 $\times$ 10^9/L) because most intracranial hemorrhages occur when platelets are in this range.[32]

TABLE 64–9. Guidelines for the Initial Management of ITP

Greater than 50,000 platelets/mm^3 (50 $\times$ 10^3/μL or 50 $\times$ 10^9/L)	No treatment
30,000–50,000 platelets/mm^3 (30–50 $\times$ 10^3/μL or 30–50 $\times$ 10^9/L)	Prednisone (1 mg/kg PO qd or no treatment)
Less than 30,000 platelets/mm^3 (30 $\times$ 10^3/μL or 30 $\times$ 10^9/L)	Prednisone (1–1.5 mg/kg per day) Anti-D immune globulin (75 mcg/kg)
Hemorrhage	Platelet transfusion IVIG (1 g/kg per day for 2–3 days) Methylprednisolone (1 g/day for 3 days)

Nonpharmacologic Therapy

Splenectomy generally is considered after 3 to 6 months if the patient continues to require 10 to 20 mg/day of prednisone to keep the platelet count greater than 30,000/mm^3 (30 $\times$ 10^3/μL or 30 $\times$ 10^9/L) or within 6 weeks of diagnosis in patients with platelet counts of less than 10,000/mm^3 (10 $\times$ 10^3/μL or 10 $\times$ 10^9/L) despite treatment. Even though individual patient response cannot be predicted, approximately two-thirds of refractory patients have a favorable response to splenectomy within a couple of days. After splenectomy, approximately 85% of adults attain a stable hemostatic response, and 70% to 80% of children attain complete remission. Within 5 to 10 years, approximately 25% of responding adult patients relapse. Laproscopic splenectomy is preferable to open splenectomy because it speeds the recovery and shortens the duration of hospitalization. The major drawback of splenectomy is bacterial sepsis, occurring at incidence rates of about 1%.

Pharmacologic Therapy

Glucocorticoids

Glucocorticoids may increase platelet production by impairing bone marrow macrophage ability to destroy platelets. Response rate to oral prednisone (1–1.5 mg/kg per day) in adults is 50% to 75% and usually occurs within the first 3 weeks. In children, severe life-threatening bleeding is treated with either high-dose oral (4–8 mg/kg per day prednisone) or parenteral (30 mg/kg per day methylprednisolone) glucocorticoids.

Intravenous Immunoglobulin (IVIG)

IVIG impairs the clearance of platelets coated with IgG by activating inhibitory receptor FcRγIIb. It is generally indicated in emergencies, during pregnancy, and in chronic management of patients refractory to other treatment options. Roughly 85% of adults have a response, but remission usually is not sustained. If treatment is indicated in children, a single dose of IVIG (0.8 g/kg) usually is effective.

Anti-D

Anti-Rh(D) can be used only in Rh(D)-positive patients. It is equal to IVIG in terms efficacy and generally is less expensive. The indications for use of anti-Rh(D) are identical to those for IVIG. Anti-D is especially desirable form of treatment in chronic ITP when the goal is to circumvent long-term exposure to corticosteroids. At doses of 25 mcg/kg per day, anti-Rh(D) may increase the platelet count in about 80% of children with acute and chronic ITP. Substantial numbers of patients treated repetitively with Rh(D) can postpone or avoid splenectomy.

Outcome Evaluation

- Monitor platelet counts as indicated clinically.
- Goal of therapy is to maintain platelet count equal or greater than 30,000/mm^3 (30 $\times$ 10^3/μL or 30 $\times$ 10^9/L).
- Monitor for signs and symptoms of bleeding.

THROMBOTIC THROMBOCYTOPENIC PUPURA

Etiology and Epidemiology

Thrombotic thrombocytopenic purpura (TTP) is a severe systemic disorder characterized by the thrombi formation within the circulation that result in the platelet consumption and subsequent thrombocytopenia. The inherited sub-type is chronic and relapsing and generally occurs in childhood. Acute idiopathic TTP, which occurs in adults, is more common and harder to treat. The estimated annual incidence of TTP is 3.7 cases per million.[33]

Pathophysiology

Endothelial cells normally synthesize vWF in the form of a high-molecular-weight polymer composed of smaller identical multimers. Each multimer is able to bind platelets, and the number of multimers on the vWF polymer is directly proportional to its platelet-binding capacity. Consequently, particularly adherent ultralarge molecules of the factor (ULvWF) are broken down to smaller size by vWF-cleaving proteases by the vWF-cleaving metalloprotease ADAMTS13 to avoid undesired clot formation. TTP results from autoantibody (probably IgG) inhibition of the vWF-cleaving protease ADAMTS13. This, in turn, elevates circulating levels of ultralarge molecules of the factor (ULvWF) leading to inappropriate platelet aggregation. Thrombocytopenia develops as a result of faster rate of platelet aggregation in comparison with megakaryocyte bone marrow production. Hemolytic anemia generally follows as a consequence of red blood cell damage by platelet clumps occluding the microcirculation. Occlusive ischemia of the brain or gastrointestinal tract is common, and renal dysfunction may occur.



Clinical Presentation and Diagnosis

Symptoms

- Flulike prodrome
  - Malaise, fever, headache and sometimes diarrhoea
- Hematologic
  - Purpura
  - Petechiae
  - Ecchymoses
  - Pallor, tiredness, and shortness of breath
- Neurologic
  - Headache, confusion, difficulty speaking, transient paralysis, numbness
- Renal failure

Laboratory Testing

- CBC
- Peripheral blood smear
- Elevated lactate dehydrogenase (LDH)
- Elevated indirect bilirubin level
- Elevated reticulocyte count
- Normal PT and aPTT
- Elevated serum creatinine

Treatment

Desired Outcomes

The main goal of TTP treatment is to prevent end-organ damage.

Nonpharmacologic Therapy

The present standard of treatment for TTP is urgent plasma exchange (PEX). If PEX is unavailable, treatment with plasma infusion and glucocorticoids is indicated until PEX is available.[34]

Plasma Exchange (PEX)

The procedure involves removal of the patient's plasma and its substitution by donor plasma. In this manner, circulating antibody against vWF-cleaving protease is removed. PEX involves placement of two intravenous lines (cannulas) into two separate veins. Blood removed through one cannula is centrifuged to separate the blood cells from the plasma. The blood cells are mixed subsequently with donor plasma and returned via the second cannula to the patient. The goal is to exchange 1 to 1.5 plasma volumes (40–60 mL/kg). The procedure generally is repeated until neurologic symptoms have resolved and a normal LDH and platelet count are maintained for several days. Approximately 85% of patients show both clinical and laboratory response within 3 weeks when PEX is initiated without delay. Although generally considered safe, catheter insertion or catheter infection complications may occur and include hemorrhage, pneumothorax, sepsis, and thrombosis. Allergic reactions to plasma can cause severe hypotension and hypoxia.

Splenectomy

Splenectomy was considered first-line treatment prior to the introduction of PEX. Today, it is reserved for patients with frequently relapsing disease and is performed safely laproscopically with excellent response rates.

Pharmacologic Therapy

Corticosteroids

Corticosteriods are used for their immunosuppressive effect in combination with PEX because they are of no benefit when used alone in this population. The most commonly used agents are methylprednisolone 1 g/day intravenously and prednisone 1 mg/kg per day orally.

Outcome Evaluation

Monitor platelet counts, hemoglobin, and LDH.



Patient Care and Monitoring

1. Obtain a complete history.
2. In a patient presenting with a bleeding or clotting disorder, an initial evaluation should include bleeding time, prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time, and platelet count.

- Platelet count
- Activated partial thromboplastin time: aPTT is performed by adding calcium phospholipids and kaolin to citrated blood and measures the time required for a fibrin clot to form. In this manner, aPTT measures the activity of intrinsic and common pathways. Prolongation of aPTT may be due to a deficiency or inhibitor for factors II, V, VIII, IX, X, XI, and XII. It also may be due to heparin, direct thrombin inhibitors, vitamin K deficiency, liver disease, or lupus anticoagulant.
- Prothrombin time: PT is performed by adding thromboplastin (tissue) factor and calcium to citrate-anticoagulated plasma, recalcifying the plasma, and measuring the clotting time. The major utility of PT is to measure the activity of the vitamin K–dependent factors II, VII, and X. The PT is used in evaluation of liver disease, to monitor warfarin anticoagulant effect, and to assess vitamin K deficiency.
- Thrombin time is an assessment of the time required for the appearance of the fibrin clot after thrombin is added to plasma. It may be affected by thrombin inhibitors or fibrinogen abnormalities. Most commonly, thrombin time is used to monitor fibrinolytic therapy.
- Bleeding time indicates how well platelets interact with blood vessel walls to form blood clots by assessing the length of time to arrest the bleeding after a standardized skin cut. The bleeding time is prolonged in thrombocytopenia, fibrinogen disorders, and collagen defects.

3. After a diagnosis is made, institute specific therapy.
4. Monitor resolution of laboratory and clinical symptoms with treatment.

ABBREVIATIONS

ADAMTS13:	vWF-cleaving metalloprotease
BU:	Bethesda units
DDAVP:	1-desamino-8-D-arginine vasopressin (desmopressin acetate)
DIC:	disseminated intravascular coagulation
FFP:	fresh-frozen plasma
HIV:	human immunodeficiency virus
HCV:	hepatitis C virus
ICH:	intracranial hemorrhage
ITP:	immune thrombocytopenic purpura
IVIG:	intravenous immunoglobulin
PCC:	prothrombin complex concentrates
PEX:	plasma exchange
rFVIIa:	recombinant factor VIIa
RICD:	recessively inherited coagulation disorders
TTP:	thrombotic thrombocytopenic purpura
ULvWF:	ultralarge molecules of vWF
VKDB:	vitamin K deficiency bleeding
vWD:	von Willebrand disease
vWF:	von Willebrand factor

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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65 Sickle Cell Disease

Tracy M. Hagemann and Teresa V. Lewis



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Explain the underlying causes of sickle cell disease and their relationship to patient signs and symptoms.
2. Identify the typical characteristics of sickle cell disease as well as symptoms that indicate complicated disease.
3. Identify the desired therapeutic outcomes for patients with sickle cell disease.
4. Recommend appropriate pharmacotherapy and nonpharmacotherapy interventions for patients with sickle cell disease.
5. Recognize when chronic maintenance therapy is indicated for a patient with sickle cell disease.
6. Describe the components of a monitoring plan to assess effectiveness and adverse effects of pharmacotherapy for sickle cell disease.
7. Educate patients about the disease state, appropriate therapy, and drug therapy required for effective treatment and prevention of complications.

Key Concepts

❶ Sickle cell disease is an inherited disorder caused by a defect in the gene for hemoglobin. Patients may have one defective gene (sickle cell trait) or two defective genes (sickle cell disease).
❷ Although most often seen in persons of African ancestry, other ethnic groups can be affected.
❸ Sickle cell disease involves multiple organ systems.
❹ Prophylaxis against pneumococcal infection reduces death during childhood.
❺ Hydroxyurea has been shown to decrease the incidence of painful crises. However, the patient population that receives hydroxyurea should be monitored carefully.
❻ Chronic transfusion therapy programs have been shown to be beneficial in decreasing the occurrence of stroke in children with sickle cell disease.
❼ Patients with fever greater than 38.5°C (101.3°F) should be evaluated, and appropriate antibiotics should include coverage for encapsulated organisms, especially pneumococcal organisms.
❽ Pain episodes usually can be managed at home. Hospitalized patients usually require parenteral analgesics. Analgesic options include opioids, nonsteroidal anti-inflammatory agents, and acetaminophen. The patient characteristics and severity of the crisis should determine the choice of agent and regimen.

Sickle cells were first identified by physician James Herrick in a 20-year-old medical student from Grenada in 1910.[1] ❶ ***Sickle cell syndrome*** *refers to a collection of autosomal recessive genetic disorders that are characterized by the presence of at least one* ***sickle hemoglobin*** *gene (HbS).*[2,3]

Sickle cell disease (SCD) is a chronic illness that is associated with frequent crisis episodes. Acute complications are unpredictable and potentially fatal. Common symptoms include excruciating musculoskeletal pain, life-threatening pneumonia-like illness, cerebrovascular accidents, and splenic and renal dysfunction.[3] As the disease progresses, patients may develop organ damage from the combination of hemolysis and infarction. Because of the complexity and severity of SCD, it is imperative that patients have access to comprehensive care with providers who have a good understanding of the countless clinical presentations and the management options of this disorder.

EPIDEMIOLOGY AND ETIOLOGY

Sickle cell trait (SCT) is the heterozygous form (HbAS) of SCD in which a person inherits one normal adult hemoglobin (*HbA*) gene and one sickle hemoglobin (*HbS*) gene. These individuals

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are carriers of the SCT and usually are asymptomatic.[3] Symptomatic disease is seen in homozygous and compound heterozygous genotypes of SCD. **Sickle cell anemia** (SCA) is the homozygous (*HbSS*) state of SCD.[3] It is the most common and severe form of SCD. Compound heterozygosity is seen when individuals inherit one copy of the mutation that causes HbS and one copy of another abnormal hemoglobin gene. One example is *HbSC* genotype, in which a person inherits the genetic mutation for hemoglobin C (HbC) in addition to *HbS*.[2–4] Compound heterozygosity also may include the coinheritance of *HbS* and one of the many different mutations of β-thalasssemia (*HbSβ*^{0}*-thalassemia* and *HbSβ*$^+$*- thalassemia*).[2–4]

SCA affects both males and females equally because it is not a sex-linked disease. ❷ *Nine percent of African Americans possess the SCT and 1 in 600 has HbSS.*[5] Two thousand infants are identified with SCD annually in the United States.[6] For every infant diagnosed with SCD, 50 are identified as carriers.[6] *HbSS* (approximately 45%) is the most common genotypic expression, followed by *HbSC* (approximately 25%), *HbSβ*$^+$*-thalassemia* (approximately 8%), and *HbSβ*^{0} *thalassemia* (approximately 2%). Other variants account for less than 1% of patients.[3,6]

Having the sickle hemoglobin gene protects heterozygous carriers from succumbing to *Plasmodium falciparum* (malaria) infection.[2] The microorganism cannot parasitize abnormal red blood cells (RBCs) as easily as normal RBCs. Consequently, persons with the heterozygous sickle gene (SCT) have a selective advantage in tropical regions where malaria is endemic. The incidence of the sickle gene in a population correlates with the historical incidence of malaria.

The highest incidence of SCD is seen in those with African heritage, but SCD also affects persons of Indian, Saudi Arabian, Mediterranean, South and Central American, and Caribbean ancestry.[6,7] There are more than 200,000 babies born each year in Africa with SCA.[7] The prevalence of SCT in Africa varies across regions, with ranges of 10% to 40% across equatorial Africa, 1% to 2% on the North African coast, and less than 1% in South Africa.[7]

Normal adult hemoglobin (HbA) is composed of two α-globin chains and two β-globin chains ($\alpha_2\beta_2$).[4] A single substitution of the amino acid valine for glutamic acid at position 6 of the β-polypeptide chain is responsible for production of a defective form of hemoglobin called *sickle hemoglobin* (HbS).[2,8] Different genetic mutations encode for other hemoglobin variants such as hemoglobin C (HbC). HbC is produced by the substitution of lysine for glutamic acid at the sixth amino acid position in the β-globulin chain.[4] The α-chains of HbS, HbA, and HbC are structurally identical. The chemical differences in the β-chain are responsible for RBC sickling and its associated sequelae.

SCA is the homozygous (*HbSS*) state of SCD in which individuals inherit the mutant hemoglobin gene (*HbS*) from both parents. The progeny of two carriers will have a 25% probability of having SCD and a 50% risk of being a carrier themselves (Fig. 65–1). β-Thalassemia can be found in conjunction with HbS. Patients with *HbSS* and *HbSβ*^{0}*- thalassemia* do not have normal β-globulin production and usually have a more severe course than those with *HbSC* and *HbSβ*$^+$*-thalassemia.*

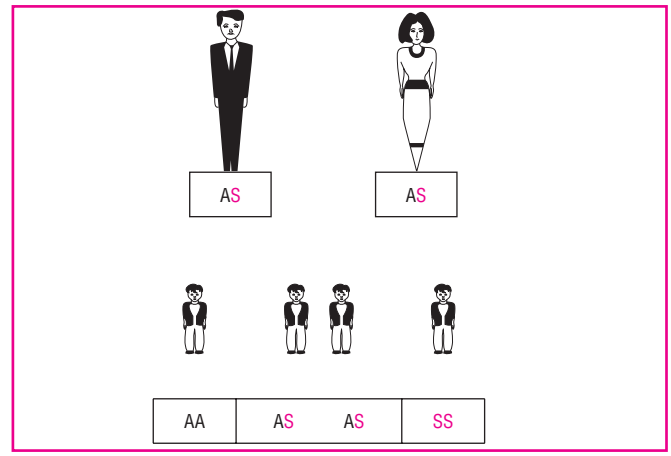


FIGURE 65–1. Sickle gene inheritance scheme for both parents with sickle cell trait (SCT). A, normal hemoglobin; S, sickle hemoglobin. Possibilities with each pregnancy: 25% normal (AA); 50% SCT (AS); 25% sickle cell anemia (SS). (From Chan CYJ, Moore R. Sickle cell disease. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1856.)

PATHOPHYSIOLOGY

Erythrocyte Physiology

A review of RBC physiology is important to understanding the pathophysiology of SCD. Pediatric RBCs possess normal hemoglobin concentrations of between 9 and 18.5 g/dL (90 to 185 g/L or 5.6–11.5 mmol/L) depending on the age of the child.[9] Adult RBCs contain 12 to 15.5 g/dL (120 to 155 g/L or 7.4–9.6 mmol/L) hemoglobin.[9] The predominant form of hemoglobin is adult hemoglobin or HbA (96%). Other forms of hemoglobin include HbA_2 and fetal hemoglobin (HbF). HbA_2 makes up less than 1% of hemoglobin in newborns. In adults, HbA_2 constitutes approximately 1.6% to 3.5%.[9] Fetal hemoglobin (HbF) is present primarily in fetal RBCs (60% to 90%), whereas adult RBCs contain less than 1% HbF.[9] HbF is the primary oxygen-transport protein in the fetus. Unlike HbA and HbS, HbF does not contain β-chains but rather two γ-globulin protein chains ($\alpha_2\beta_2$).[4] Shortly before birth, fetal hemoglobin undergoes conversion from γ-chains to β-chains. After birth, only a small proportion of red cell clones remain to produce HbF. Certain physiologic conditions, such as severe anemia, hematopoietic stem cell transplantation, and chemotherapy, can caused increased production of HbF. Both water and hemoglobin contents in the RBCs determine the mean corpuscular hemoglobin concentration (MCHC). Passive diffusion and active transport regulate intracellular cation and volume contents, which determine the intracellular viscosity of RBCs. Normal RBCs are biconcave in shape. The elasticity of young erythroid cells enables them to

deform and squeeze through capillaries (Fig. 65–2). As RBCs age, MCHC increases, deformability decreases, and the cells are removed by the reticuloendothelial system.

Impaired circulation, destruction of RBCs, and vascular stasis are three known problems that are responsible primarily for the clinical manifestations of SCD. These pathologic findings are likely due to HbS polymerization and RBC membrane damage (Fig. 65–3).

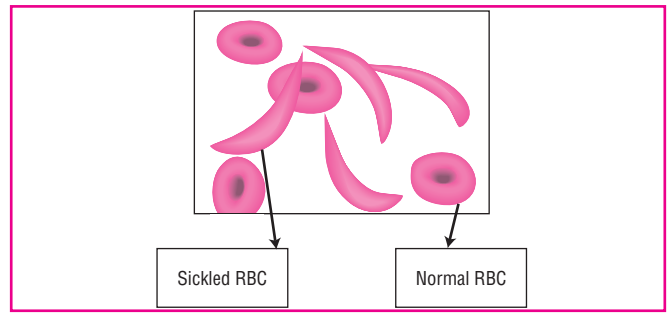


FIGURE 65–2. Elongated sickle-shaped and normal discoid-shaped red blood cells. (From Chan CYJ, Moore R. Sickle cell disease. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1856.)

Sickle Hemoglobin Polymerization

The primary event in the molecular pathogenesis of SCD involves polymerization of deoxygenated HbS. Since RBCs are packaged with such a high concentration of hemoglobin (32–34 g/dL, 320 to 340 g/L or 19.9–21 mmol/L), it is important

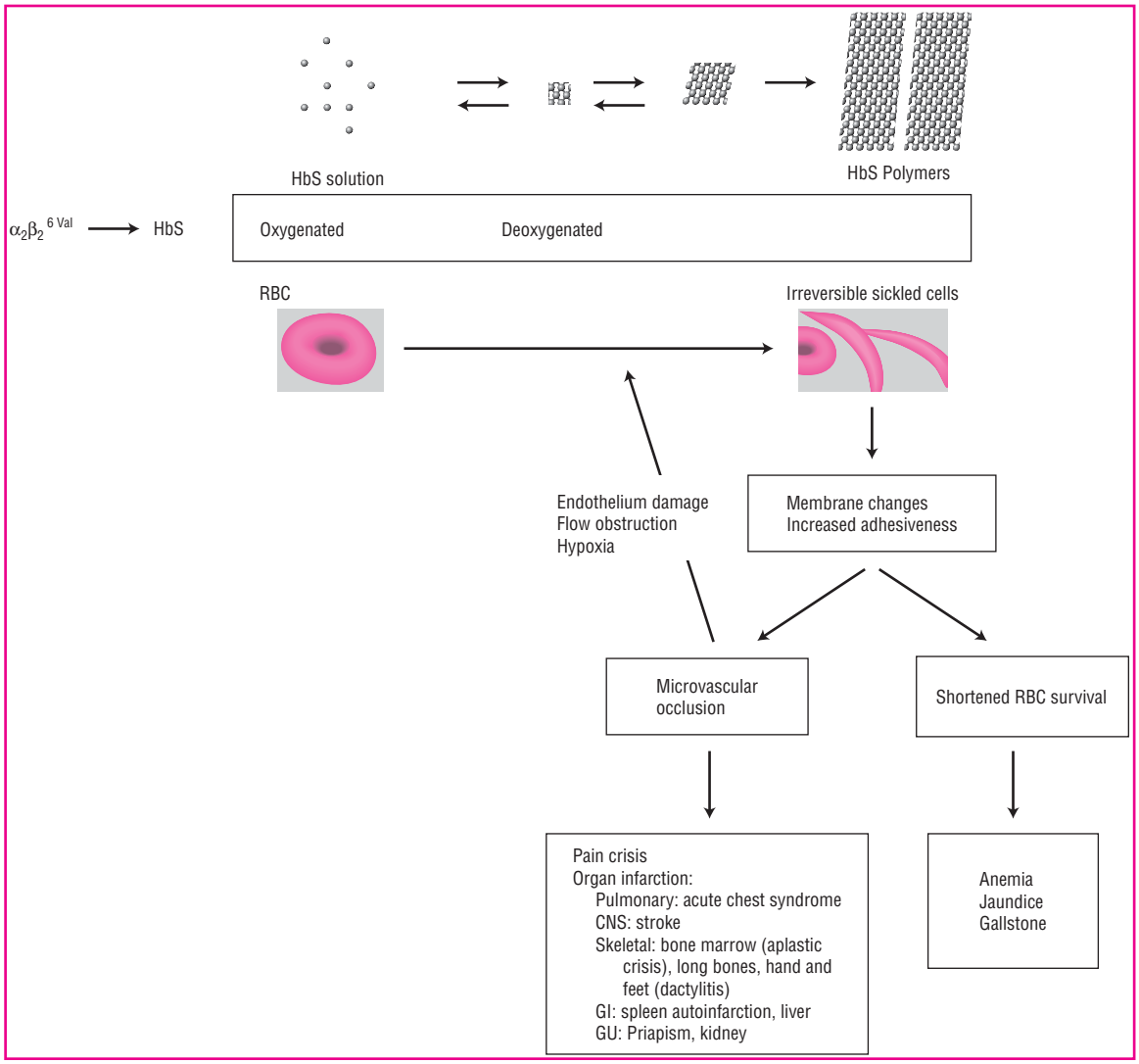


FIGURE 65–3. Pathophysiology of sickle cell disease. (From Chan CYJ, Moore R. Sickle cell disease. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1857.)

that the proteins be extremely soluble.[8] HbS carries oxygen normally, and when oxygenated, the solubility of HbS and HbA are the same. Once the oxygen is unloaded to the tissues, HbS solubility decreases to approximately 17 g/dL (170 g/L or 10.6 mmol/L). This promotes hydrophobic interactions between the hemoglobin molecules and polymerization.[8] Valine can bind to complementary sites on adjacent globin chains, resulting in intermolecular binding and formation of ropelike fibers that align with others to form a bundle.[2] The deoxy-HbS begins to form semisolid aggregate structures. This distorts the RBC into the characteristic crescent or sickle shape. Polymerization of deoxy-HbS is influenced by the degree of red cell deoxygenation, MCHC, temperature, intracellular pH, intraerythrocytic HbS concentration, and intracellular HbF concentration.[2]

Viscosity of Erythrocytes and Sickle Cell Adhesion

When HbS becomes reoxygenated, the polymers within the RBCs disappear, and the cells eventually return to normal shape. Vasoocclussion is caused by a combination of factors. Repeated assaults on RBCs from sickling and unsickling can lead to cell membrane damage, loss of membrane flexibility, and rearrangement of surface phospholipids. Damage to cell membranes can interfere with ion transport, leading to loss of potassium and water. This creates dehydrated, dense sickle cells and irreversible sickle cells (ISCs). ISC's are the densest cells, and they tend to remain sickled even when oxygenated. Rigid ISCs can become trapped in microvasculature, leading to cell fragmentation and chronic hemolysis and thus contributing to short survival of RBCs. The life span of sickled RBCs is markedly shorter (10–20 days) than that of normal RBCs (100–120 days). As intracellular membrane viscosity of HbS-containing RBCs increases, blood viscosity increases, which further contributes to vasoocclussion.[10] There is also increasing evidence that suggests that sickle cells adhere to vascular endothelium.[2,10] The combined effects of decreased RBC deformability, slow transit through microcirculation, and adhesion to vascular endothelium contribute to obstruction of small and sometimes large blood vessels. The resulting local tissue hypoxia can accentuate the pathologic process of SCD.

Protective Hemoglobin Types

Fetal hemoglobin binds oxygen more tightly than HbA, and it has a decreased propensity to sickling. HbA_2 also possesses this characteristic but to a lesser extent. RBCs that contain HbF sickle less readily than cells without. ISCs are found to have low HbF concentrations. In some patients, higher HbF may ameliorate the disease.

Other Pathophysiologic Effects

Other factors may be responsible for the pathogenesis of some of the clinical features of SCD. Sickle cells can obstruct blood flow to the spleen, leading to functional asplenia, which is loss of splenic function despite having an intact spleen. These patients also may have deficient opsonization. Impaired splenic function can increase the propensity to infection by encapsulated organisms, particularly *Streptococcus pneumoniae*.[11] Additionally, coagulation abnormalities are not uncommon because almost every component of hemostasis is altered in SCD.

CLINICAL PRESENTATION AND DIAGNOSIS

Diagnosis

Table 65–1 shows the clinical features of SCT and SCD. SCD usually is identified by routine neonatal screening programs using hemoglobin electrophoresis, thin-layer isoelectric

TABLE 65–1. Clinical Features of Sickle Cell Trait and Sickle Cell Disease

Condition	Clinical Presentation
Sickle cell trait (*HbAS*)	Generally asymptomatic Females may have frequent urinary tract infections Microscopic hematuria occurs rarely Gross hematuria can occur spontaneously or with heavy intensity exercise Normal Hgb values
Sickle cell anemia (*HbSS*)	Painful vaso-occlusive crises are the hallmark of SCD Chronic hemolytic anemia is common Patients may develop infarction of the spleen, liver, bone marrow, kidney, brain, and lungs Gallstones and priapism also may develop Slow healing lower extremity ulcers may develop usually after infection or trauma Hgb 7–10 g/dL (70–100 g/L or 4.4–6.2 mmol/L)
Sickle hemoglobin C (*HbSC*)	Vaso-occlusive crises are less common and occur later in life Assocated with painless hematuria Aseptic necrosis of bone is a rare occurrence Other complications include ocular disease and pregnancy-related problems Mild anemia (Hgb 10–14 g/dL) (100–140 g/L or 6.2–8.7 mmol/L)
Sickle β^+-thalassemia (*HbSβ^+-thalassemia*)	Milder clincal course than sickle cell disease because of production of HbA Vaso-occulssive crises are rare Aseptic necrosis is a rare occurrence Hgb 10–14 g/dL (100–140 g/L or 6.2–8.7 mmol/L) with microcytosis
Sickle β^0-thalassemia *(HbSβ^0-thalassemia)*	Severity of disease is similar to sickle cell anemia and Vaso-occlussive crises are common No HbA production Hgb 7–10 g/dL (70–100 g/L or 4.4–6.2 mmol/L) with microcytosis

Adapted from DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005, Table 101-1.

focusing, high-performance liquid chromatography, or DNA analysis.[6] All tests are comparable in accuracy.[6] Hemoglobin electrophoresis is recommended by the National Institutes of Health as the method of choice, with isoelectric focusing as an alternative.[11] Positive screening results should be confirmed with a second sample. This should be done before the child is 2 months of age and using a different screening method.[6]

Morbidity and Mortality

Thirty years ago, complications from SCD contributed to high mortality. It was estimated that approximately 50% of patients with SCD did not survive to reach adulthood.[5] Since that time, data suggest improvement in mortality rates for patients with SCD. The median survival age for individuals with HbSS in the United States in 1994 was estimated to be 42 years for men and 48 years for women.[13] Recent reports suggest 85% survival by 18 years of age.[5] Predictors for increased morbidity in children younger than 10 years include having **dactylitis** (**hand-foot syndrome**) before 1 year of age, severe anemia in the second year of life [Hgb concentration less than 7 g/dL (70 g/L or 4.4 mmol/L)], and leukocytosis in the absence of infection (white blood count greater than 15,000/mm^3 [15 × 10^9/L]).[13,14] Infection is the leading cause of death in children younger than 3 years of age.[13,14] For adults, having more symptomatic disease (e.g., acute pain crises, anemic events, **acute chest syndrome**, renal insufficiency, cerebrovascular complications, and pulmonary disease) is associated with increased risk for early death[3,13] (Tables 65–2 and 65–3). Today, with longer survival for SCD, chronic manifestations of the disease contribute to the morbidity later in life (Table 65–4).

TABLE 65–2. Acute Complications of Sickle Cell Disease (SCD)

Infection[a]

Clinical features: SCD carries a high risk for overwhelming sepsis due to functional asplenia and failure to make antibodies against encapsulated organisms; patients should be evaluated for temperature greater than 38.5°C. A low threshold for empiric therapy is recommended.

Pathogens: Streptococcus pneumoniae (most common), *Haemophilus influenzae, Salmonella, Mycoplasma pneumoniae*, *Chlamydia*, and viruses (parvovirus B19)

Evaluation: Physical examination, complete blood count (CBC) with reticulocyte, urinalysis, chest x-ray, and cultures (blood, urine, and throat); lumbar puncture if toxic-looking or presenting with signs of meningitis; needle aspirate in patients with findings suggestive of osteomyelitis

Cerebrovascular Accidents (Stroke)[b]

Clinical features: Incidence is four times higher for HbSS than HbSC. Initial episode most often occurs during the first 10 years of life. "Silent infarcts" as evidenced by changes on magnetic resonance imaging (MRI) have been reported in 21.8% of HbSS and may be associated with increased risk of stroke and decreased neurocognitive function.

Cause: Most common is cerebrovascular occlusion. Other causes include intracranial hemorrhage, cardiac embolisms, infection, and clotting disorders.

Signs and symptoms: Headache, vomiting, stupor, hemiparesis, aphasia, visual disturbances, and seizure; transient ischemic attack is a strong predictor for stroke. Behavioral and performance changes may be present in patients with asymptomatic infarction.

Evaluation: Perform computed tomography (CT) scan and MRI for evaluation of acute event. Perform magnetic resonance angiography for asymptomatic infarction. Perform transcranial Doppler to detect abnormal velocity and identify high-risk patients. Perform electroencephalography if there is a history of seizure.

Acute Chest Syndrome (ACS)[c]

Clinical features: ACS occurs in 15% to 43% of patients and is responsible for up to 25% of deaths. Risk factors include young age, low HbF level, high Hgb and WBCs, winter seasons, and reactive airway disease. Recurrences are up to 80% and can lead to chronic lung disease in adulthood.

Signs and symptoms: New infiltration on chest, x-ray accompanied by fever, cough, dyspnea, chest pain, hypoxia, leukocytosis. Can progress to acute respiratory distress syndrome and death.

Cause: Exact cause remains unknown but pulmonary sickling resulting in infraction is the key element. Proposed etiologies include: infectious *(S. pneumoniae, H. influenzae, Chlamydia, Mycoplasma*, and viral) and noninfectious (fat embolization from bone infarction, hypoventilation secondary to pain, narcotics, etc).

Evlauation: Close monitoring of pulmonary status, blood gases (if indicated), oxygen saturation, chest x-ray, blood and sputum cultures, CBC, bronchoscopy with lavage (if needed)

Priapism[d]

Clinical features: Priapism is defined as a painful and unwanted erection, which is classified as stuttering (less than 3 hours), often multiple prolonged (more than 3 hours). Up to 89% of males with SCD will have at least one episode by age 20. The mean age of the initial episode is 12 years of age. Repeated episodes can cause fibrosis and impotence.

Cause: Sickling in the sinusoids of the penis

Signs and symptoms: Prepubertal children often present with stuttering priapism. Older males can present with prolonged episodes that last for days and should be managed as medical emergencies. Urinary obstruction can occur in severe cases.

Evaluation: Physical examination; monitor duration of episode and for signs of urinary retention.

[a]From Fixler et al,[47] National Institutes of Health,[6] Dover et al,[48] Hord et al,[49] and Smithy-Whitley et al.[50]
[b]From Fixler et al,[47] Dover et al,[45] Pegelow et al,[51] Kral et al,[52] and Miller et al.[53]
[c]From Dean et al,[54] Siddiqui et al,[55] Vichinsky et al,[56] Neumayr et al,[57] and Vichinsky et al.[58]
[d]From Fixler et al,[47] National Institutes of Health,[6] and Dover et al.[48]
HbF, fetal hemoglobin; HbSC, sickle-hemoglobin C; HbSS, homozygous sickle hemoglobin; Hgb, hemoglobin; WBC, white blood cell.

TABLE 65–3. Sickle Cell Crisis

Vaso-Occlusive Pain Crisis[a]

Clinical features: Acute painful infarction without changes in Hgb; almost all patients with SCA will have episodes of acute pain. Recurrent acute crises result in bone, joint, and organ damage and chronic pain. Vaso-occlusive crisis most commonly involves the bones, liver, spleen, brain, lungs, and penis. Acute long bone pains may be accompanied by signs of inflammation, making it difficult to differentiate from osteomyelitis. Abdominal involvement may resemble a surgical abdomen. Precipitating factors include infection, extreme weather conditions, dehydration, and stresses.

Signs and symptoms: Deep throbbing pain; local tenderness, erythema, and swelling may be seen. Fever and leukocytosis are common. Dactylitis usually occurs in young infants. Jaundice and increased transaminases present if liver is involved.

Evaluation: Frequent physical examination, complete blood count (CBC), reticulocyte, and urinalysis; based on symptomatology, the following may be needed: needle aspiration to rule out osteomyelitis, abdominal studies (x-ray, computed tomography scan, etc), liver function tests, bilirubin, culture, and chest x-ray.

Aplastic Crisis[b]

Clinical features: Acute decrease in Hgb with decreased reticulocyte count (usually less than 1%); transient suppression of RBC production in response to bacterial or viral infection, most common being parvovirus B19

Signs and symptoms: Headache, fatigue, dyspnea, pallor, and tachycardia; may also present with fever, upper respiratory or gastrointestinal infection symptoms.

Evalution: CBC, reticulocyte count, x-ray, cultures (blood, urine, and throat), parvovirus titers

Acute Splenic Sequestration Crisis[c]

Clinical features: Acute exacerbation of anemia due to sequestration of large blood volume by the spleen. More commonly seen in patients with functioning spleens (e.g., infants and adults with HbSC disease); onset often is associated with viral or bacterial infections; recurrences are common and can be fatal.

Signs and symptoms: Sudden onset of fatigue, dyspnea, and distended abdomen; rapid decrease in Hgb and Hct with elevated reticulocyte count, abdominal pain, splenomegaly, vomiting, hypotension, and shock

Evaluation: Close monitoring of vital signs, spleen size, and oxygen saturation, CBC, reticulocyte, and cultures

[a]From Fixler et al,[47] National Institutes of Health,[6] Dover et al,[48] and Yale.[45]
[b]From Fixler et al,[47] National Institutes of Health,[6] Dover et al,[48] and Kellermayer et al.[59]
[c]From Fixler et al,[47] National Institutes of Health,[6] and Dover et al.[48]
HbSC, sickle-hemoglobin C; Hgb, hemoglobin; RBC, red blood cell; SCA, sickle cell anemia.

TABLE 65–4. Chronic Complications of Sickle Cell Disease (SCD)

System	Complications
Auditory	Sensorineural hearing loss due to sickling in cochlear vasculature with hair cell damage
Cardiovascular	Cardiomegaly, myocardial ischemia, murmurs, and abnormal electrocardiogram; patients with SCD have lower blood pressure (BP) than the normal population; normal BP values for SCD should be used for diagnosis of hypertension ("relative" hypertension); heart failure usually is related to fluid overload
Dermatologic	Painful leg ulcers; failure to heal occurs in 50% of patients; recurrences are common
Genitourinary	Renal papillary necrosis, hematuria, hyposthenuria, proteinuria, nephritic syndrome, tubular dysfunction, chronic renal failure, impotence
Growth and development	Delay in growth (weight and height) and sexual development; decreased fertility; increased complications during pregnancy; depression may be more prevalent than in general population, especially in patients with unstable disease
Hepatic and biliary	Cholelithiasis, biliary sludge, acute and chronic cholecystitis, and cholestasis (can be progressive and life-threatening)
Neurologic	"Silent" brain lesions on magnetic resonance imaging are associated with poor cognitive and fine motor functions; pseudotumor cerebri (case report)
Ocular	Retinal or vitreous hemorrhage, retinal detachment, transient or permanent visual loss; central retinal vein occlusion
Pulmonary	Pulmonary fibrosis, pulmonary hypertension, cor pulmonale
Renal	Hematuria, hyposthenuria (inability to concentrate urine maximally), tubular dysfunction, enuresis during early childhood, acute renal failure can also occur
Skeletal	Aseptic necrosis of ball-and-socket joints (shoulder and hip); prostheses may be needed due to permanent damage; bone marrow hyperplasia resulting in growth disturbances of maxilla and vertebrae
Spleen	Asplenia (autosplenectomy or surgical splenectomy)

From Fixler et al,[47] National Institutes of Health,[6] Dover et al,[48] Kral et al,[52] Vichinsky et al,[58] Gladwin et al,[60] Henry et al,[61] Mukisi-Mukaza et al,[62] Hasan et al,[63] Babalola et al,[64] de Montalembert et al,[65] Hassan et al,[66] and Schatz et al.[67]

Complications

Treatment of SCD is aimed at the preventing and/or minimizing acute and chronic complications, including infection, acute chest syndrome, neurologic damage, and the various forms of sickle cell crises, including vaso-occlusive pain, splenic sequestration, and aplastic crisis. The acute and chronic complications are summarized in Tables 65–2, 65–3, and 65–4.



Signs and Symptoms

Sickle Cell Trait

❸ *SCD involves multiple organ systems, and its clinical manifestations vary greatly between and among genotypes (see Table 65–1).*

- Dehydration during periods when water conservation is necessary
- Microscopic hematuria (presence of blood in the urine)
- Women with SCT also can have frequent urinary tract infections, especially during pregnancy.

Sickle Cell Disease

- Vaso-occlusion
- Hemolytic anemia
- Pneumonia
- Splenomegaly is also a common finding.
- Children younger than 3 years of age can present with dactylitis (hand-foot syndrome), which is painful swelling of the hands and feet.

Sickle Cell Anemia

- Chronic anemia
- Fever and pallor
- Arthralgia
- Scleral icterus
- Abdominal pain
- Weakness
- Anorexia
- Fatigue
- Enlargement of the liver, spleen, and heart
- Hematuria

Serologic Findings

- Low hemoglobin (Hgb) concentration, low HbF, and increased reticulocytes, platelets, and white blood cell (WBC) counts
- The peripheral blood smear demonstrates sickle forms (see Fig. 65–2).

Growth and Development

- Delayed growth and sexual development
- Protuberant abdomen with exaggerated lumbar lordosis, usually an asthenic appearance with rather long extremities and tapered fingers, and frequently a barrel-shaped chest

TREATMENT

Desired Outcomes

Multidisciplinary, regularly scheduled care is required over the lifetime of the SCD patient with the goal of reduction of both complications and hospitalizations. Comprehensive care should include medical, educational, and psychosocial aspects, as well as counseling.

Therapeutic interventions for SCD should be targeted at preventing and/or minimizing the symptoms related to the disease and its complications. The goals of treatment are to reduce or eliminate the patient's symptoms; decrease the frequency of sickle crises, including vaso-occlusive pain crises; prevent the development of complications; and maintain or improve the quality of life through decreased hospitalizations and decreased morbidity. Specific therapeutic options may

- Maintain or increase the hemoglobin level to the patient's baseline
- Increase the HbF concentration
- Decrease the HbS concentration
- Prevent infectious complications
- Prevent or effectively manage pain
- Prevent central nervous system damage, including stroke

General Management

Patients should be educated to recognize the signs and symptoms of complications that would require urgent evaluation. Patients and parents of children with SCD should be educated to read a thermometer properly and to seek immediate medical care when a fever develops or signs of infection occur. With acute illnesses, prompt evaluation is important because deterioration may occur rapidly. Fluid status should be monitored to avoid dehydration or overhydration, both of which may worsen complications of SCD. Patients in acute distress should maintain oxygen saturation at 92% or at their baseline. Any supplemental oxygen requirements should be evaluated.[6,27]



Patient Encounter 1

An 18-month-old girl is presenting for a routine check-up. She was diagnosed with sickle cell anemia at birth, identified through neonatal screening. Today, her hemoglobin is 8.6 g/dL (86 g/L or 5.3 mmol/L) and she is afebrile.

- What acute complications is she at risk for developing?
- What preventative treatment should she receive?
- What additional information do you need to know before creating a plan for this patient?

Nonpharmacologic Therapy

Patients should avoid smoking and excessive alcohol intake. Patients with SCD should maintain adequate hydration and should be educated to avoid extreme temperature changes and to dress properly in hot and cold weather. Physical exertion that leads to complications should be avoided.[6] Regular examinations, including ophthalmic, renal, pulmonary, and cardiac, are required to monitor for organ damage. A treatment overview is shown in Table 65–5.

TABLE 65–5. Management of Sickle Cell Disease

	Options and Comments
Health Maintenance	
Infection prophylaxis	• Pneumococcal vaccines (PCV 7 and PPV 23) • Penicillin prophylaxis for children less than 5 years old • Annual influenza vaccine
Induction of fetal hemoglobin	• Hydroxyurea is the primary agent • Other agents are butyrates (arginine butyrate and sodium phenylbutyrate), decitabine, clotrimazole, and erythropoietin • Combination HbF inducers have been proposed
Chronic transfusion therapy	• Primary indication: stroke prevention in pediatric patients • May also reduce pain crisis and acute chest syndrome • Goal: maintain HbS less than 30%
Future prospects	
Transplantation	• May potentially cure the disease • Most experience is with HLA-matched donors; umbilical cord blood transplantation is being evaluated
Crises and Complications	
Fever and infection	• Broad-spectrum antibiotic: cefotaxime or ceftriaxone (clindamycin for cephalosporin allergy); vancomycin for staphylococcal and resistant pneumococcal organisms
Stroke	• Fluids • Acetaminophen or ibuprofen for fever • Exchange transfusion • Initiate chronic transfusion therapy to prevent recurrent strokes
Acute chest syndrome	• Broad-spectrum antibiotics (include *Mycoplasma coverage*) • Bronchodilator if wheezing or history of reactive airway disease • Fluids • Pain management • Transfusion
Priapism	• Hydration • Pain management • Urology consult for other options (intrapenile injection or surgery)
Aplastic crisis	• Supportive care • Transfusion for severe symptomatic anemia
Sequestration crisis	• Transfusion • Broad-spectrum antibiotic • Splenectomy in severe cases
Pain crises	• Hydration • Analgesics

HbF, fetal hemoglobin; HbS, sickle hemoglobin; HLA, human leukocyte antigen. *From Fixler et al,[47] National Institutes of Health,[6] Dover et al,[48] Pegelow et al,[51] Neumayr et al,[57] Vichinsky et al,[58] Yale,[45] Adamikiewicz et al,[17] Advisory Committee on Immunization Practices,[18] Committee on Infectious Diseases,[16] Sickle Cell Disease Care Consortium,[27] Falletta et al,[19] Kennedy et al,[21] Rodriguez-Cortes,[68] Rabb et al,[69] Charache et al,[70] Nathan,[28] Cokic et al,[71] Gladwin et al,[72] Charache et al,[22] Steinbert et al,[23] National Heart, Lung and Blood Institute,[74] Zimmerman et al,[25] Wilson et al,[26] Najean et al,[74] Atweh et al,[75] Resar et al,[76] Sauntharajah et al,[77] Scothorn et al,[78] Pegelow et al,[79] Russell et al,[80] Adams et al,[81] Harmatz et al,[82] Walters et al,[83] Atkins et al,[32] Brachet et al,[84] Baron et al,[85] Walters et al,[33] Knight-Madden et al,[35] Sullivan et al,[36] Li et al,[86] Mantadakis et al,[37] Dahm et al,[87] Jacob et al,[42] Berde et al,[43] Stinson et al,[44] Christensen et al,[88] and Elander et al.[79]*

Pharmacologic Therapy

Health Maintenance

Immunizations

Children with SCD should receive the required immunizations as recommended by the American Academy of Pediatrics and the Advisory Committee on Immunization Practices.[15] Additionally, influenza vaccine should be administered yearly to SCD patients 6 months of age and older, including adult patients. Any SCD patient who is scheduled for splenectomy should receive the vaccine for meningococcal disease if over 2 years of age.[16]

Because patient with SCD have impaired splenic function, they are less adequately protected against encapsulated organisms such as *S. pneumoniae, Hemophilus influenzae,* and *Salmonella.* ❹ *The use of pneumococcal vaccine in SCD patients has decreased the rates of morbidity and mortality dramatically.* However, there are still groups of SCD children who continue to have high rates of invasive pneumococcal infections.[17] Two pneumococcal vaccines are available. The 7-valent conjugate vaccine (PCV 7: Prevnar) is indicated for infants and children and provides good protection against the seven most common isolates seen in this age range. Administer the first dose of PCV 7 between 6 weeks and 6 months of age, followed by two additional doses at 2-month intervals and a fourth dose at 12 to 15 months of age. The 23-valent polysaccharide vaccine (PPV 23: Pneumovax 23) is indicated for children over 2 years of age. Because PPV 23 is a polysaccharide vaccine, children younger than 2 years of age do not respond well. PPV 23 contains the 23 most common isolates of *S. pneumoniae* seen in older children and adults. Because of the difference serotypes seen in the two vaccines, it is recommended that SCD children receive both vaccines, with a dose of PPV 23 administered after the child turns 2 years of age. The dose of PPV 23 should be separated from the last dose of PCV 7 by at least 2 months. An additional dose of PPV 23 should be considered in children 3 to 5 years of age to ensure antibody response. All adults with SCD also should be vaccinated once with PPV 23. Because some children fall behind on their childhood vaccinations, a catchup schedule is presented in Table 65–6.[16]

TABLE 65–6. Pneumococcal Immunization for Children with Sickle Cell Disease

	Recommended Schedule
Previously Unvaccinated	
Age 2–6 months	**PCV 7 (Prevnar):** 3 doses 6–8 wk apart; then 1 dose at 12–15 months
Age 7–11 months	**PCV 7 (Prevnar):** 2 doses 6–8 wk apart; then 1 dose at 12–15 months
Age greater than or equal to 12–23 months	**PCV 7 (Prevnar):** 2 doses 6–8 wk apart
Age 24–59 months	**PCV 7 (Prevnar):** 2 doses 6–8 wk apart **PPV 23 (Pneumovax):** 2 doses; first dose at least 6–8 wk after last PCV 7 dose; second dose 3–5 years after the first PPV 23 dose
Age 5 years or older	**PCV 7 (Prevnar):** 1 dose **PPV 23 (Pneumovax):** 2 doses; first dose at least 6–8 wk after last PCV 7 dose; second dose 3–5 years (for those age 10 years or younger) or more than 5 years (for those age 10 years or older) after the first PPV 23 dose
Previously Vaccinated	
Age 12–23 months, incomplete PCV 7 series	**PCV 7 (Prevnar):** 2 doses 6–8 wk apart
Age 24–59 months, received four doses	**PPV 23 (Pneumovax):** 2 doses; first dose at least 6–8 wk after last PCV 7 dose; second dose 3–5 y after the first PPV 23 dose of PCV 7
Age 24–59 months, three doses of PCV 7 given before 24 months of age	**PCV 7 (Prevnar):** 1 dose **PPV 23 (Pneumovax):** 2 doses; first dose at least 6–8 wk after last PCV 7 dose; second dose 3–5 years after the first PPV 23 dose
Age 24–59 months, 1 dose PPV 23 given	**PCV 7 (Prevnar):** 2 doses 6–8 wk apart; first dose at least 8 wk after PPV 23 dose **PPV 23 (Pneumovax):** second dose 3–5 years after first PPV 23
Age 5 years or older, received PPV 23	**PCV 7 (Prevnar):** 1 dose 6–8 wk after PPV 23 **If only received 1 dose of PPV 23 (Pneumovax):** Second dose 6–8 wk after PCV 7 *and* 3–5 years (for those age 10 years or less) or more than 5 years (for those age 10 years or older) after the first PPV 23 dose

PCV 7, 7-valent pneumococcal conjugated vaccine; PPV 23, 23-valent pneumococcal polysaccharide vaccine. *From Advisory Committee on Immunization Practices,[18] Committee on Infectious Diseases,[16] and Sickle Cell Disease Care Consortium.[27]*

Penicillin

❹ *Children with SCD should receive prophylactic penicillin until at least the age of 5 years, even if they have been immunized appropriately with PCV 7 against pneumococcal infections.* Penicillin V potassium typically is initiated at age 2 months with a dose of 125 mg orally twice daily until age 3 years and then 250 mg orally twice daily until 5 years of age. The intramuscular use of benzathine penicillin 600,000 units every 4 weeks from age 6 months to 6 years is also an option for noncompliant patients. Penicillin-allergic patients may receive erythromycin 10 mg/kg twice daily. Penicillin prophylaxis usually is not continued in children over the age of 6 years but may be considered in patients with a history of invasive pneumococcal infection or surgical splenectomy.[6,18–20]

Folic Acid

Folic acid supplementation with 1 mg daily generally is recommended in adult SCD patients, women considering pregnancy, and any SCD patient with chronic hemolysis.[6] Because of accelerated erythropoiesis, these patients have an increased need for folic acid. There are conflicting studies in the SCD population, especially among infants and children, but if the child has chronic hemolysis, supplementation is recommended.[21]

Fetal Hemoglobin Inducers

Fetal hemoglobin (HbF) induction in patients with SCD, especially those with frequent crises, has been shown to decrease RBC sickling and RBC adhesion. A direct relationship between HbF concentrations and the severity of disease have been demonstrated in studies.[3]

Hydroxyurea

Hydroxyurea is a ribonucleotide reductase inhibitor that prevents DNA synthesis and traditionally has been used in chemotherapy regimens. Studies in the 1990s also found that hydroxyurea increases HbF levels as well as increasing the number of HbF-containing reticulocytes and intracellular HbF. Other beneficial effects of hydroxyurea include antioxidant properties, reduction of neutrophils and monocytes, increased intracellular water content leading to increased red cell deformability, decreased red cell adhesion to endothelium, and increased levels of nitric oxide, which is a regulator involved in physiologic disturbances.[22]

❺ *Hydroxyurea reduced the frequency of hospitalizations and the incidences of pain, acute chest syndrome, and blood transfusions by almost 50% in a landmark trial in adult SCD patients with moderate to severe disease.* Hemoglobin and HbF concentrations increased, and hemolysis decreased.[22] A follow-up study demonstrated a 40% reduction in mortality over a 9-year period in patients continuing to receive hydroxyurea.[23] Not all patients responded equally, so hydroxyurea may not be the answer for all patients.

The use of hydroxyurea in children and adolescents with SCD has been investigated, and similar results were reported as in adult trials, with no adverse effects on growth and development.[6,24,25]

The most common adverse effect of hydroxyurea in reported studies is myelosuppression. Long-term adverse effects are unknown, but myelodysplasia, acute leukemia, and chronic opportunistic infections have been reported.[26] Hydroxyurea is teratogenic in high doses in animal studies, and this is a concern that should be addressed with patients. Normal pregnancies with no birth defects have been reported in some women receiving hydroxyurea, but close monitoring and weighing risk versus benefit to the patient are vitally important. Hydroxyurea is excreted in breast milk and should be avoided in lactating mothers.[27]

Hydroxyurea should be considered in SCD with frequent vaso-occlusive crises, severe symptomatic anemia, repeated history of acute chest syndrome (ACS), or other history of severe vaso-occlusive crisis (VOC) complications.[6] The prevention of organ damage or reversal of previous damage has not been shown to occur with chronic use of hydroxyurea.

Hydroxyurea is available in 200-, 300-, 400-, and 500-mg capsules. Extemporaneous liquid preparations can be prepared for children who cannot swallow capsules. Doses should start at 10 to 15 mg/kg daily in a single dose, which can be increased



Patient Encounter 2

LK is a 15-year-old girl with history of sickle cell disease (HbS).

PMH
- Cholecystectomy at age 11 years
- Admitted for vaso-occlusive crises five times over the past year
- Acute chest syndrome at age 13 and 14
- Immunizations up to date
- Multiple blood transfusions

FH
Father with SC trait; mother with SCD.

SH
Student in ninth grade. Denies alcohol or drug use. Is sexually active.

Meds
- Lortab 7.5-mg tablets PO q4–6hours prn for pain
- Ibuprofen 600 mg PO three times daily prn for pain
- Folic acid 1 mg PO daily
- The medical team wants to start LK on hydroxyurea.

- Is she a candidate for hydroxyurea?
- What initial laboratory work is required before initiating hydroxyurea?
- Identify treatment goals for hydroxyurea in LK
- What is the initial dose, and how will you monitor for efficacy?
- What patient counseling is needed?
- How will you monitor for toxicity?

after 8 to 12 weeks if blood counts are stable and there are no side effects. Individualize the dosage based on the patient's response and the toxicity seen. With close monitoring, doses can be increased 5 mg/kg per day up to 35 mg/kg daily.[22]

Closely monitor patients for efficacy and toxicity while they are receiving hydroxyurea. Monitor mean corpuscular volume (MCV) because it increases as the level of HbF increases. If the MCV does not increase with hydroxyurea use, the marrow may be unable to respond, the dose may not be adequate, or the patient may be noncompliant.[27] HbF levels also can be monitored to assess response. Assess blood counts every 2 weeks during dose titration and then every 4 to 6 weeks once the dose is stabilized. Temporary discontinuation of therapy is warranted if the hemoglobin level is less than 5 g/dL (50 g/L or 3.1 mmol/L), the absolute neutrophil count is less than 2000/mm^3 (2×10^9/L), platelets are less than 80,000/mm^3 (80×10^9/L), or reticulocytes are less than 80,000/mm^3 (80×10^9/L) if the hemoglobin is less than 9 g/dL (90 g/L or 5.6 mmol/L). Monitor for increases in serum creatinine and transaminases. Once the patient has recovered, hydroxyurea may be restarted with a dose that is 2.5 to 5 mg/kg less than the dose associated with the patient's toxicity. Doses then may be increased by 2.5 to 5 mg/kg daily after 12 weeks with no toxicity.

Administer prophylactic folic acid supplementation to SCD patients receiving hydroxyurea because folate deficiency may be masked by the use of hydroxyurea.

5-Aza-2′-Deoxycytine (Decitabine)

For patients who do not respond to hydroxyurea, 5-azacytidine and 5-aza-2'-deoxycytidine (decitabine) may be useful. Both induce HbF by inhibiting methylation of DNA, preventing the switch from γ- to β-globulin production. Decitabine appears to be safer and more potent than 5-azacytadine. In a small study in adults refractory to hydroxyurea, decitabine 0.2 mg/kg subcutaneously one to three times weekly was associated with an increase in HbF in all patients. Additionally, RBC adhesion was reduced. Neutropenia was the only significant toxicity reported.[6]

Combinations of HbF inducers

Very limited information is available on the use of combination therapy for potentiation of HbF production. Erythropoietin has shown inconsistent results in small numbers of patients. When used with hydroxyurea, erythropoietin has been shown to increase HbF to a greater extent than hydroxyurea alone, and although more studies are needed, this may provide an option for patients who do not respond to hydroxyurea alone.[27]

Chronic Transfusion Therapy

Chronic transfusion therapy is warranted to prevent serious complications from SCD, including stroke and recurrence. ❻ *Especially in children, chronic transfusions have been shown to decrease stroke recurrence from approximately 50% to 10% over 3 years.* Without chronic transfusions, approximately 70% of ischemic stroke patients will have another stroke. Chronic transfusion therapy also may be used to prevent vaso-occlusive pain and ACS, as well as prevent progression of organ damage. Patients receiving chronic transfusion therapy report increased energy levels, improved quality of life, and better exercise tolerance. Patients in whom chronic transfusion therapy should be considered include those with severe or recurrent ACS, debilitating pain, splenic sequestration, recurrent **priapism,** chronic organ failure, transient ischemic attacks, abnormal transcranial Doppler studies, intractable leg ulcers, severe chronic anemia in the presence of cardiac failure, and complicated pregnancies.[6,27]

Several methods of transfusion may be used, including simple transfusion, exchange transfusion, or erythrocytapheresis. The goal of chronic transfusion therapy is to maintain the HbS level at less than 30% (0.30) of total hemoglobin concentration. Transfusions usually are administered every 3 to 4 weeks depending on the HbS concentration. For secondary stroke prevention, current studies have indicated that lifelong transfusion may be required, with an increased incidence of recurrence once transfusions are stopped.[6]

The benefits of transfusion should be weighed against the risks. Risks associated with transfusions include alloimmunization (sensitization to the blood received), hyperviscosity, viral transmission, volume overload, iron overload, and transfusion reactions. Approximately 18% to 30% of SCD patients who receive transfusions will experience alloimmunization, which can be minimized by the use of leukocyte-reduced RBCs or HLA-matched units. Viral transmission is still a concern despite increased screening of blood donors and units. While the risk of contracting acquired immune deficiency syndrome (AIDS) has decreased dramatically, hepatitis C remains a concern. All SCD patients should be vaccinated for hepatitis A and B and should be monitored serially for hepatitis C and other infections. Parvovirus occurs in 1 in every 40,000 units of RBCs and can be associated with acute anemia and multiple sickle cell complications.[6] Iron overload remains a concern among patients maintained on chronic transfusions for greater than 1 year. Counsel patients to avoid excessive dietary iron, and monitor serum ferritin regularly. Chelation therapy with deferoxamine or deferasirox should be considered when the serum ferritin level is greater than 1500 to 2000 ng/mL (1500–2000 mcg/mL). Deferoxamine should be initiated at 20 to 40 mg/kg daily (to a maximum of 1–2 g/day) over 8 to 12 hours subcutaneously and has been associated growth failure.[6] Monitor children receiving deferoxamine for adequate growth and development on a regular basis. Deferoxamines should be initiated at 20 mg/kg daily and is available in a tablet that should be dispersed in water, orange juice, or apple juice and taken orally 30 minutes before food.[30,31] Monitor all chelation patients for auditory and ocular changes on a yearly basis. Exchange transfusions also may be helpful in cases of iron overload.

Sickle cell hemolytic transfusion reaction syndrome is a unique problem in SCD patients. Owing to alloimmunization, an acute or delayed transfusion reaction may occur. Delayed reactions typically occur 5 to 20 days after transfusion. Alloantibodies and autoantibodies resulting from previous

transfusions can trigger the reaction, in which patients develop symptoms suggestive of a pain crisis or worsening symptoms if they are already in crisis. A severe anemia after transfusion also may occur owing to a rapid decrease in hemoglobin and hematocrit, along with a suppression of erythropoiesis. Further transfusions may worsen the clinical picture owing to autoimmune antibodies. Recovery may occur only after ceasing all transfusions and is evidenced by a gradual increase in hemoglobin with reticulocytosis.[6,27]

Allogeneic Hematopoietic Stem Cell Transplant

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only potential cure for SCD. The best candidates are children with SCD who are younger than 16 years of age with severe complications who have an identical HLA-matched donor, usually a sibling. The transplant-related mortality rate is between 5% and 10%, and graft rejection is approximately 10%. Other risks include secondary malignancies, development of seizures or intracranial bleeding, and infection in the immediate posttransplant period.[6,25,32,33]

Experience with HSCT in adult patients with SCD is very limited. Umbilical cord blood and hematopoietic cells from nonmatched donors are alternatives, but use is limited.[6,33]

Acute Complications

Transfusions for Acute Complications

Red cell transfusion is indicated in patients with acute exacerbations of baseline anemia; in cases of severe vaso-occlusive episodes, including ACS, stroke, and acute multiorgan failure; and in preparation for procedures that will require the use of general anesthesia or ionic contrast products. Transfusions also may be useful in patients with complicated obstetric problems, refractory leg ulcers, refractory and prolonged pain crises, and severe priapism. Hyperviscosity may occur if the hemoglobin level is increased to greater than 10 to 11 g/dL (100 to 110 g/L or 6.2–6.8 mmol/L). Volume overload leading to congestive heart failure is more likely to occur if the anemia is corrected too rapidly in patients with severe anemia and should be avoided.[6,27]

Infection and Fever

❼ *Any fever greater than 38.5°C in a SCD patient should be evaluated immediately (see Table 65–2), and the patient should have a blood culture drawn and be started on antibiotics that provide empirical coverage for encapsulated organisms.*[27] Patients who should be hospitalized include:

- Infants younger than 1 year of age
- Patients with a previous sepsis or bacteremia episode
- Patients with temperatures in excess of 40°C (104°F)
- Patients with WBC counts greater than 30,000/mm^3 (30 × 10^9/L) or less than 500/mm^3 (0.5 × 10^9/L) and/or platelets less than 100,000/mm^3 (100 × 10^9/L) with evidence of other acute complications
- Acutely ill appearing individuals

Broad intravenous antibiotic coverage for the encapsulated organisms can include ceftriaxone or cefotaxime. For patients with true cephalosporin allergy, clindamycin may be used. If staphylococcal infection is suspected owing to previous history or the patient appears acutely ill, vancomycin should be initiated. Macrolide antibiotics, such as erythromycin and azithromycin, may be initiated if *Mycoplasma* pneumonia is suspected. While the patient is receiving broad-spectrum antibiotics, their regular use of penicillin for prophylaxis can be suspended. Fever should be controlled with acetaminophen or ibuprofen. Because of the risk of dehydration during infection with fever, increased fluid may be needed.[6,27]

Bone infarcts or sickling in the periosteum usually is indicated by pain and swelling over an extremity. Osteomyelitis also should be considered. *Salmonella* species are the most common cause of osteomyelitis in SCD children, followed by *Staphylococcus aureus.* [27] Select an appropriate antibiotic to cover the suspected organisms empirically.

Cerebrovascular Accidents

Acute neurologic events, such as stroke, will require hospitalization and close monitoring. Patients should have physical and neurologic examinations every 2 hours.[27] Acute treatment may include exchange transfusion or simple transfusion to maintain hemoglobin at around 10 g/dL (100 g/L or 6.2 mmol/L) and HbS concentration at less than 30%. Patients with a history of seizure may need anticonvulsants, and interventions for increased intracranial pressure should be initiated if necessary. Children with a history of stroke should be initiated on chronic transfusion therapy. Adults presenting with ischemic stroke should be considered for thrombolytic therapy if it has been less than 3 hours since the onset of symptoms.[6,27]

Early detection of ischemic stroke can be done with the use of transcranial Doppler ultrasonography. In the Stroke Prevention Trial in Sickle Cell Anemia (STOP) study, screening with this method followed by transfusion significantly reduced the incidence of stroke.[29] Screening is recommended in all patients over 2 years of age.

Acute Chest Syndrome

ACS will require hospitalization for appropriate management of symptoms and to avoid complications. Patients should be encouraged to use incentive spirometry at least every 2 hours. Incentive spirometry helps the patient to take long, slow breaths to increase lung expansion. Appropriate management of pain is important, but analgesic-induced hypoventilation should be avoided. Patients should maintain appropriate fluid balance because overhydration can lead to pulmonary edema and respiratory distress. Infection with gram-negative, gram-positive, or atypical bacterial is common in ACS, and early use of broad-spectrum antibiotics, including a macrolide, quinolone, or cephalosporin, is recommended. Fat emboli, from infarction of the long bones, may lead to ACS. Oxygen therapy should be used in any patient presenting with respiratory distress or

hypoxia. Oxygen saturations, measured by pulse oximeter, should be maintained at 92% or above. Transfusions are indicated often, and patients who present with wheezing may require inhaled bronchodilators.[6,34,35]

The use of corticosteroids is controversial. While they may decrease the inflammation and endothelial cell adhesion seen with ACS, their use also has been associated with higher readmission rates for other complications. Tapered corticosteroids, nitric oxide therapy, and L-arginine are being evaluated for use in ACS in studies.[34,36]

Priapism

Stuttering priapism, where erection episodes last anywhere from a few minutes to less than 2 hours, resolves spontaneously. Erections lasting more than 2 hours should be evaluated promptly. By age 18, approximately 90% of SCD males will have had at least one episode of priapism. Goals of therapy are to provide pain relief, reduce anxiety, provide detumescense, and preserve testicular function and fertility. Initial treatment should include aggressive hydration and analgesia. Transfusion may or may not be helpful but should be considered in anemic patients. Avoid the use of ice packs owing to the risk of tissue damage.[6,27]

Both vasoconstrictors and vasodilators have been used in the treatment of priapism. Vasoconstrictors are thought to work by forcing blood out of the cavernosum and into the venous return. Aspiration of the penile blood followed by intracavenous irrigation with epinephrine (1:1,000,000 solution) has been effective with minimal complications.[37] In severe cases, surgical intervention to place penile shunts has been used, but there is a high failure rate, and the risk of complications, from skin sloughing to fistulas, limits its use.

Pseudoephedrine dosed at 30 to 60 mg/day taken at bedtime has been used to prevent or decrease the number of episodes of priapism.[6] Terbutaline 5 mg has been used orally to prevent priapism with mixed results.[38,39] Leuprolide, a gonadotropin-releasing hormone, also has been used for this indication. Hydroxyurea may be helpful in some patients. The use of antiandrogens is under investigation.[6,27]

Treatment of Acute Complications

Aplastic Crisis

Most patients in aplastic crisis will recover spontaneously. Therefore, treatment is supportive. If anemia is severe or symptomatic, transfusion may be indicated. Infection with human parvovirus B19 is the most common cause of aplastic crisis. Isolate infected patients because parvovirus is highly contagious. Pregnant women should avoid contact with infected patients because midtrimester infection with parvovirus may cause hydrops fetalis and stillbirth.[6,27]

Sequestration Crisis

RBC sequestration in the spleen in young children may lead to a rapid drop in hematocrit, resulting in hypovolemia, shock, and death. Treatment is RBC transfusion to correct the hypovolemia, as well as broad-spectrum antibiotics because infections may precipitate the crisis.[6,27]

Recurrent episodes are common and can be managed with chronic transfusions and splenectomy. Observation is used commonly in adults because their episodes are milder. Splenectomy usually is delayed until after age 2 years of age to lessen the risk of postsplenectomy septicemia. Patients with chronic hypersplenism should be considered for splenectomy.[6,40]

Vaso-Occlusive Pain Crisis

The mainstay of treatment for vaso-occlusive crisis includes hydration and analgesia (see Table 65–7). Pain may involve the extremities, back, chest, and abdomen. ⓢ *Patients with mild pain crises may be treated as outpatients with rest, warm compresses to the affected (painful) area, increased fluid intake, and oral analgesia. Patients with moderate to severe crises should be hospitalized.* Infection should be ruled out because it may trigger a pain crisis, and any patient presenting with fever or critical illness should be started on empirical broad-spectrum antibiotics. Patients who are anemic should be transfused to their baseline. Intravenous or oral fluids at 1.5 times maintenance is recommended. Close monitoring of the patient's fluid status is important to avoid overhydration, which can lead to ACS, volume overload, or heart failure.[6,27]

Aggressive pain management is required in patients presenting in pain crisis. Assess pain on a regular basis (every 2–4 hours), and individualize management to the patient. The use of pain scales may help with quantifying the pain rating. Obtain a good medication history of what has worked well for the patient in the past. Use acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) for treatment of mild to moderate pain. Patients with bone or joint pain who require intravenous medications may be helped by the use of ketorolac, the only injectable NSAID available. Because of the concern for side effects, including gastrointestinal bleeding, ketorolac should be used only for a maximum of 5 consecutive days. Monitor for the total amount of acetaminophen given daily because many products contain acetaminophen. Maximum dose of acetaminophen for adults is 4 g/day, and for children, five doses over a 24-hour period.[41] Add an opioid if pain persists or if pain is moderate to severe in nature. Combining an opioid with an NSAID can enhance the analgesic effects without increasing adverse effects.[42–44]

Severe pain should be treated with an opioid such as morphine, hydromorphone, methadone, or fentanyl. Moderate pain can be treated effectively in most cases with a weak opioid such as codeine or hydrocodone, usually in combination with acetaminophen. Meperidine should be avoided owing to its relatively short analgesic effect and its toxic metabolite, normeperidine. Normeperidine may accumulate with repeated dosing and can lead to central nervous system side effects including seizures.

Intravenous opioids are recommended for use in the treatment of severe pain owing to a rapid onset of action and ease in titration. Intramuscular injection should be avoided.

TABLE 65–7. Management of Acute Pain of SCD

Principles

- Treat underlying precipitating factors
- Avoid delays in analgesia administration
- Use pain scale to assess severity
- Choice of initial analgesic should be based on previous pain crisis pattern, history of response, current status, and other medical conditions
- Schedule pain medication; avoid as-needed dosing
- Provide rescue dose for breakthrough pain
- If adequate pain relief can be achieved with one or two doses of morphine, consider outpatient management with a weak opioid; otherwise hospitalization is needed for parenteral analgesics
- Frequently assess to evaluate pain severity and side effects; titrate dose as needed
- Treating adverse effects of opioids is part of pain management
- Consider nonpharmacologic intervention
- Transition to oral analgesics as the patient improves; choose an oral agent based on previous history, anticipated duration, and ability to swallow tablets; if sustained-release products are used, a fast-release product is also needed for breakthrough pain

Analgesic Regimens

Mild to moderate pain:

Acetaminophen with codeine
Dose based on codeine—children: 1 mg/kg per dose every 6 hours; adult: 30–60 mg/dose

Hydrocodone + acetaminophen
Dose based on hydrocodone—children: 0.2 mg/kg per dose every 6 hours; adults: 5–10 mg/dose

Anti-inflammatory agents
Use with caution in patients with renal failure (dehydration) and bleeding
Ibuprofen: children: 10 mg/kg every 6–8 hours; adult; 200–400 mg/dose
Naproxen: 5 mg/kg every 12 hours; adult 250–500 mg/dose
Ibuprofen + hydrocodone: Each tablet contains 200 mg ibuprofen and 7.5 mg hydrocodone per tablet; only for older children who can swallow tablets

Moderate to severe pain:

Morphine: 0.1–0.15 mg/kg per dose every 3–4 hours for children; 5–10 mg/dose for adults
Continuous infusion: 0.04–0.05 mg/kg per hour; titrate to effect

Hydromorphone: 0.015 mg/kg per dose every 3–4 hours for children; 1.5–2 mg/dose for adults
Continuous infusion: 0.004 mg/kg per hour; titrate to effect

Intravenous anti-inflammatory agents:
Ketorolac: 0.5 mg/kg up to 30 mg/dose every 6 hours

Patient-controlled analgesics:
Morphine: 0.01–0.03 mg/kg per hour basal; demand 0.01–0.03 mg/kg every 6–10 minutes; 4 hours lock out 0.04–0.06 mg/kg
Hydromorphone: 0.003–0.005 mg/kg per hour basal; demand 0.003–0.05 mg/kg every 6–10 minutes; 4 hours lock out 0.4–0.6 mg/kg

Rescue therapy:
For breakthrough, give $^1/_4$ to $^1/_2$ of the scheduled dose as bolus every 1–2 hours; assess amount of rescue dose used in 8–12 hours and readjust scheduled dose or infusion rate as needed

Other adjunct therapy:
Hydration, heating pads, relaxation, and distraction
Stool softener and/or stimulants for constipation
Antihistamine for itching
Antiemetics for nausea or vomiting

From Yale,[45] Jacob et al,[42] Berde et al,[43] Stinson et al,[44] Christensen et al,[88] and Elander et al.[89]

Analgesia should be individualized and titrated to effect either by scheduled doses or continuous infusion. The use of continuous infusion will avoid the fluctuations in blood levels between doses that is seen with bolus dosing. As needed dosing of analgesia is appropriate only for breakthrough pain or uncontrolled pain. Patient-controlled analgesia (PCA) is used commonly and allows the patient to have control over his or her analgesic breakthrough dosing. As the pain crisis resolves, the pain medications can be tapered. Physical therapy and relaxation therapy can be helpful adjuvants to analgesia.[42–45]

Tolerance to opioids is seen when patients have had continuous long-term use of the medications and can be managed during acute crises by using a different potent opioid or using a larger dose of the same medication. Adverse effects associated with the use of opioids include respiratory depression, itching, nausea and vomiting, constipation, and drowsiness. Patients on continuous infusions of opioids should be on continuous pulse oximeter to assess oxygen saturations. Monitor the patient for oxygen saturations less than 92%. Oxygen should be administered as needed to keep the saturations above 92%. Itching can



Patient Encounter 3

CC: "My right leg and lower back hurt badly."

HPI: CD is a 21-year-old African-American man diagnosed with SCD at birth. He has had repeated pain crises (average of about two per year) and presents today with another. He started feeling ill yesterday, and this morning he woke up with increased pain and a cough.

PMH
Frequent pain crises, acute chest syndrome last year, priapism

FH
Mother with sickle cell trait; father with sickle cell disease. Father died at age 36 from stroke. Has an older brother with SCD and a younger sister with SCT.

SH
CD is a college student. He lives in the dorm. Enjoys basketball.

PE
- Wt 64 kg (141 lbs), ht 6 ft (183 cm), BP 130/80, HR 90, RR 30, temp 40°C (104°F)
- **Lungs:** Decreased breath sounds in bases
- **Skin:** Warm, dry, tender, and increased warmth in right leg, nailbeds dusky, poor capillary refill
- **HEENT:** Sclera slightly yellow

Meds
- Tylenol 3, 2 tablets PO q4–6hours prn for pain
- Pseudoephedrine 30 mg PO twice daily

Allergies: NKDA

Laboratory Data
All within normal limits except
- Hemoglobin: 6.2 g/dL (62 g/L or 3.8 mmol/L)
- Hematocrit: 30% (0.30)
- WBC: 20,000/mm^3 (20 × 10^9/L)
- Total bilirubin: 2.2 mg/dL (37.6 µmol/L)

Based on the information presented, create a care plan for this patient's vaso-occlusive crisis. Your plan should include:

- A statement of the drug-related needs and/or problems
- The goals of therapy
- A patient-specific detailed therapeutic plan
- A plan for follow-up and monitoring to determine whether the goals have been achieved and adverse effects avoided

be managed with an antihistamine such as diphenhydramine. Nausea and vomiting can be treated and managed with the administration of antiemetics such as promethazine or the 5-HT$_3$ antagonists, but the use of promethazine is contraindicated in children younger than 2 years of age. Assess stool frequency in all patients on a continuous opioid, and start stool softeners or laxatives as needed. Excessive sedation is difficult to control, and the concurrent use of an opioid with diphenhydramine or other sedative medications can exacerbate the drowsiness, leading to hypoxemia. A continuous very low dose of naloxone, an opioid antagonist, has been used in some cases where the adverse effects such as itching are unbearable.[46]

OUTCOME EVALUATION

SCD treatment and prevention are considered successful when complications are minimized. The major outcome parameters are a decrease in morbidity and mortality, measured by the number of hospitalizations, and the extent of end-organ damage seen over time. SCD is a chronic disease that cannot be cured, except with transplantation.

Starting with birth, SCD patients should have regularly scheduled health assessments and interventions when necessary. Obtain a urine analysis, complete blood count, liver function tests, ferritin or serum iron level and total iron-binding capacity, blood urea nitrogen (BUN), and creatinine on at least a yearly basis and more often for children younger than 5 years of age to monitor for complications. All SCD patients also should have regular screening of their hearing and vision.

All patients and parents of children with SCD should have a plan for what to do in the event of symptoms of infection or pain. Obtain a medication history when patients are admitted to the hospital. Assess compliance with prophylactic penicillin and childhood immunization schedules in all pediatric SCD patients.



Patient Care and Monitoring

1. Assess the patient's symptoms to determine whether the patient should be evaluated by a physician and/or receive immediate care. Determine the type of symptoms, onset of symptoms, frequency and exacerbating factors. Does the patient have evidence of SCD-related complications?
2. Review any available diagnostic data to determine the severity and status of the patient's SCD. *When was the patient last hospitalized for SCD complications?*
3. Obtain a thorough history of prescription, nonprescription, and natural drug product use. For pain control, determine which treatments have been helpful to the patient in the past. *Is the patient currently taking any medications on a chronic basis?*
4. Educate the patient on lifestyle modifications that may lessen complications. These include maintaining adequate hydration status, avoiding extreme temperature changes, dressing appropriately for hot or cold weather, and avoiding physical exertion, smoking, and excessive alcohol intake.
5. Is the patient up to date on immunizations? Has the patient received his or her annual influenza vaccine? If not, why?

(Continued)

6. Is the patient taking appropriate doses of pain medication to achieve effect? If not, why?
7. Develop a plan to assess the effectiveness of pain medications.
8. Determine if the patient is a candidate for hydroxyurea therapy.
9. Assess improvement in quality-of-life measures, such as physical, psychological, and social functioning and well-being.
10. Evaluate the patient for the presence of adverse drug reactions, drug allergies, and drug interactions.
11. Stress the importance of adherence with the therapeutic regimen, including lifestyle modifications. Recommend a therapeutic regimen that is easy for the patient/parent to accomplish.
12. Provide patient education on disease state, lifestyle modifications, and drug therapy; including:

- Possible complications of SCD, both long and short term
- When to take medications
- What potential adverse effects may occur
- Which drugs may interact with the medication therapy
- Warning signs to report to the physician (e.g., increased or new pain, sudden headache, bleeding or bruising, fever, loss of energy, loss of appetite)

ABBREVIATIONS

ACS:	acute chest syndrome
HbA:	normaladult hemoglobin
HbAS:	one normal and one sickle hemoglobin gene
HbC:	hemoglobin C
HbF:	fetal hemoglobin
HbS:	sickle hemoglobin
HbSβ^0-thalassemia:	one sickle hemoglobin and one β^0-thalassemia gene
HbSβ^+-thalassemia:	one sickle hemoglobin and one β^+-thalassemia gene
HbSC:	one sickle hemoglobin and one hemoglobin C gene
HbSS:	homozygous sickle hemoglobin
Hgb:	hemoglobin
HSCT:	hematopoietic stem cell transplantation
ISC:	irreversibly sickled cell
MCHC:	mean corpuscular hemoglobin concentration
MCV:	mean corpuscular volume
NSAID:	nonsteroidal anti-inflammatory drug
PCA:	patient-controlled analgesia
PCV 7:	7-valent pneumococcal conjugate vaccine
PPV 23:	23-valent pneumococcal polysaccharide vaccine
RBC:	red blood cell
SCA:	sickle cell anemia
SCD:	sickle cell disease
SCT:	sickle cell trait
STOP:	Stroke Prevention Trial in Sickle Cell Anemia
WBC:	white blood cell
VOC:	vaso-occlusive crisis

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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66 Antimicrobial Regimen Selection

Catherine M. Oliphant and Karl Madaras-Kelly



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Describe how antimicrobials differ from other drug classes in terms of their effects on individual patients as well as on society as a whole.
2. Recognize that antimicrobial resistance is an inevitable consequence of antimicrobial therapy.
3. Identify two guiding principles to consider when treating patients with antimicrobials, and apply these principles in patient care.
4. Differentiate between microbial colonization and infection based on patient history, physical examination, and laboratory and culture results.
5. Evaluate and apply at least six major drug-specific considerations when selecting antimicrobial therapy.
6. Evaluate and apply at least seven major patient-specific considerations when selecting antimicrobial therapy.
7. Select empirical antimicrobial therapy based on spectrum-of-activity considerations that provide a measured response proportional to the severity of illness. Provide a rationale for why a measured response in antimicrobial selection is appropriate.
8. Identify and apply five major principles of patient education and monitoring response to antimicrobial therapy.
9. Identify two common causes of patients failing to improve while on antimicrobials, and recognize other less common but potential reasons for antimicrobial failure.

Key Concepts

❶ An inevitable consequence of exposing microbes to antimicrobials is that some organisms will develop resistance to the antimicrobial.

❷ Antimicrobials are different from other classes of pharmaceuticals because they exert their action on bacteria infecting the host as opposed to acting directly on the host.

❸ Two guiding principles to consider when treating patients with antimicrobials are (1) make the diagnosis and (2) do no harm!

❹ Only bacteria that cause disease should be targeted with antimicrobial therapy, and colonizing flora should be left intact whenever possible.

❺ Bacterial cultures should be obtained prior to antimicrobial therapy in patients with a systemic inflammatory response, risk factors for antimicrobial resistance, or infections where diagnosis or antimicrobial susceptibility is uncertain.

❻ Empirical therapy should be based on patient- and antimicrobial-specific factors such as the anatomic location of the infection, the likely pathogens associated with the presentation, the potential for adverse effects, and the antimicrobial spectrum of activity.

❼ Drug-specific considerations in antimicrobial selection include the spectrum of activity, effects on nontargeted microbial flora, appropriate dose, pharmacokinetic and pharmacodynamic properties, adverse-effect and drug-interaction profile, and cost.

❽ Key patient-specific considerations in antimicrobial selection include recent previous antimicrobial exposures, identification of the anatomic location of infection through physical examination and diagnostic imaging, history of drug allergies, organ dysfunction that may affect drug clearance, immunosuppression, pregnancy, and compliance.

❾ Patient education, deescalation of antimicrobial therapy based on culture results, monitoring for clinical response and

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adverse effects, and appropriate duration of therapy are important treatment components.

⑩ Inadequate diagnosis resulting in poor initial antimicrobial selection, poor source control, or the development of a new infection with a resistant organism is a relatively common cause of antimicrobial failure.

The discovery of antimicrobials is among the greatest medical achievements of the twentieth century. Prior to the antimicrobial era, patients who contracted common infectious diseases developed significant morbidity or perished. The discovery of penicillin in 1927, followed by the subsequent discovery of other antimicrobials, contributed to a significant decline in infectious disease–related mortality during the next five decades. However, since 1980, infectious diseases related mortality in the United States have begun to increase, in part owing to increases in antimicrobial resistance.

The discovery of virtually every new class of antimicrobials has occurred in response to the development of bacterial resistance and loss of clinical effectiveness to existing antimicrobials. ❶ *An inevitable consequence of exposing microbes to antimicrobials is that some organisms will develop resistance to the antimicrobial.* Today, there are dozens of antimicrobial classes and hundreds of antimicrobials available for clinical use. However, in many cases, differences in mechanisms of action between antimicrobials are minor, and the microbiologic properties of the agents are similar. ❷ *Antimicrobials are different from other classes of pharmaceuticals because they exert their action on bacteria infecting the host as opposed to acting directly on the host.* Because use of an antimicrobial in one patient affects not only that patient but also other patients if they become infected with resistant bacteria, correct selection, use, and monitoring of clinical response are paramount.

❸ *There are two guiding principles to consider when treating patients with antimicrobials: (1) make the correct diagnosis and (2) do no harm!* Frequently, patients with infections may present with signs and symptoms that are nonspecific for infection and may be confused with other noninfectious disease. Not only is it important to determine if a disease process is of infectious origin, but it is also important to determine the specific causative pathogen of the infection. Antimicrobials vary in their ability to inhibit or kill different species of bacteria, or their ***spectrum of activity.*** Antimicrobials that kill many different species of bacteria are called *broad-spectrum antimicrobials,* whereas antimicrobials that kill only a few different species of bacteria are called *narrow-spectrum antimicrobials.* One might argue that treating everybody with very broad antimicrobial coverage will increase the likelihood that a patient will get better without making a definitive diagnosis. However, counter to this argument is the principle of "Do no harm!" Very broad antimicrobial coverage does increase the likelihood of empirically targeting a causative pathogen; unfortunately, the development of secondary infections caused by selection of antimicrobial-resistant nontargeted pathogens is a common problem. In addition, adverse events are thought to complicate up to 10% of all antimicrobial therapy, and for select agents, the adverse-event rate is much higher.[1] Therefore, the overall goal of antimicrobial therapy should be to cure the patient's infection; limit harm by minimizing patient risk for adverse effects, including secondary infections; and limit societal risk from antimicrobial-resistant bacteria.

EPIDEMIOLOGY AND ETIOLOGY

Infectious disease–related illnesses, particularly respiratory tract infections, are among the most common reasons patients seek medical care.[2] Three of the top 20 prescription medicines dispensed in the United States during 2004 were antimicrobials, with total prescriptions exceeding 220 million.[3] Approximately two-thirds of outpatient antimicrobial use is prescribed for respiratory tract infections, and the Centers for Disease Control and Prevention (CDC) estimate that approximately one-third to one-half of all outpatient antimicrobials are used inappropriately to treat nonbacterial processes.[4] Prescription of antimicrobials in hospitalized patients is also common because up to one-half of all patients receive at least one antimicrobial during hospitalization. In addition, the CDC estimates that almost 2 million **nosocomial** or hospital-acquired infections and 90,000 related deaths occur annually.[5] Generally nosocomial infections tend be associated with more antimicrobial-resistant strains of bacteria. In recent years, there has been a shift in the etiology of some community-acquired infections. Increasingly, infections owing to antimicrobial-resistant pathogens, traditionally nosocomial in origin, are being identified in ambulatory-care settings. Reasons for this change include an aging populace, improvement in the management of chronic comorbid conditions including immunosuppressive conditions, and increases in outpatient management of more debilitated patients. The converging bacterial etiologies and increasing resistance in all health care environments emphasize the need to "make the diagnosis."

PATHOPHYSIOLOGY

Normal Flora and Endogenous Infection

Many areas of the human body are colonized with bacteria—this is known as ***normal flora***. Infections often arise from one's own normal flora (also called an *endogenous infection*). Endogenous infection may occur when there are alterations in the normal flora (e.g., recent antimicrobial use may allow for overgrowth of other normal flora) or disruption of host defenses (e.g., a break or entry in the skin). Knowing what organisms reside where can help to guide empirical antimicrobial therapy (Fig. 66–1). In addition, it is beneficial to know what anatomic sites are normally sterile. These include the cerebrospinal fluid, blood, and urine.

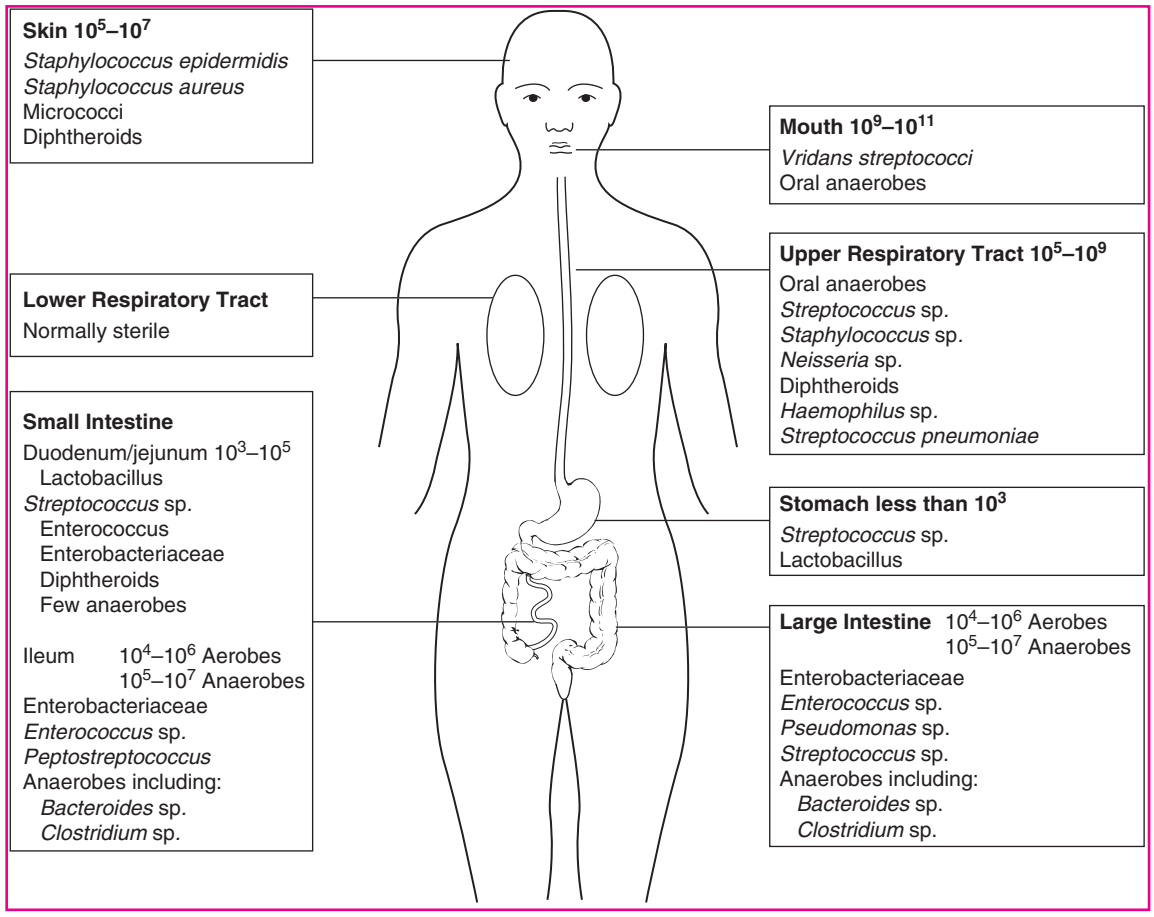


FIGURE 66–1. Normal flora and concentrations of bacteria (organisms per milliliter).

Determining Colonization versus Infection

Infection refers to the presence of bacteria that are causing disease (e.g., the organisms are found in normally sterile anatomic sites or in nonsterile sites with signs/symptoms of infection). *Colonization* refers to the presence of bacteria that are not causing disease. ❹ *Only bacteria that cause disease should be targeted with antimicrobial therapy, and non-disease-producing colonizing flora should be left intact.* It is important to differentiate infection from colonization because antimicrobial therapy targeting bacterial colonization is inappropriate and may lead to the development of resistant bacteria.

Exogenously Acquired Bacterial Infections

Infections acquired from an external source are referred to as *exogenous infections*. These infections may occur as a result of human-to-human transmission, contact with exogenous bacterial populations in the environment, and animal contact. Resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* spp. (VRE) may colonize hospitalized patients or patients who access the health care system frequently. It is key to know which patients have acquired these organisms because patients generally become colonized prior to developing infection, and colonized patients should be placed in isolation (per infection-control policies) to minimize transmission to other patients.

Contrasting Bacterial Virulence and Resistance

Virulence refers to the pathogenicity or disease severity produced by an organism. Many bacteria may produce toxins or possess growth characteristics that contribute to their pathogenicity. Some virulence factors allow the organism to avoid the immune response of the host and cause significant disease. Virulence and resistance are different microbial characteristics. For example, *Streptococcus pyogenes,* a common cause of skin infections, produces toxins that can cause severe disease, yet it is very susceptible to penicillin. *Enterococcus faecium* is a highly resistant organism but is frequently a colonizing flora that causes disease primarily in the immunocompromised.



Patient Encounter, Part 1

HPI

A 72-year-old man with a history of congestive heart failure, diabetes, hypertension, and hyperlipidemia presents to the local emergency room with complaints of increasing shortness of breath, cough productive of yellow-green sputum, chest pain, fever, and malaise. He was hospitalized 12 days ago for urosepsis, for which he received 10 days of levofloxacin.

PMH

- Congestive heart failure, diabetes mellitus × 22 years, hypertension, hyperlipidemia
- Chronic renal insufficiency: baseline SCr 1.8 mg/dL (137.3 μmol/L)

FH

- Father died of a myocardial infarction at age 75.
- Mother died of complications after cerebrovascular accident (CVA) at age 87.

SH

- Retired accountant
- Alcohol: 2 to 3 drinks per day

Meds

- Enalapril 10 mg bid
- Metoprolol XL 25 mg daily
- Furosemide 40 mg daily
- Insulin glargine (Lantus) 30 units SC qhs
- Glipizide 10 mg daily
- Atorvastatin 20 mg daily
- Aspirin 81 mg daily
- Home oxygen at 2 L/minute

- What information in the history supports an infectious etiology?
- Is this patient at risk for resistant pathogens? Why?

CLINICAL PRESENTATION AND DIAGNOSIS

Physical Examination

Findings on physical examination, along with the clinical presentation, can help to provide the anatomic location of the infection. Once the anatomic site is identified, the most probable pathogens associated with disease can be determined based on likely endogenous or exogenous flora.

Fever often accompanies infection and is defined as a rise in body temperature above the normal 98.6°F (37°C). Oral and axillary temperatures may underestimate core temperature by at least 1°F, whereas rectal temperatures best approximate core temperatures. Fever is a host response to bacterial toxins. However, bacterial infections are not the sole cause of fever. Fever also may be caused by other infections (e.g., fungal or viral), medications (e.g., penicillins, cephalosporins, salicylates, and phenytoin), trauma, or other medical conditions (e.g., autoimmune disease, malignancy, pulmonary embolism, and hyperthyroidism). Some patients with infections may present with hypothermia (e.g., patients with overwhelming infection). Elderly patients may be afebrile, as may those with



Clinical Presentation

- Review of symptoms consistent with an infectious etiology?
- Signs and symptoms may be nonspecific (e.g., fever) or specific.
- Specific signs and symptoms are beyond the scope of this chapter (see disease-state-specific chapters for these findings).

Patient History

- History of present illness
- Comorbidities
- Current medications
- Allergies
- Previous antibiotic exposure (May provide clues as to colonization or infection with new specific pathogens or pathogens that may be resistant to certain antimicrobials)
- Previous hospitalization or health care utilization (Also a key determinant in selecting therapy because the patient may be at risk for specific pathogens and/or resistant pathogens)
- Travel history
- Social history
- Pets/animal exposure
- Occupational exposure
- Environmental exposure

Physical Findings

- Findings consistent with an infectious etiology?
- Vital signs
- Body system abnormalities (e.g., rales, altered mental status, localized inflammation, erythema, warmth, edema, pain, and pus)

Diagnostic Imaging

- Radiographs (x-rays)
- Computed tomographic (CT) scans
- Magnetic resonance imaging (MRI)
- Labeled leukocyte scans

Non-Microbiologic Laboratory Studies

- White blood cell count with differential
- Erythrocyte sedimentation rate
- C-reactive protein

Microbiologic Studies

- Gram stain
- Culture and susceptibility testing



Patient Encounter, Part 2: Review of Symptoms, Physical Examination, and Laboratory Data

ROS

Patient with malaise, wheezing, dyspnea, cough, chest pain, and chills. No reports of emesis or diarrhea but with decreased appetite.

PE

- **VS:** BP 160/88, P 84, RR 28, T 39.1°C, O_2sat 86%, Ht 6 ft, 0 in, Wt 80 kg
- **HEENT:** Dry mucous membranes
- **Chest:** Rales and rhonchi R greater than L; diminished breath sounds RML and RLL
- **CV:** Tachycardic with regular rhythm; normal heart sounds

Laboratory Data

- WBC 18,800/mm^3, segs 80%, bands 10%, lymphs 10%
- SCr 2.5 mg/dL (190.8 μmol/L)
- Glucose 322 mg/dL (17.9 mmol/L)
- Sputum Gram stain: less than 10 epithelial cells, greater than 25 WBCs, predominance of gram-negative bacilli

Chest X-Ray

Pulmonary infiltrate right middle and lower lobes of right lung

- What findings on physical examination are suggestive of an infectious process?
- What laboratory findings and/or diagnostic studies have been performed to help establish the presence of an infection?
- Are these laboratory and diagnostic studies suggestive of an infection?
- What is your working diagnosis based on this patient encounter?

localized infections (e.g., urinary tract infection).[6] For others, fever may be the only indication of infection. For example, neutropenic patients may not have the ability to mount normal immune responses to infection (e.g., infiltrate on chest x-ray, pyuria on urinalysis, and erythema or induration around catheter site), and the only finding may be fever.

Imaging Studies

Imaging studies also may help to identify anatomic localization of the infection. These studies usually are performed in conjunction with other tests to establish or rule out the presence of an infection. X-rays are performed commonly to establish the diagnosis of pneumonia, as well as the severity of disease (single versus multilobe involvement). CT scans are a type of x-ray that produces a three-dimensional image of the combination of soft tissue, bone, and blood vessels. In contrast, MRI use electromagnetic radio waves to produce two- or three-dimensional images of soft tissue and blood vessels with less detail of bony structures. MRI produce more detailed images of soft tissues and organs than CT scans, whereas CT scans produce more detailed images of bones.

Non-Microbiologic Laboratory Studies

Common non-microbiological laboratory tests include the white blood cell (WBC) count and differential, erythrocyte sedimentation rate (ESR), and determination of the C-reactive protein level. In most cases, the WBC count is elevated in response to infection, but it may be decreased owing to overwhelming or long-standing infection. The differential is the percentage of each type of WBC (Table 66–1). In response to infection, neutrophils leave the bloodstream and enter the tissue to "fight" against the offending pathogens (i.e., leukocytosis). During an infection, immature neutrophils (e.g., bands) are released at an increased rate to help fight infection, leading to what is known as a *bandemia or left shift.* Therefore, a WBC count differential is key to determining if an infection is present. It is important to note that some patients may present with a normal total WBC with a left shift (e.g., the elderly). The erythrocyte sedimentation rate (ESR) and C-reactive protein are nonspecific markers of inflammation. They increase as a result of the acute-phase reactant response, which is a response to inflammatory stimuli such as infection or tissue injury. These tests may be used as markers of infectious disease response because they are elevated when the disease is acutely active and usually fall in response to successful treatment. Clinicians may use these tests to monitor a patient's response to therapy in osteomyelitis and infective endocarditis. These tests should not be used to diagnose infection because they may be elevated in noninfectious inflammatory conditions (e.g., rheumatoid arthritis, polymyalgia rheumatica, and temporal arteritis).

Microbiologic Studies

Microbiologic studies that allow for direct examination of a specimen (e.g., sputum, blood, or urine) also may aid in a presumptive diagnosis and give an indication of the characteristics of the infecting organism. Generally, microbial cultures are obtained with a Gram stain of the cultured material.

A Gram stain of collected specimens can give rapid information that can be applied immediately to patient care. A Gram stain is performed to identify if bacteria are present and to determine morphologic characteristics of bacteria (such as gram-positive or gram-negative or shape—cocci, bacilli). Certain specimens do not stain well or at all and must be identified by alternative staining techniques (*Mycoplasma* spp., *Legionella* spp., *Mycobacterium* spp.) Figure 66–2 identifies bacterial pathogens as classified by Gram stain and morphologic characteristics. The presence of WBCs on a Gram stain indicates inflammation and suggests that the identified bacteria are pathogenic. The Gram stain may be useful in judging a sputum specimen's adequacy. For example, the presence of epithelial

TABLE 66–1. White Blood Cell Count and Differential

Type of Cell	Normal Value	Function	Abnormalities
Neutrophil	Segs 40%–60% Bands 3%–5%	Phagocytic	Leukocytosis • Bacterial infections • Fungal infections • Physiologic stress • Tissue injury (e.g. myocardial Infarction) • Medications (e.g. corticosteroids) Leukopenia • Long-standing infection • Cancer • Medications (e.g., chemotherapy)
Lymphocyte	20–40%	T cells (cell-mediated immunity) B cells (humoral antibody response)	Lymphocytosis • Viral infections (e.g., mononucleosis) • Tuberculosis • Fungal infections Lymphopenia • human immunodeficiency virus
Monocyte	2%–8%	Phagocytic Precursor to macrophage	Monocytosis • Tuberculosis • Protozoal infections • Leukemia
Eosinophil	1%–4%	Antigen-antibody reactions	Eosinophilia • Hypersensitivity reactions, including medications • Parasitic infections
Basophil	Less than 1%		Hypersensitivity reactions

cells on sputum Gram stain suggests that the specimen is either poorly collected or contaminated. A poor specimen can give misleading information with regard to the underlying pathogen and is a waste of laboratory personnel time and patient cost.

Culture and susceptibility testing provides additional information to the clinician to guide appropriate therapy. Specimens are placed in or on culture media that provide the proper growth conditions. Once the bacteria grow on culture media, they can be identified through a variety of biochemical tests. Once a pathogen is identified, susceptibility tests can be performed to various antimicrobial agents. The *minimum inhibitory concentration* (MIC) is a standard susceptibility test. The MIC is the lowest concentration of antimicrobial that inhibits visible bacterial growth after approximately 24 hours (Fig. 66–3). Breakpoint and MIC values determine if the organism is susceptible (S), intermediate (I), or resistant (R) to an antimicrobial. The *breakpoint* is the concentration of the antimicrobial that can be achieved in the serum after a normal or standard dose of that antimicrobial. If the MIC is below the breakpoint, the organism is considered to be susceptible to that agent. If the MIC is above the breakpoint, the organism is said to be resistant. Reported culture and susceptibility results generally do not provide MIC values but report the S, I, and R results.

❺ *In general, bacterial cultures should be obtained prior to initiating antimicrobial therapy in patients with a systemic inflammatory response, risk factors for antimicrobial resistance, or infections where diagnosis or antimicrobial susceptibility is uncertain.* The decision to culture depends on the sensitivity and specificity of the physical findings, diagnostic examination findings, and whether or not the pathogens are readily predictable. Culture and susceptibility testing usually is not warranted in a young, otherwise healthy woman who presents with signs and symptoms consistent with a urinary tract infection (UTI) because the primary pathogen, *Escherichia coli,* is readily predictable. Cultures and susceptibility testing are routine for sterile-site specimens (e.g., blood and spinal fluid), as well as for material presumed to be infected (e.g., material obtained from joints and abscesses). Cultures need to be interpreted with caution. Poor specimen collection technique and processing speed can result in misleading information and inappropriate use of antimicrobials.

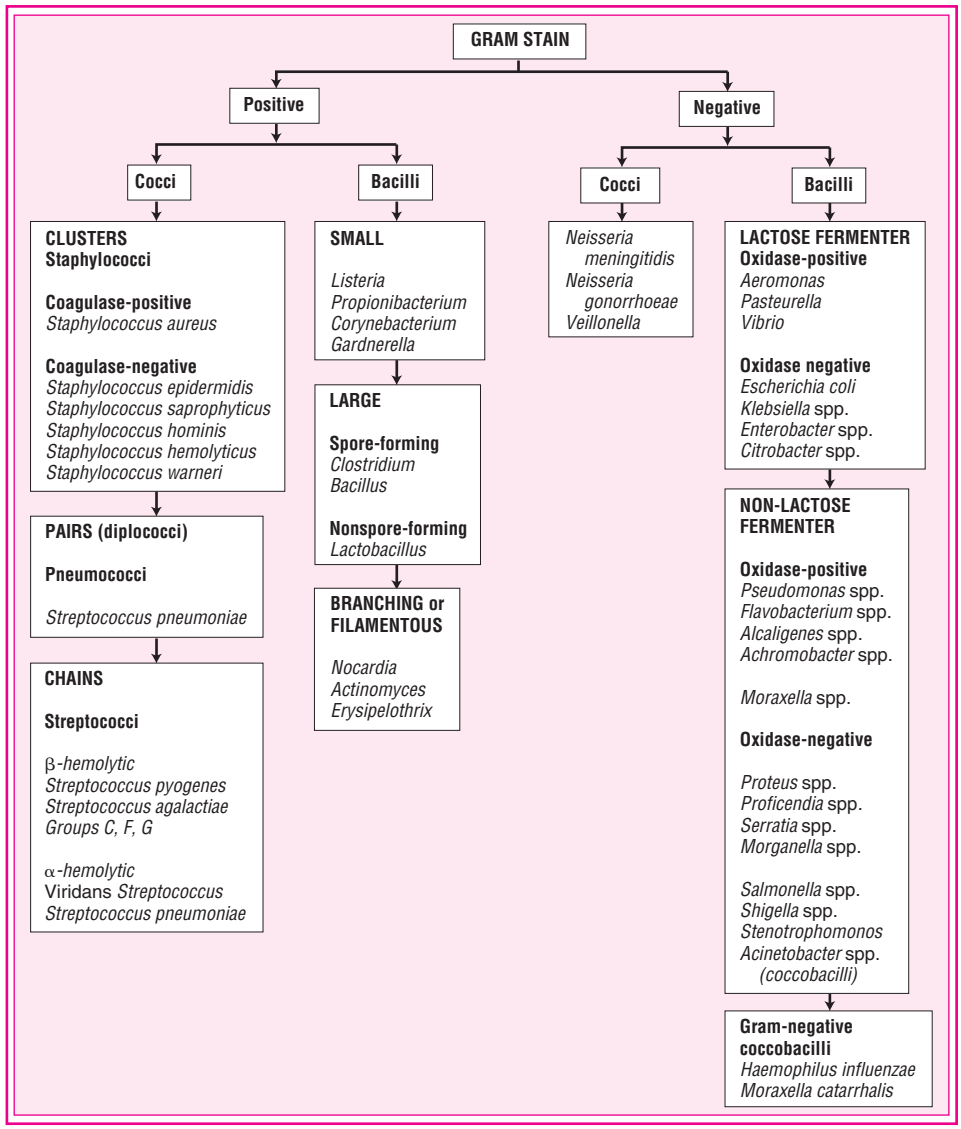


FIGURE 66–2. Important bacterial pathogens classified according to Gram stain and morphologic characteristics. (Reprinted from Rybak MJ, Aeschlimann JR. Laboratory tests to direct antimicrobial pharmacotherapy. In: In DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1894.)

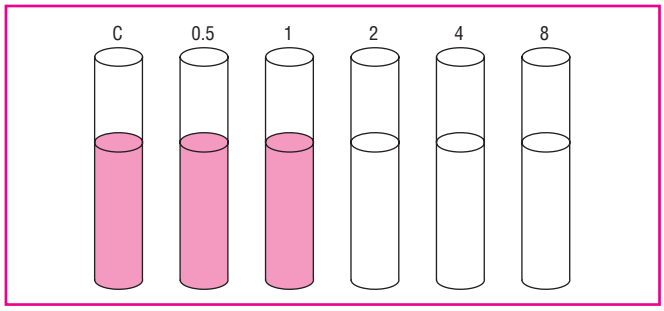


FIGURE 66–3. Macrotube minimal inhibitory concentration (MIC) determination. The growth control (C), 0.5 mg/dL, and 1 mg/dL tubes are visibly turgid, indicating bacterial growth. The MIC is read as the first clear test tube (2 mg/dL). (Reprinted from Rybak MJ, Aeschlimann JR. Laboratory tests to direct antimicrobial pharmacotherapy. In: In DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 1897.)

TREATMENT

General Approach to Treatment, Including Nonantimicrobial Treatment

While selection of antimicrobial therapy may be a major consideration in treating infectious diseases, it may not be the only therapeutic intervention. Other important therapies may include adequate hydration, ventilatory support, and other supportive medications. In addition, antimicrobials are unlikely to be effective if the process or source that leads to the infection is not controlled. ***Source control*** refers to this process and may involve removal of prosthetic materials such as catheters and infected tissue or drainage of an abscess. Source-control considerations should be a fundamental component of any infectious diseases treatment. It is also important to recognize that there may be many different antimicrobial regimens that may cure the patient. While the following therapy sections



Patient Encounter, Part 3: Empirical Selection of Antibiotics

Based on the information presented, select an empirical antimicrobial regimen for this patient. Your plan should include (1) a tentative infectious diagnosis or source, including likely pathogens or resistant organisms, (2) a specific antimicrobial(s) regimen, including drug(s), dose, and route of administration, (3) description of any ancillary treatments, and (4) a rationale for your empirical antimicrobial selection based on drug- and patient-specific considerations.

provide factors to consider when selecting antimicrobial regimens, an excellent and more in-depth resource for selecting antimicrobial regimens for a variety infectious diseases is the *Infectious Diseases Society of America Guidelines*.[7]

Antimicrobial Considerations in Selecting Therapy

❻ *Drug-specific considerations in antimicrobial selection include spectrum of activity, effects on nontargeted microbial flora, appropriate dose, pharmacokinetic and pharmacodynamic properties, adverse-effect and drug-interaction profile, and cost* (Table 66–2).

Spectrum of Activity and Effects on Nontargeted Flora

Most initial antimicrobial therapy is empirical because cultures usually have not had sufficient time to identify a pathogen. ❼ *Empirical therapy should be based on patient- and antimicrobial-specific factors such as the anatomic location of the infection, the likely pathogens associated with the presentation, the potential for adverse effects in a given patient, and the antimicrobial spectrum of activity.* Prompt initiation of appropriate therapy is paramount in hospitalized patients who are critically ill. Patients who receive initial antimicrobial therapy that provides coverage against the causative pathogen survive at twice the rate of patients who do not receive adequate therapy initially.[8]

TABLE 66–2. Considerations for Selecting Antimicrobial Regimens

Drug-Specific	Patient-Specific
Spectrum of activity and effects on nontargeted flora	Anatomic location of infection
Dosing	Antimicrobial history
Pharmacokinetic properties	Drug allergy history
Pharmacodynamic properties	Renal and hepatic function
Adverse-effect potential	Concomitant medications
Drug-interaction potential	Pregnancy or lactation
Cost	Compliance potential

Empirical selection of antimicrobial spectrum of activity should be related to the severity of the illness. Generally, acutely ill patients may require broader-spectrum antimicrobial coverage, whereas less ill patients may be managed initially with narrow-spectrum therapy. While a detailed description of antimicrobial pathogen– specific spectrum of activity is beyond the scope of this chapter, this information can be obtained readily from a number of sources.[9,10]

Collateral damage is defined as the development of resistance occurring in a patient's nontargeted antimicrobial flora that can cause secondary infections. For example, clindamycin is an excellent antimicrobial for treating streptococcal infections. However, many antimicrobials can treat this relatively susceptible pathogen. Clindamycin also readily selects for resistance in a nontargeted organism that may be present in the intestinal tract, namely, *Clostridium difficile*. Collateral damage is manifested because clindamycin is considered to be a major risk factor for *C. difficile*–associated diarrhea.[11] If several different antimicrobials possess activity against a targeted pathogen, the antimicrobial that is least likely to be associated with collateral damage may be preferred.

Single versus Combination Therapy

A common subject of debate involves the need to provide similar bacterial coverage with two antimicrobials for serious infections. Proponents state that double coverage may be synergistic, prevent the emergence of resistance, and improve outcome. However, there are few clinical examples in the literature to support these assertions. Examples where double coverage is considered superior are limited to infections associated with large bacterial inocula and in species that are known to readily develop resistance such as active tuberculosis or enterococcal endocarditis.[12,13] A study of patients with *Pseudomonas aeruginosa* infections, an intrinsically resistant organism, demonstrated that empirical double coverage with two antipseudomonal antimicrobials improved survival.[14] The analysis found that combination therapy increased the likelihood of appropriate empirical coverage; however, once organism susceptibilities were known, there was no difference in outcome between double coverage and monotherapy. In summary, double antimicrobial coverage with similar spectra of activity may be beneficial for selected infections associated with high bacterial loads or for initial empirical coverage of critically ill patients in whom antimicrobial-resistant organisms are suspected. Monotherapy usually is satisfactory once antimicrobial susceptibilities are established.

Antimicrobial Dose

Clinicians should be aware that dosage regimens with the same drug maybe different depending on the infectious process. For example, ciprofloxacin, a fluoroquinolone, has various dosage regimens based on site of infection. The dosing for uncomplicated UTIs is 250 mg twice daily for 3 days. For complicated UTIs, the dose is 500 mg twice daily for 7 to

14 days. Severe complicated pneumonia requires a dosage regimen of 750 mg twice daily for 7 to 14 days. Clinicians are encouraged to use dosing regimens designed for treatment of the specific diagnosed infection because they have demonstrated proven efficacy and are most likely to minimize harm.

Pharmacokinetic Properties

Pharmacokinetic properties of an antimicrobial may be important in antimicrobial regimens. *Pharmacokinetics* refers to a mathematical method of describing a patient's drug exposure in vivo in terms of absorption, distribution, metabolism, and elimination. *Bioavailability* refers to the amount of antimicrobial that is absorbed orally relative to an equivalent dose administered intravenously. Drug-related factors that may affect oral bioavailability include the salt formulation of the antimicrobial, the dosage form, and the stability of the drug in the gastrointestinal tract. Frequently, absorption may be affected by gastrointestinal tract blood flow. All patients that manifest systemic signs of infection such as hypotension or hypoperfusion should receive intravenous antimicrobials to ensure drug delivery. In almost all cases where patients have a functioning gastrointestinal tract and are not hypotensive, antimicrobials with almost complete bioavailability (greater than 80%) such as the fluoroquinolones, fluconazole, and linezolid may be given orally. With antimicrobials with modest bioavailability (e.g., many β-lactams), the decision to choose an oral product will depend more on the severity of the illness and the anatomic location of the infection. In sequestered infections, where higher systemic concentrations of antimicrobial may be necessary to reach the infected source (e.g., meningitis) or for antimicrobials with poor bioavailability, intravenous formulations should be used.

Several points regarding how the antimicrobial distributes into tissue are worth mentioning. First, only antimicrobials not bound to albumin are biologically active. Protein binding is likely clinically irrelevant in antimicrobials with low or intermediate protein binding. However, highly protein bound antimicrobials (greater than 50%) also may not be able to penetrate sequestered compartments, such as cerebral spinal fluid, resulting in insufficient concentration to inhibit bacteria. Second, some drugs may not achieve sufficient concentrations in specific compartments based on distribution characteristics. For example, *Legionella pneumophilia* is a nonenteric gram-negative organism that causes severe pneumonia. The organism is known to survive and reside inside pulmonary macrophages. Treatment with an antibiotic that works by inhibiting bacterial cell wall synthesis, such as a cephalosporin, will be ineffective because it only distributes into extracellular host tissues. However, macrolide or fluoroquinolone antimicrobials, which concentrate in human pulmonary macrophages, are highly effective against pneumonia caused by this organism.

Many antimicrobials undergo some degree of metabolism once ingested. Metabolism may occur via hepatic, renal, or non-organ-specific enzymatic processes. The route of elimination of the metabolic pathway may be exploited for infections associated with tissues related to the metabolic pathways. For example, many fluoroquinolone antimicrobials are metabolized only in part and undergo renal elimination. Urinary concentrations of active drug are many times those achieved in the systemic circulation, making several of these agents good choices for UTIs.

Pharmacodynamic Properties

Pharmacodynamics describes the relationship between drug exposure and pharmacologic effect of antibacterial activity or human toxicology. Antimicrobials generally are categorized based on their concentration-related effects on bacteria. Concentration-dependent pharmacodynamic activity occurs where higher drug concentrations are associated with greater rates and extents of bacterial killing. Concentration-dependent antimicrobial activity is maximized when peak antimicrobial concentrations are high. In contrast, *concentration-independent activity* refers to a minimal increase in the rate or extent of bacterial killing with an increase in antimicrobial dose. Concentration-independent antimicrobial activity is maximized when these antimicrobials are dosed to maintain blood and/or tissue concentrations above the MIC in a time-dependent manner. Fluoroquinolones, aminoglycosides, and metronidazole are examples of antimicrobials that exhibit concentration-dependent activity, whereas β-lactam and glycopeptide antimicrobials exhibit concentration-independent activity. Pharmacodynamic properties have been optimized to develop new dosing strategies for older antimicrobials. Examples include single-daily-dose aminoglycoside or β-lactam therapy administered by continuous infusion. The product labeling for many new antimicrobials takes pharmacodynamic properties into account.

Antimicrobials also can be classified as possessing bactericidal or bacteriostatic activity in vitro. Bactericidal antibiotics generally kill at least 99.9% (3 log reduction) of a bacterial population, whereas bacteriostatic antibiotics possess antimicrobial activity but reduce bacterial load by less than 3 logs. Clinically, bactericidal antibiotics may be necessary to achieve success in infections such as endocarditis or meningitis. A full discussion of the application of antimicrobial pharmacodynamics is beyond the scope of this chapter, but excellent sources of information are available.[15]

Adverse-Effect and Drug-Interaction Properties

A major concern when selecting antimicrobial regimens should be the propensity for the regimen to cause adverse effects and the potential for interaction with other drugs. Patients may possess characteristics or risk factors that increase their likelihood of developing an adverse event, emphasizing the need to obtain a good patient medical history. In general, if several different antimicrobial options are available, antimicrobials with a low propensity to cause specific adverse events should selected, particularly for patients with

risk factors for a particular complication. Risk factors for adverse events may include the coadministration of other drugs that are associated with a similar type of adverse event. For example, coadministration of the known nephrotoxin gentamicin with vancomycin increases the risk for nephrotoxicity compared with administration of either drug alone.[16] Other drug interactions may predispose the patient to dose-related toxicity through inhibition of drug metabolism. For example, erythromycin has the potential to prolong cardiac QT intervals in a dose-dependent manner, potentially increasing the risk for sudden cardiac death. A cohort study of patients taking oral erythromycin found that patients with concomitantly prescribed medications that inhibited the metabolism of erythromycin exhibited a fivefold increase in cardiac death versus controls.[17]

Antimicrobial Cost

A final consideration in selecting antimicrobial therapy relates to cost. It is important to remember that the most inexpensive antimicrobial is not necessarily the most cost-effective antimicrobial. Antimicrobial costs constitute a relatively small portion of the overall cost of care. Frequently, regulatory studies are not designed to identify differences in hospital length of stay, less common adverse events, monitoring costs, collateral damage, or antimicrobial-specific resistance issues, all of which may contribute to medical costs. Careful consideration of antimicrobial microbiologic, pharmacologic, and patient-related factors such as compliance and a variety of clinical outcomes is necessary to establish the cost versus benefit of an antimicrobial in a given patient. If there is no difference or a small difference in these factors, the least costly antimicrobial may be the best choice.

Patient Considerations in Antimicrobial Selection

❸ *Key patient-specific considerations in antimicrobial selection include recent previous antimicrobial exposures, identification of the anatomic location of infection through physical examination and diagnostic imaging, history of drug allergies, pregnancy or breast-feeding status, organ dysfunction that may affect drug clearance, immunosuppression, compliance, and the severity of illness (see Table 66–2)*

Host Factors

Host factors can help to ensure selection of the most appropriate antimicrobial agent. Age is an important factor in antimicrobial selection. With regard to dose and interval, renal and hepatic function varies with age. Populations with diminished renal function include neonates and the elderly. Hepatic function in the neonate is not fully developed, and drugs that are metabolized or eliminated by this route may produce adverse effects. For example, sulfonamides and ceftriaxone may compete with bilirubin for binding sites and may result in hyperbilirubinemia and kernicterus. Gastric acidity also depends on age; the elderly and children younger than 3 years of age tend to be achlorhydric. Drugs that need an acidic environment (e.g., ketoconazole) are not well absorbed, and those whose absorption is enhanced in an alkaline environment will have increased concentrations (e.g., penicillin G).

Disruption of host defenses owing to intravenous catheters, indwelling Foley catheters, burns, trauma, surgery, and increased gastric pH (secondary to antacids, H_2 blockers, and proton pump inhibitors) may place patients at higher risk for infection. Breaks in and entry into the skin provide a route for infection because the natural barrier of the skin is disrupted. Increased gastric pH can allow for bacterial overgrowth and has been associated with an increased risk of pneumonia.[18]

Recognizing the presumed site of infection and most common pathogens associated with the infectious source should guide antimicrobial choice, dose, and route of administration. For example, community-acquired pneumonia is caused most commonly by *S. pneumoniae, E. coli* is the primary cause of uncomplicated UTIs, and staphylococci and streptococci are implicated most frequently in skin and skin-structure infections (e.g., cellulitis).

Patients with a history of recent antimicrobial use may have altered normal flora or harbor resistant organisms. If a patient develops a new infection while on therapy, fails therapy, or has received antimicrobials recently, it is prudent to prescribe a different class of antimicrobial because resistance is likely. Previous hospitalization or health care utilization (e.g., residing in a nursing home, hemodialysis, and outpatient antimicrobial therapy) are risk factors for the acquisition of nosocomial pathogens, which are often resistant organisms.

Antimicrobial allergies are some of the most common drug-related allergies reported and have significant potential to cause adverse events. In particular, penicillin-related allergy is common and can be problematic because there is an approximately 4% cross-reactivity with cephalosporins as well as carbapenems.[19] In general, a patient's medical history should be reviewed to determine the offending β-lactam and nature of the allergic reaction. In some cases, patients with mild or nonimmunologic reactions may receive a β-lactam antimicrobial with low cross-reactive potential. However, patients with a history of physical findings consistent with IgE-mediated reactions such as anaphylaxis, urticaria, or bronchospasm should not be administered any type of β-lactam antimicrobial, including cephalosporins, unless there are no other alternatives. Administration of potentially cross-reactive agents in this situation should occur only under controlled conditions, and some patients may need to undergo desensitization. If the specific medical history relating to a reported allergy cannot be obtained, the patient should be assumed to have had an IgE-mediated reaction and should be managed in a similar manner.

Renal and/or hepatic function should be considered in every patient prior to initiation of antimicrobial therapy. In general, most antimicrobials undergo renal elimination and

exhibit decreased clearance with diminished renal function, and dosing adjustments are found readily in the literature.[20] In contrast, dosing adjustments for antimicrobials that are not eliminated renally are less well documented. Failure to adjust the antimicrobial dose or interval may result in drug accumulation and an increase in adverse effects.

Concomitant administration of other medications may influence the selection of the antimicrobial, dose, and monitoring. Medications that are commonly associated with drug interactions include, but are not limited to, warfarin, rifampin, phenytoin, digoxin, theophylline, multivalent cations (e.g., calcium, magnesium, and zinc), and sucralfate. Drug interactions between antimicrobials and other medications may occur via the cytochrome P-450 system, protein-binding displacement, and alteration of vitamin K–producing bacteria. Interactions may result in increased concentrations of one or both agents, increasing the risk of adverse effects or additive toxicity. A key consideration in selecting antimicrobial regimens starts with obtaining a good patient medical and drug history, recognizing drug-specific adverse-event characteristics, and anticipating potential problems proactively. If it is necessary to use an antimicrobial with a relatively high incidence of adverse effects, informing patients of the risks and benefits of therapy, as well as what to do if an adverse effect occurs, may improve patient compliance and may facilitate patient safety.

Antimicrobial agents must be used with caution in pregnant and nursing women. Some agents are either known or likely to be teratogenic (e.g., metronidazole), and others pose potential threats to the fetus or infant (e.g., quinolones, tetracyclines, and sulfonamides). For some agents, avoidance during a specific trimester of pregnancy is warranted. Pharmacokinetic variables also are altered during pregnancy. Both the clearance and volume of distribution are increased during pregnancy. As a result, increased dosages and/or more frequent administration of certain drugs may be required to achieve adequate concentrations. While a detailed description is beyond the scope of this chapter, this information can be obtained from a number of sources.[21,22]

Compliance is essential to ensure efficacy of a particular agent. Patients may stop taking their antibiotics once the symptoms subside and save them for a "future" infection. If the patient does not complete the course of therapy, the infection may not be eradicated, and resistance may emerge. Self-medication of saved antibiotics may be inappropriate and harmful and may select for resistant organisms. Poor patient adherence may be due to adverse effects, tolerability, cost, and lack of patient education.

OUTCOME EVALUATION

Figure 66–4 provides an overview of patient- and antimicrobial agent–specific factors to consider when selecting an antimicrobial regimen. It further delineates monitoring of therapy and actions to take depending on the patient's response to therapy. The duration of therapy depends on patient response and type of infection being treated.



Patient Encounter, Part 4: Patient Care and Monitoring

Update

The patient was admitted to the hospital with a presumptive diagnosis of health care–associated pneumonia (based on the recent hospitalization). He received intravenous hydration with normal saline, 5 L oxygen via face mask, an insulin infusion to control his glucose, and empirical antimicrobial therapy with piperacillin-tazobactam 2.25 g intravenously every 6 hours and vancomycin 1 g intravenously every 24 hours. All other medications are continued with the exception of the diabetes medications.

After 48 hours of therapy, the following parameters are obtained:

PE

- **VS:** BP 145/82, P 77, RR 22, T 37.9°C, O_2sat 92% on 4 L
- **Repeat chest x-ray:** Increased fluid density in bases, infiltrate unchanged, rales and rhonchi unchanged

Laboratory Data

- WBC 13,200 cells/mm^3
- SCr 1.9 mg/dL (145 µmol/L)
- Glucose 181 mg/dL (10.0 mmol/L)
- Urine and blood cultures × 2: Negative
- Sputum culture: 3+ *P. aeruginosa*

Sensitivity Report

Cefepime	Sensitive
Piperacillin/taz.	Sensitive
Imipenem	Resistant
Gentamicin	Sensitive
Amikacin	Sensitive
Ciprofloxacin	Resistant

- What information suggests improvement in the patient's condition?
- Do any of the antimicrobial doses need to be adjusted for changes in organ function?
- Should antimicrobial therapy be modified based on the culture results?
- Can the antimicrobial therapy be converted from intravenous to oral therapy?

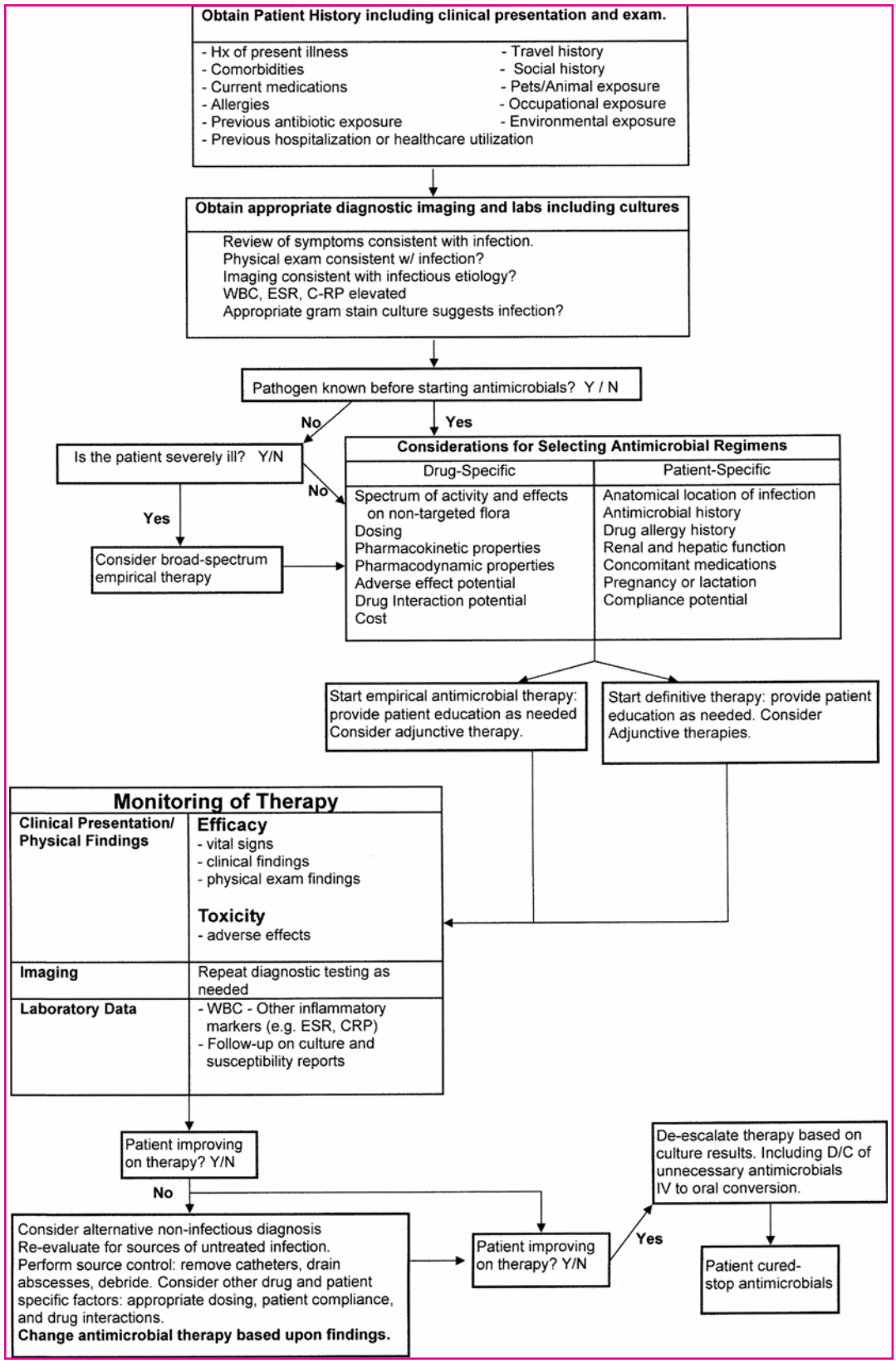


FIGURE 66–4. Approach to selection of antimicrobial therapy.



Patient Care and Monitoring

After selection and initiation of antimicrobial regimen, there are a number of additional patient care and monitoring considerations that should be addressed to improve the likelihood of a successful outcome. ❾ *Patient education, deescalation of antimicrobial therapy based on culture results, monitoring for clinical response and adverse effects, and appropriate duration of therapy are important.*

Patient Education

Provide patient education with regard to appropriate use of antimicrobials (e.g., dose, interval), adverse effects, and drug interactions (which may play a role in therapy failure and increased toxicity).

Therapeutic Monitoring

Monitor for therapeutic response by assessing efficacy and toxicity of the antimicrobial regimen.

- Clinical presentation/physical findings
  - *Efficacy:* Assess vital signs (monitor for return to normal or lack of altered findings, e.g., fever), physical examination findings, patient's subjective impression
  - *Toxicity:* Monitor and assess for adverse effects and evaluate antimicrobial serum concentrations when appropriate to minimize toxicity and improve outcomes
- Diagnostic imaging: Diagnostic testing is disease-state-dependent.
- Laboratory data
  - Monitor and assess laboratory data: WBC count with differential (goal is a reduction in WBC count if elevated initially and resolution of left shift), renal and/or hepatic function (consider need for dosage adjustments), other labs as indicated (e.g., ESR, CRP).
  - Follow up on culture and susceptibility reports with subsequent deescalation of therapy, if possible.
  - Reculture of specimens is not performed routinely except in few cases (e.g., endocarditis) or where a secondary infection is suspected because data may be misleading and lead to the addition of broader or more powerful antimicrobials

Modifying Empirical Therapy Based on Cultures and Clinical Response

If a successful clinical response occurs and culture results are available, therapy should be deescalated. ***Deescalation*** refers to decreasing antimicrobial regimen spectrum of activity to provide coverage against specific antimicrobial-sensitive pathogens recovered from culture. The purpose of deescalation therapy is to minimize the likelihood of secondary infections owing to antimicrobial-resistant organisms. In cases where a specific organism is recovered that has a known preferred agent of choice, therapy might be changed to that specific agent. For example, antistaphylococcal penicillins are considered to be the agents of choice for methicillin-susceptible *S. aureus* owing to their bactericidal activity and narrow-spectrum activity and may be preferable to other antibiotic regimens. In other cases, empirical coverage might be discontinued if a specific suspected pathogen is excluded by culture or an alternative, noninfectious diagnosis is established. In addition, intravenous antimicrobials frequently are more expensive than oral therapy. Therefore, it is desirable to convert therapy to oral antimicrobials with a comparable antimicrobial spectrum or specific pathogen sensitivity as soon as the patient improves clinically.

Failure of Antimicrobial Therapy

While many infections respond readily to antimicrobials, some infections do not. A relatively common question when a patient's condition fails to improve relates to whether the antimicrobial therapy has failed? Changing antimicrobials generally is one of the easiest interventions relative to other options. However, it is important to remember that antimicrobial therapy comprises only a portion of the overall disease treatment, and there may be many factors that contribute to a lack of improvement. ❿ *In general, inadequate diagnosis resulting in poor initial antimicrobial or other nonantibiotic drug selection, poor source control, and the development of a new infection with a resistant organism are relatively common causes of antimicrobial failure.* It is important to remember that an infection-related diagnosis may be difficult to establish and generally has two components: (1) differentiating infection-from non-infection-related disease and (2) providing adequate empirical spectrum of activity if the cause is infectious. Failure of improvement in a patient's condition should warrant broadening the differential diagnosis to include non-infection-related causes, as well as considering other potential infectious sources and/or pathogenic organisms. Another common cause of failure is poor source control. A diagnostic search for unknown sources of infection and removal of indwelling devices in the infected environment or surgical drainage of abscesses should be undertaken if the patient's condition is not improving. Less common but still frequent causes of therapeutic failure include the development of secondary infections. In this case, the patient generally improves but relapses after some period of improvement. The emergence of resistance to a targeted pathogen while on antimicrobial therapy can be associated with clinical failure but usually is limited to tuberculosis, pseudomonads, or other gram-negative enterics. Drug- and patient-specific factors such as appropriate dosing, patient compliance, and drug interactions can be associated with therapeutic failure and also should be considered. A common assumption is that the correct diagnosis was made, but the patient was not treated long enough with antimicrobials. There are certain types of infections (e.g., endocarditis or osteomyelitis) that the standard of care is to treat for prolonged periods of time (i.e., weeks or months). However, the optimal duration

of therapy for many infectious diseases is somewhat subjective. Recently, studies of several infectious processes have suggested that shorter durations of therapy can result in similar clinical outcomes as longer durations of therapy, frequently with fewer complications or secondary infections.[24,25] In this period of extensive antimicrobial resistance, clinicians should keep abreast of recommendations related to shorter duration of therapy.

CONCLUSION

Antimicrobial regimen selection is a complex process involving the integration of a multitude of factors. The guiding principles of make the diagnosis and do no harm must be considered when choosing an antimicrobial for a given patient. In summary, when infection is suspected, rapid and accurate diagnosis should be followed by early intervention that includes administration of appropriately dosed antibiotics with appropriate empirical spectrums. Deescalation to suitable narrow-spectrum antibiotics if susceptibilities are known should occur as soon as possible, and therapy should be stopped as soon as the patient is cured. These fundamental actions improve infectious disease outcomes and minimize collateral damage and adverse effects.

ABBREVIATIONS

MRSA:	methicillin-resistant *Staphylococcus aureus*
VRE:	vancomycin-resistant *Enterococcus*
CT:	computed tomography
MRI:	magnetic resonance imaging
MIC:	minimal inhibitory concentration
CDC:	Centers for Disease Control and Prevention
WBC:	white blood cell
ESR:	erythrocyte sedimentation rate
CRP:	C-reactive protein

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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67 Central Nervous System Infections

S. Diane Goodwin and Charles E. Hartis



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Describe the signs, symptoms, and clinical presentation of central nervous system (CNS) infections.
2. Discuss the pathophysiology of CNS infections and the impact on antimicrobial treatment regimens (such as dosing and CNS penetration).
3. List the most common pathogens causing CNS infections, and identify risk factors for infection with each pathogen.
4. State the goals of therapy for CNS infections.
5. Design appropriate empirical antimicrobial regimens for patients suspected of having CNS infections caused by each of the following pathogens (taking age, vaccine history, and other patient-specific information into account), and analyze the impact of antimicrobial resistance on both empirical and definitive therapy: *Neisseria meningitidis* meningitis, *Streptococcus pneumoniae* meningitis, *Haemophilus influenzae* meningitis, *Listeria monocytogenes* meningitis, group B *Streptococcus* meningitis, gram-negative bacillary meningitis, postneurosurgical infection, CNS shunt infection, herpes simplex encephalitis.
6. Modify empirical antimicrobial regimens based on laboratory data and other diagnostic criteria.
7. Discuss the management of close contacts of patients diagnosed with CNS infections.
8. Discuss the role of vaccines and other prophylactic therapies in the prevention of CNS infections.
9. Describe the role of adjunctive agents (such as dexamethasone) in the management of CNS infections.
10. Describe the components of a monitoring plan to assess efficacy and adverse effects of therapy for CNS infections.

Key Concepts

❶ Meningitis is a neurologic emergency that requires prompt recognition, diagnosis, and management to prevent death and residual neurologic defects. Patients with fever, headache, and neck stiffness should be evaluated for meningitis.

❷ Ideally, lumbar puncture to obtain cerebrospinal fluid (CSF) for direct examination and laboratory analysis, as well as blood cultures and other relevant cultures, should be obtained before initiation of antimicrobial therapy. However, initiation of antimicrobial therapy should not be delayed if a pretreatment lumbar puncture cannot be performed.

❸ The treatment goals for central nervous system (CNS) infections are to prevent death and residual neurologic deficits, eradicate or control causative microorganisms, ameliorate clinical signs and symptoms, and identify measures (such as vaccination and suppressive therapy) to prevent future infections.

❹ Prompt initiation of intravenous high-dose cidal antimicrobial therapy directed at the most likely pathogen(s) is essential due to the high morbidity and mortality associated with CNS infections; parenteral (intravenous) therapy is administered for the full course of therapy for CNS infections to ensure adequate CSF penetration throughout the course of treatment.

❺ Empirical therapy should be directed at the most likely pathogen(s) for a specific patient, taking into account age, risk factors for infection (including underlying disease and immune dysfunction, vaccine history, and recent exposures), CSF Gram stain results, CSF antibiotic penetration, and local antimicrobial resistance patterns.

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❻ Empirical antimicrobial therapy should be modified on the basis of laboratory data and clinical response.
❼ Close contacts of patients with CNS infections should be evaluated for possible antimicrobial prophylaxis.
❽ The adjunctive agent dexamethasone has been shown to improve outcomes in selected patient populations with meningitis.
❾ Components of a monitoring plan to assess the efficacy and safety of antimicrobial therapy of CNS infections include clinical signs and symptoms and laboratory data (such as CSF findings, culture, and sensitivity data).

The term *central nervous system* (CNS) *infections* describes a variety of infections involving the brain and spinal cord and associated tissues, fluids, and membranes, including meningitis, encephalitis, brain abscess, shunt infections, and postoperative infections (see Glossary). ❶ *CNS infections, such as meningitis, are considered neurologic emergencies that require prompt recognition, diagnosis, and management to prevent death and residual neurologic deficits.* Improperly treated, CNS infections are associated with high rates of morbidity and mortality. Despite advances in care, the overall mortality of bacterial meningitis remains greater than 20%, and at least 10% to 30% of survivors are afflicted with neurologic impairment, including hearing loss, **hemiparesis,** and learning disabilities.[1–3] Antimicrobial therapy and preventive vaccines have revolutionized management and improved outcomes of bacterial meningitis and other CNS infections dramatically.

EPIDEMIOLOGY AND ETIOLOGY

Compared with many other types of infections, CNS infections are less common, with 4 to 6 cases of meningitis reported per 100,000 adults annually.[4] However, the severity of these infections demands prompt medical intervention and treatment. CNS infections can be caused by bacteria, fungi, mycobacteria, viruses, and spirochetes.

Bacterial meningitis is the most common cause of CNS infections. An epidemiologic review of bacterial meningitis in 1995 revealed that *Streptococcus pneumoniae* (pneumococcus) was the most common pathogen (47%), followed by *Neisseria meningitidis* (meningococcus, 25%), group B *Streptococcus* (12%), *Listeria monocytogenes* (8%), and *Haemophilus influenzae* (Hib) (7%).[5] Vaccines directed against bacteria causing meningitis and related infections (such as pneumonia and ear infections) have reduced the risk of infections due to *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* type b dramatically. Prior to the availability of Hib conjugate vaccines, Hib meningitis or other invasive disease was documented in 1 in 200 children by the age of 5 years.[5] Widespread use of the Hib vaccine has reduced the incidence of invasive Hib disease by 99% and has shifted the age distribution of bacterial meningitis to older age groups (from 15 months in 1986 to 25 years in 1995).[1,6] Recent data indicate that routine use of the 7-valent conjugate pneumococcal vaccine in children not only has reduced the incidence of invasive pneumococcal disease in children but also has reduced invasive pneumococcal disease in adults 50 years of age and older by 28%.[7]

Neurosurgical procedures may place patients at risk for meningitis due to bacteria (such as *Staphylococcus aureus*, coagulase-negative staphylococci, and gram-negative bacilli) acquired at the time of surgery or in the postoperative period. In addition to bacteria, other pathogens may cause meningitis in at-risk patients. Immunocompromised patients, such as solid-organ transplant patients and patients living with human immunodeficiency virus (HIV) infection, are at risk for fungal meningitis with *Cryptococcus neoformans* (see Chap. 84). Tuberculosis can spread from pulmonary sites to cause clinical disease in the CNS (see Chap. 67). Life-threatening viral encephalitis and meningitis can occur in otherwise healthy, young individuals, as well as in patients immunocompromised by age or other factors. Because the treatments for different types of CNS infections are often very different, it is important to pay close attention to patients' risk factors when choosing empirical antimicrobial therapy. Patients at extremes of age, those living in close contact with others, and those with immune defects are most susceptible to meningitis. Risk factors for CNS infections can be classified as follows:

- *Environmental*—recent exposures (such as close contact with meningitis or respiratory tract infection, contaminated foods), active or passive exposure to cigarette smoke, close living conditions
- *Recent infection in the patient*—respiratory infection, otitis media, sinusitis, mastoiditis
- *Immunosuppression*—anatomic or functional asplenia, sickle cell disease, alcoholism, cirrhosis, immunoglobulin or complement deficiency, cancer, HIV/AIDS, debilitated state of health
- *Surgery, trauma*—neurosurgery, head trauma, CSF shunt, cochlear implant

Non-infectious causes of meningitis include malignancy, medications, autoimmune disease (such as lupus), and trauma.[8,9] The most common pathogens causing bacterial meningitis, by age group and other risk factors, are found in Table 67–1.

PATHOPHYSIOLOGY

Meningitis is an inflammation of the membranes of the brain and spinal cord (**meninges**) and the cerebrospinal fluid (CSF) in contact with these membranes, whereas encephalitis is an inflammation of the brain tissue. CSF flows through the subarachnoid space, insulating and protecting delicate CNS tissue. CSF is produced within the ventricles of the brain and flows downward through the spinal cord, serving as a continuous flushing mechanism for the CNS.

TABLE 67–1. Most Likely Pathogens and Recommended Empirical Therapy, by Risk Factor, for Bacterial Meningitis[14,24]

Predisposing Factor	Most Likely Pathogens	Recommended Empirical Antibiotic Therapy
Age		
Less than 3 months	Group B *Streptococcus* *Escherichia coli* *Klebsiella pneumoniae* *Listeria monocytogenes*	Ampicillin *plus* cefotaxime or aminoglycoside
3 months to less than 18 years	*Neisseria meningitidis* *Streptococcus pneumoniae* *Hemophilus influenzae*	Cefotaxime or ceftriaxone *plus* vancomycin
18 years to less than 60 years	*Neisseria meningitides* *Streptococcus pneumoniae*	Cefotaxime or ceftriaxone *plus* vancomycin
60 years or older	*Streptococcus pneumoniae* Gram-negative bacilli *Listeria monocytogenes*	Cefotaxime or ceftriaxone *plus* vancomycin *plus* ampicillin
Immunocompromised	*Streptococcus pneumoniae* *Neisseria meningitidis* *Listeria monocytogenes* Gram-negative bacilli (including *Pseudomonas aeruginosa*)	Cefotaxime or ceftriaxone *plus* vancomycin *plus* ampicillin (double antibiotic coverage against *Pseudomonas* if suspected)
Surgery, Trauma		
Postneurosurgical infection	*Staphylococcus aureus* (including MRSA) Coagulase-negative *Staphylococcus* (including MRSE) Gram-negative bacilli (including *Pseudomonas aeruginosa*)	Vancomycin *or* linezolid *plus* ceftazidime or cefepime or meropenem
Penetrating head trauma	*Staphylococcus aureus* (including MRSA) Coagulase-negative *Staphylococcus* Gram-negative bacilli (including *Pseudomonas aeruginosa*)	Vancomycin *or* linezolid *plus* ceftazidime or cefepime or meropenem (double antibiotic coverage against *Pseudomonas* if suspected)
CSF shunt	Coagulase-negative *Staphylococcus* (including MRSE) *Staphylococcus aureus* (including MRSA) Gram-negative bacilli (including *Pseudomonas aeruginosa*)	Vancomycin *or* linezolid *plus* ceftazidime or cefepime or meropenem (double antibiotic coverage against *Pseudomonas* if suspected)

MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*.
Adapted, with permission.

Over the past two decades, much has been learned about the pathophysiology of bacterial meningitis and other CNS infections. The blood-brain barrier and blood-CSF barrier are made of specialized tissue capillaries that isolate the brain from substances circulating in the bloodstream or colonizing nearby tissues. To initiate a CNS infection, pathogens must gain entry into the CNS by **contiguous** spread, **hematogenous** seeding, direct inoculation, or reactivation of latent infection. **Contiguous** spread occurs when infections in adjacent structures (such as sinus cavities or the middle ear) invade directly through the blood-brain barrier (such as Hib). **Hematogenous** seeding occurs when a more remote infection causes bacteremia that seeds the CSF (such as pneumococcal pneumonia). Reactivation of latent infection results from dormant viral, fungal, or mycobacterial pathogens in the spine, brain, or nerve tracts. Direct inoculation of bacteria into the CNS is the result of trauma, congenital malformations, or complications of neurosurgery.

Once through the blood-brain barrier, pathogens thrive and replicate due to limited host defenses in the CNS. Figure 67–1 depicts the pathophysiologic changes associated with meningitis. Neurologic tissue damage is the result of the host's immune reaction to bacterial cellular components (such as lipopolysaccharide, teichoic acid, and peptidoglycan) that triggers **cytokine** production, particularly tumor necrosis factor α (TNF-α) and interleukin 1 (IL-1), as well as other mediators of inflammation.[10] Bacteriolysis resulting from antibiotic therapy further contributes to the inflammatory process. **Cytokines** increase permeability of the blood-brain barrier, allowing influx of neutrophils and other host defense cells that contribute to the development of cerebral edema and increased intracranial pressure characteristic of meningitis.[11] The increase in intracranial pressure is responsible for the hallmark clinical signs and symptoms of meningitis: headache, neck stiffness, altered mental status, photophobia, and seizures. Unaltered, these pathophysiologic changes may result in cerebral ischemia and death.

The CNS response to infection is evident by demonstrable changes in the CSF. ❷ *Ideally, lumbar puncture to obtain CSF for direct examination and laboratory analysis, as well as blood cultures and other relevant cultures, should be obtained before*

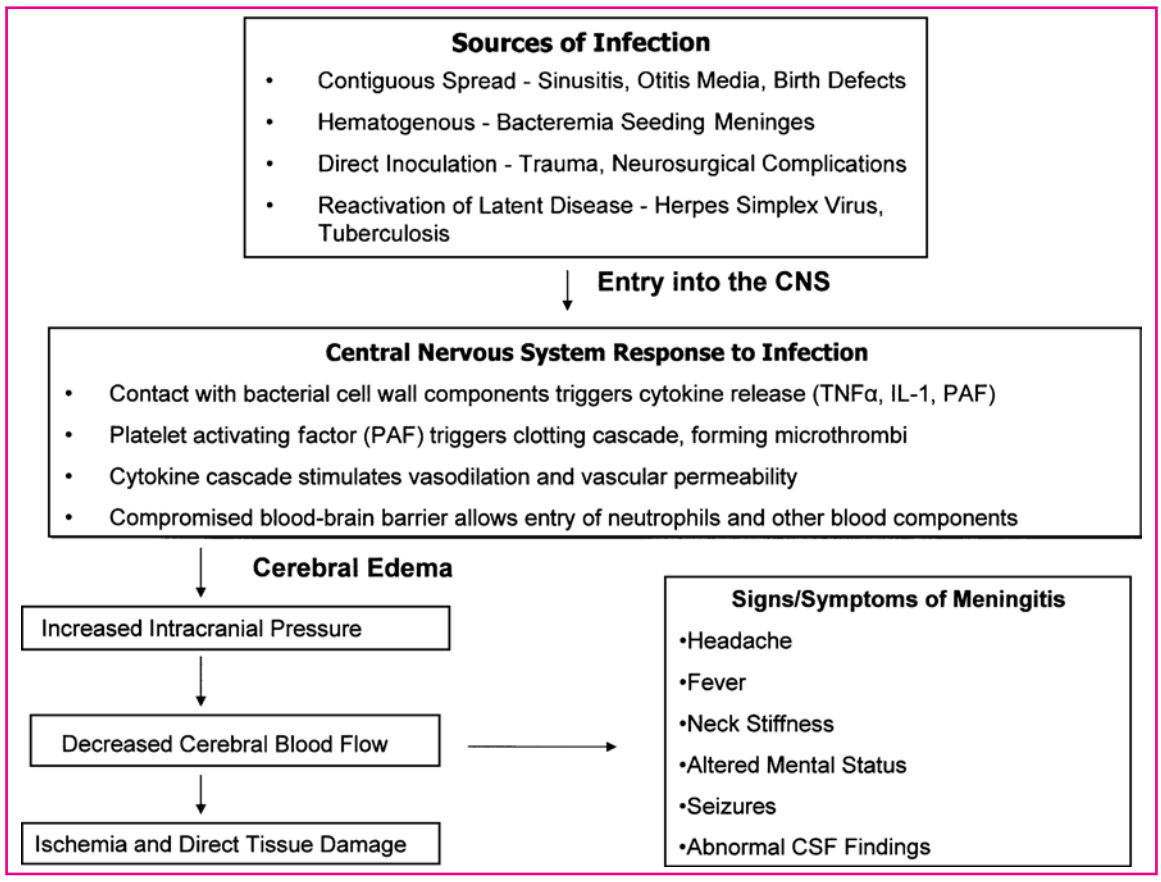


FIGURE 67–1. Pathophysiology of bacterial meningitis.

initiation of antimicrobial therapy. However, initiation of antimicrobial therapy should not be delayed if a pretreatment lumbar puncture cannot be performed.

Normal CSF has a characteristic composition in terms of protein and glucose content, as well as cell count. Table 67–2 lists CSF findings observed in the absence of infection, as well as in patients with bacterial, viral, fungal, and tuberculous meningitis.

CLINICAL PRESENTATION AND DIAGNOSIS

A high index of suspicion should be maintained for patients at risk for CNS infections. Prompt recognition and diagnosis are essential so that antimicrobial therapy can be initiated as quickly as possible. A medical history (including risk factors for infection and history of possible recent exposures) and

TABLE 67–2. Central Nervous System Response to Infection (Cerebrospinal Fluid Findings)[4,15,24]

	Normal CSF	Bacterial Infection	Viral Infection	Fungal Infection	Tuberculosis
WBC (mm^3, $\times 10^9$/L)	Less than 5 (less than 0.005)	1000–greater than 5000 (1.0–greater than 5.0)	100–1000 (0.1–1)	100–400 (0.1–0.4)	50–500 (0.05–0.5)
WBC differential (%, predominant cell type)	Greater than 85% monocytes	At least 80% PMNs	50% lymphocytes (PMNs early)	Greater than 50% lymphocytes	Greater than 80% lymphocytes (PMNs early)
Protein (mg/dL, mg/L)	20–45 (200–450)	Greater than 100 (greater than 1000)	50–100 (500–1000)	100–200 (1000–2000)	40–150 (400–1500)
Glucose (mg/dL, mmol/L); CSF: serum glucose ratio	45–80 (2.5–4.44) At least 0.6 serum glucose	5–40 (0.28–2.22) less than 0.4 serum glucose	30–70 (1.67–3.89) 0.6 serum glucose	Less than 30–70 (less than 1.67–3.89) less than 0.4 serum glucose	Less than 30–70 (less than 1.67–3.89) less than 0.4 serum glucose
CSF stain	Negative	Positive Gram stain (60%–90%)	Negative	Positive India ink stain (*Cryptococcus*)	Positive acid-fast bacilli stain

PMNs, polymorphonuclear neutrophils.



Clinical Presentation and Diagnosis of CNS Infections

General

- Evaluate patient risk factors and recent exposures.
- Evaluate other possible causes: space-occupying lesion (which may or may not be malignant), drug-induced CNS disease, autoimmune disease, and trauma.[8,9]

Signs and Symptoms[2]

- 95% of patients with bacterial meningitis have two of four of the following: headache, fever, neck stiffness, and altered mental status.
- Headache (87%)
- Nuchal rigidity (stiff neck) (83%)
- Fever (77%)
- Nausea (74%)
- Altered mental status (i.e., confusion, lethargy, and obtundation) (69%)
- Focal neurologic defects (including positive **Brudzinski's sign** and **Kernig's sign**) (33%)
- Seizures
- Malaise, restlessness
- Photophobia
- Skin lesions (diffuse petechial rash observed in 50% of patients with meningococcal meningitis)
- Signs and symptoms in neonates, infants, and young children: nonspecific findings, such as altered feeding and sleep patterns, vomiting, irritability, lethargy, bulging fontanel, seizures, respiratory distress, and petechial/purpuric rash[12]
- Predictors of an unfavorable outcome: seizures, focal neurologic findings, altered mental status, papilledema, hypotension, septic shock, and pneumococcal meningitis[3]

Laboratory Tests[4,13,14]

- CSF examination via lumbar puncture (LP, spinal tap); contraindicated in patients with cardiorespiratory compromise, ncreased intracranial pressure and papilledema, focal neurologic signs, seizures, bleeding disorders, abnormal level of consciousness, and possible brain herniation [a computed tomographic scan (CT) should be performed before LP if there is a question of a CNS mass to avoid potential for brain herniation] (Table 67–2 for specific CSF findings):
  - Elevated opening pressure (may be decreased in neonates, infants, and children)
  - Cloudy CSF
  - Decreased glucose
  - Elevated protein
  - Elevated WBC count (differential provides clues to offending pathogen)
  - Gram stain (adequate for diagnosis in 60% to 90% of patients with bacterial meningitis)
  - Culture and sensitivity (positive in 70% to 85% without prior antibiotic therapy, positive in less than 20% who have had prior therapy)
  - If CSF Gram stain and/or culture is negative, rapid diagnostic tests (such as latex agglutination) may be useful; these tests are positive even if bacteria are dead.
  - **Polymerase chain reaction** (**PCR;** DNA amplification of the most common bacterial meningitis pathogens) may be useful to help exclude bacterial meningitis.
  - Elevated CSF lactate and C-reactive protein
- Blood cultures (at least two cultures, one "set"; positive in 66%)
- Scraping of skin lesions (such as rash) for direct microscopic examination and culture
- Other cultures should be obtained as clinically indicated (such as sputum).
- WBC count with differential
- Fungal meningitis: CSF culture, CSF and serum cryptococcal antigen titers, microscopic examination of CSF specimens
- Tuberculous meningitis: CSF culture, PCR evaluation (preferred), and acid-fast stain

physical examination yield important information to help guide the diagnosis and treatment of meningitis.

TREATMENT

Goals of Therapy

The introduction of antibiotic therapy and vaccines has reduced dramatically the mortality associated with bacterial meningitis.[15] Prior to these advances, bacterial meningitis was almost universally fatal, and those few patients who survived often suffered from debilitating residual neurologic deficits, such as permanent hearing loss. Although significant improvements have been made, the fatality rate of pneumococcal meningitis remains above 20% likely due to its occurrence in debilitated patient populations.

❸ *The treatment goals for CNS infections are to prevent death and residual neurologic deficits, eradicate or control causative microorganisms, ameliorate clinical signs and symptoms, and identify measures to prevent future infections (such as vaccination and suppressive therapy).* These goals should be accomplished with minimal adverse drug reactions and interactions. Surgical debridement should be employed, if appropriate (as in postneurosurgical infections and brain abscess). Supportive care, consisting of hydration, electrolyte replacement, antipyretics, antiemetics, analgesics, antiepileptic drugs, and wound care (for surgical wounds), is an important adjunct to antimicrobial therapy, particularly early in the treatment course.

Treatment Principles

❹ *Prompt initiation of intravenous high-dose cidal antimicrobial therapy directed at the most likely pathogen(s) is essential due to the high morbidity and mortality associated with CNS infections.* Although there are no prospective studies that relate

timing of antibiotic administration to clinical outcome in bacterial meningitis, a longer duration of symptoms and more advanced disease before treatment initiation increase the risk of a poor outcome.[3,13,16] Two retrospective studies reported that initiation of antibiotic therapy as soon as possible after bacterial meningitis is suspected or proven (even before hospitalization) reduces mortality and neurologic sequelae, as long as antibiotics were started before a score of 10 was reached on the **Glasgow coma scale**.[17,18] Rapid sterilization of CSF is very important; delayed CSF sterilization after approximately 24 hours of antibiotic therapy increases the risk of neurologic sequelae, including moderate to profound hearing loss.[19,20] If dexamethasone is to be used (see Key Concept 8), it should be administered prior to or at the same time as the first dose of antibiotic therapy.

Meningitis occurs in an area with limited host defenses. Bacterial replication occurs rapidly in the absence of complement and specific antibodies directed toward common bacterial pathogens.[21] High-dose parenteral bactericidal antibiotic therapy is required to treat meningitis effectively. Data from animal studies and patients demonstrate better outcomes when bactericidal antibiotic therapy (versus bacteriostatic therapy) is used to sterilize the CSF.[22] However, successful treatment of meningitis has been reported with bacteriostatic agents. High doses of parenteral therapy are required to achieve CSF antibiotic concentrations adequate to rapidly sterilize the CSF and reduce the risk of complications. The presence of infection in the CSF reduces the activity of some classes of antibiotics. For example, the decreased pH of CSF associated with meningitis significantly reduces the activity of aminoglycoside antibiotics.[23]

Antimicrobial pharmacokinetics and pharmacodynamics must be considered when designing treatment regimens for CNS infections. Ability of antibiotics to reach and achieve effective concentrations at the infection site is the key to treatment success. In experimental models of meningitis, maximum bactericidal activity is achieved when CSF concentrations exceed the minimum bactericidal concentration (MBC) of the infecting pathogen by 10- to 30-fold.[12] In general, low-molecular-weight lipophilic antibiotics that are un-ionized at physiologic pH and not highly protein bound penetrate best into CSF and other body tissues and fluids.[21,23] In addition to drug characteristics, integrity of the blood-brain barrier determines antibiotic penetration into CSF. The CSF penetration of most, but not all, antibiotics is enhanced by the presence of infection and inflammation. Sulfonamides, trimethoprim, chloramphenicol, rifampin, and most antitubercular drugs achieve therapeutic CSF levels even without meningeal inflammation.[24] Most β-lactams and related antibiotics (i.e., carbapenems and monobactams), vancomycin, quinolones, acyclovir, linezolid, and colistin achieve therapeutic CSF levels in the presence of meningeal inflammation.[24] Amino-glycosides, first-generation cephalosporins, second-generation cephalosporins (except cefuroxime), clindamycin, and amphotericin do not achieve therapeutic CSF levels, even with inflammation, but clindamycin does achieve therapeutic brain tissue levels.[24]

An adequate duration of therapy is required to treat meningitis successfully (Table 67–3). ❹ *Parenteral (intravenous) therapy is administered for the full course of therapy for CNS infections to ensure adequate CSF penetration throughout the course of treatment.* Antibiotic treatment (and dexamethasone, if used as a treatment adjunct) reduces the inflammation associated with meningitis, which, in turn, reduces the penetration of some antibiotics into the CSF. To ensure adequate antibiotic concentrations throughout the treatment course, parenteral administration is continued for the full treatment course. Carefully selected patients who have close medical monitoring and follow-up may be able to receive a portion of their parenteral meningitis treatment on an outpatient basis.[13,25] A management algorithm for adults with suspected bacterial meningitis, as recommended by the Infectious Diseases Society of America (IDSA), is summarized in Fig. 67–2.

Empirical Antimicrobial Therapy

After expeditious work-up (i.e., evaluation of risk factors, clinical signs and symptoms, and laboratory data) and diagnosis, prompt and aggressive antimicrobial therapy is initiated. Appropriate empirical treatment is of the utmost importance in patients with suspected CNS infections. In most patients, a diagnostic lumbar puncture will be performed before beginning antibiotics, but this never should delay initiation of antimicrobials. ❺ *Empirical therapy should be directed at the most likely pathogen(s) for a specific patient, taking into account age, risk factors for infection (including underlying disease and immune dysfunction, vaccine history, and recent exposures), CSF Gram stain results, CSF antibiotic penetration, and local antimicrobial resistance patterns.* Results of the CSF Gram stain may be used to help narrow empirical therapy for bacterial meningitis. In the absence of a positive Gram stain, empirical therapy should be continued for at least 48 to 72 hours, when meningitis may, in most cases, be ruled out by CSF findings inconsistent with bacterial meningitis, negative CSF culture, and negative PCR evaluations. A repeat lumbar puncture may be useful in the absence of other findings. Table 67–1 outlines recommendations for empirical antibiotic therapy for bacterial meningitis by most likely pathogen(s) and patient risk factors.

Impact of Antimicrobial Resistance on Treatment Regimens for Meningitis

Development of resistance to β-lactam antibiotics, including penicillins and cephalosporins, has significantly impacted the management of bacterial meningitis. Approximately 17% of United States pneumococcal CSF isolates are resistant to penicillin, and 3.5% of CSF isolates are resistant to cephalosporins.[26] The Clinical and Laboratory Standards Institute (CLSI) has set a lower ceftriaxone susceptibility breakpoint for pneumococcal CSF isolates (1 mg/L) than for isolates from non-CNS sites (2 mg/L). Increasing pneumococcal resistance to penicillin G

TABLE 67–3. Pathogen-Based Definitive Treatment for Central Nervous System Infections

Pathogen	Recommended and Alternative Antimicrobial Therapy (Adult Doses; Pediatric Doses)	Adverse Effects/Safety Monitoring	Duration (Days)
Neisseria meningitidis	***Standard Therapy***		*7*
Penicillin MIC 0.1 mg/L	Penicillin G 4 million units IV every 4 hours *or*	Hypersensitivity (rash, anaphylaxis), diarrhea	
	Ampicillin 2 g IV every 4 hours	Hypersensitivity (rash, anaphylaxis), diarrhea	
	Alternative Therapies		
	Ceftriaxone 2 g IV every 12 hours *or* Cefotaxime 2 g IV every 4 hours	Ceftriaxone only: LFT elevation, **pseudocholelithiasis**	
Penicillin MIC 0.1–1 mg/L	***Standard Therapy***		
	Ceftriaxone *or* cefotaxime		
	Alternative Therapies		
	Moxifloxacin 400 mg IV every 24 hours *or*	Nausea/vomiting/diarrhea, dizziness, headache, QT prolongation	
	Meropenem 2 g IV every 8 hours *or*	Rash, hypersensitivity, diarrhea	
	Chloramphenicol 1–1.5 g IV every 6 hours	Rash, diarrhea, seizures, anemia, gray baby syndrome, hypersensitivity, neurotoxicity (last choice due to toxicities)	
Streptococcus pneumoniae	***Standard Therapy***		10–14
Penicillin MIC 0.1 mg/L	Penicillin G *or* ampicillin		
	Alternative Therapies		
	Ceftriaxone *or* cefotaxime *or* chloramphenicol		
Penicillin MIC 0.1–1 mg/L (ceftriaxone/cefotaxime-sensitive strains)	***Standard Therapy***		
	Ceftriaxone *or* cefotaxime		
	Alternative Therapies		
	Cefepime 2 g IV every 8 hours *or* meropenem		
Penicillin MIC 2 mg/L or greater	***Standard Therapy***		
	Vancomycin 15 mg/kg IV every 8–12 hours (with dosing based on serum levels) *plus* ceftriaxone *or* cefotaxime	Vancomycin: rash, red man's syndrome (if infused too quickly) nephrotoxicity, neutropenia, thrombocytopenia	
	Alternative Therapies		
	Moxifloxacin		
Cefotaxime/ceftriaxone MIC at least 1 mg/L	***Standard Therapy***		
	Vancomycin plus ceftriaxone *or* cefotaxime		
	Alternative Therapies		
	Moxifloxacin		
Haemophilus influenzae	***Standard Therapy***		*7*
β-Lactamase-negative	Ampicillin		
	Alternative Therapies		
	Ceftriaxone *or* cefotaxime *or* cefepime *or*		
	Moxifloxacin *or* chloramphenicol		
β-Lactamase-positive	***Standard Therapy***		
	Ceftriaxone *or* cefotaxime		
	Alternative Therapies		
	Cefepime *or* moxifloxacin *or* chloramphenicol		

LFT, liver function tests; MIC, minimum inhibitory concentration.
Adapted, with permission, from ref. 14.

(*Continued*)

TABLE 67–3. Pathogen-Based Definitive Treatment for Central Nervous System Infections *(Continued)*

Pathogen	Recommended and Alternative Antimicrobial Therapy (Adult Doses; Pediatric Doses)	Adverse Effects/Safety Monitoring	Duration (Days)
Listeria monocytogenes	***Standard Therapy*** Ampicillin *or* penicillin G *plus* gentamicin (5 mg/kg per day, dosing based on serum levels) ***Alternative Therapies*** Trimethoprim-sulfamethoxazole (TMP-SMX) 10–20 mg/kg TMP IV per day in divided doses every 6–8 hours *or* meropenem	Gentamicin: nephrotoxicity, ototoxicity TMP-SMX: Rash, Stevens-Johnson syndrome, bone marrow suppression, nausea/vomiting, hepatotoxicity	At least 26
Streptococcus agalactiae (group B *Streptococcus*)	***Standard Therapy*** Ampicillin *or* penicillin G ***Alternative Therapies*** Ceftriaxone *or* cefotaxime		14–21
Enterobacteriaceae	***Standard Therapy*** Ceftriaxone *or* cefotaxime ***Alternative Therapies*** Aztreonam 2 g IV every 6–8 hours Moxifloxacin *or* meropenem *or* TMP-SMX *or* ampicillin	 Phlebitis, fever, rash, headache, confusion, seizures	21 (longer duration may be required for neonates)
Pseudomonas aeruginosa	***Standard Therapy*** Cefepime *or* Ceftazidime 2 g IV every 8 hours *or* meropenem (addition of aminoglycoside should be considered) ***Alternative Therapies*** Aztreonam *or* ciprofloxacin 400 mg IV every 8–12 hours (addition of aminoglycoside should be considered)	 Hypersensitivity, rash, anemia, neutropenia, eosinophilia, LFT elevation Nausea/vomiting/diarrhea, dizziness, headache, rash, confusion, seizures	At least 21 days
Staphylococcus aureus Methicillin-susceptible	***Standard Therapy*** Nafcillin *or* oxacillin 1.5–3 g every 4 hours ***Alternative Therapies*** Vancomycin *or* meropenem	 Rash, nausea/vomiting/diarrhea, acute interstitial nephritis Hepatotoxicity, red-orange discoloration of body fluids, skin rash, hepatic enzyme induction	3–4 weeks (4–6 weeks if shunt involved)
Methicillin-resistant	***Standard Therapy*** Vancomycin *plus* Rifampin 600 mg PO or IV daily if shunt involved ***Alternative Therapies*** Linezolid 600 mg IV every 12 hours *or* TMP-SMX	 Thrombocytopenia, neutropenia, nausea/vomiting/diarrhea, LFT elevation	
Staphylococcus epidermidis	***Standard Therapy*** Vancomycin *plus* rifampin 600 mg PO or IV daily if shunt involved ***Alternative Therapies*** Linezolid		3–4 weeks (4–6 weeks if shunt involved)
Herpes simplex virus	***Standard Therapy*** Acyclovir 10 mg/kg IV every 8 hours (adults) Acyclovir 20 mg/kg IV every 8 hours (neonates) ***Alternative Therapy*** Foscarnet 120–200 mg/kg IV per day in divided doses every 8–12 hours	 Nephrotoxicity, crystalluria, nausea/vomiting, neurotoxicity, phlebitis Nephrotoxicity, electrolyte imbalances, nausea/vomiting, headache, penile ulceration, thrombophlebitis, seizures	14–21 (21 for neonates)

LFT, liver function tests; MIC, minimum inhibitory concentration.
Adapted, with permission, from ref. 14.

(*Continued*)

TABLE 67–3. Pathogen-Based Definitive Treatment for Central Nervous System Infections (*Continued*)

	Pediatric Doses of Selected Agents Used in Bacterial Meningitis Treatment		
	Neonates, 0–7 Days	**Neonates, 8–28 Days**	**Infants and Children**
Ampicillin	150 mg/kg IV per day in divided doses every 8 hours	200 mg/kg IV per day in divided doses every 6–8 hours	300 mg/kg IV per day in divided doses every 6 hours
Cefepime	—	—	150 mg/kg per day in divided doses every 8 hours
Cefotaxime	100–150 mg/kg IV per day in divided doses every 8–12 hours	150–200 mg/kg IV per day in divided doses every 6–8 hours	225–300 mg/kg per day in divided doses every 6–8 hours
Ceftriaxone	—	—	80–100 mg/kg IV per day in divided doses every 12 hours
Gentamicin	5 mg/kg IV per day in divided doses every 12 hours (with dosing based on serum levels)	7.5 mg/kg IV per day in divided doses every 8 hours (with dosing based on serum levels)	7.5 mg/kg IV per day in divided doses every 8 hours (dosing based on serum levels)
Meropenem	—	—	120 mg/kg IV per day in divided doses every 8 hours
Nafcillin/oxacillin	75 mg/kg IV per day in divided doses every 8–12 hours	Nafcillin: 100–150 mg/kg IV per day in divided doses every 6–8 hours Oxacillin: 150–200 mg/kg IV per day in divided doses every 6–8 hours	200 mg/kg IV per day in divided doses every 6 hours max, 2 gm pediatrics greater than 3 months of age
Penicillin G	0.15 million units/kg IV per day in divided doses every 8–12 hours	0.2 million units/kg IV per day in divided doses every 6–8 hours	0.3 million units/kg IV per day in divided doses every 4–6 hours
Vancomycin	20–30 mg/kg IV per day in divided doses every 8–12 hours	30–45 mg/kg IV per day in divided doses every 6–8 hours	60 mg/kg IV per day in divided doses every 6 hours

LFT, liver function tests; MIC, minimum inhibitory concentration.
Adapted, with permission, from ref. 14.

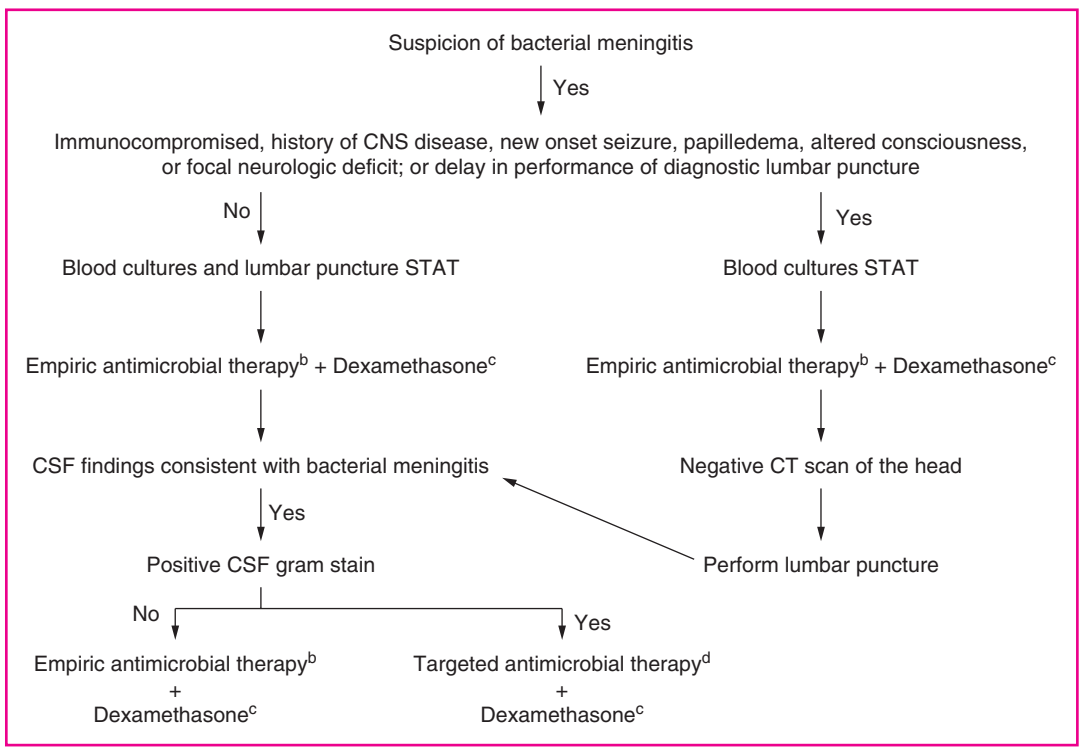


FIGURE 67–2. Management algorithm for adults with suspected bacterial meningitis.[a] [a]Management algorithm is similar for infants and children with suspected bacterial meningitis. [b]See Table 67–1 for empirical treatment recommendations. [c]See text for specific recommendations for use of adjunctive dexamethasone in adults with bacterial meningitis. [d]See Table 67–3 for pathogen-based definitive treatment recommendations. (Adapted, with permission, ref. 14.)

has changed empirical treatment regimens to the combination of a third-generation cephalosporin plus vancomycin. Recognition of relative and high-level resistance to *N. meningitidis* in the laboratory, as well as in clinical treatment failures, has led to greater use of third-generation cephalosporins for empirical therapy of meningococcal meningitis.[16] Previously, ampicillin was the cornerstone of treatment for *H. influenzae* meningitis. Now, treatment of suspected or proven β-lactamase-mediated Hib meningitis requires a third-generation cephalosporin. Increasing rates of methicillin-resistant *S. aureus* (about one-third of staphylococcal CSF isolates) and coagulase-negative staphylococci require the use of vancomycin for empirical therapy when these pathogens are suspected.[26] Global and local resistance patterns should be taken into account when designing empirical treatment regimens for bacterial meningitis.

Pathogen-Directed Antimicrobial Therapy

❻ *Empirical antimicrobial therapy should be modified on the basis of laboratory data and clinical response.* If cultures or other diagnostics, such as CSF Gram stain or antigen or antibody tests indicate a specific pathogen, therapy should be adjusted quickly as needed to ensure adequate coverage for the offending pathogen(s). Table 67–3 outlines recommended definitive pathogen-directed treatment regimens, recommended treatment duration, and key adverse effects that should be monitored during antibiotic therapy for meningitis. Treatment considerations for selected pathogens causing CNS infections are summarized below.

Neisseria meningiditis Meningitis

N. meningiditis most commonly causes CNS infections in children and young adults. An estimated 1400 to 2800 cases of meningococcal meningitis occur annually in the United States, with a mortality of about 10%.[27] From 11% to 19% of survivors of meningococcal meningitis experience long-term sequelae, including hearing loss, limb loss, and neurologic deficits.[27] Nearly all meningococcal disease is caused by five serogroups: A, B, C, Y, and W-135. In the United States, serotypes B, C, and Y each are responsible for approximately 30% of cases.

Meningococcal meningitis is observed most commonly in individuals living in close quarters (such as college students and military personnel). Although infants younger than 1 year of age are at highest risk, nearly 60% of cases occur in patients over 11 years of age.[27,28] *N. meningitidis* colonizes the nasopharynx and usually is transmitted via inhaled respiratory droplets from patients or asymptomatic carriers. A subclinical bacteremia typically ensues, seeding the **meninges.** Meningococcal disease is often (~50%) associated with a diffuse petechial rash, and patients may experience behavioral changes. Patients may develop fulminant meningococcal sepsis, characterized by shock, disseminated intravascular coagulation (DIC), and multiorgan failure.[16,28] Meningococcal sepsis has a poor prognosis and carries a mortality rate of up to 80%.[16] Patients with suspected meningococcal infection should be kept on respiratory isolation for the first 24 hours of treatment.[4]

Traditionally, high-dose penicillin G was the treatment standard for meningococcal disease. However, increasing penicillin resistance requires that third-generation cephalosporins now be used for empirical treatment until in vitro susceptibilities are known.[23] Patients with a history of type I penicillin allergy or cephalosporin allergy may be treated with vancomycin. Treatment should be continued for 7 days, after which no further treatment is necessary.

Prevention of meningococcal disease by vaccination is a key to reducing the incidence of meningococcal meningitis. College freshmen living in dormitories, military recruits, patients undergoing splenectomy, and patients with complement deficiency should receive the meningococcal vaccine.[27] Both the older polysaccharide meningococcal vaccine and the new quadrivalent conjugate meningococcal vaccine protect against four of the five serotypes causing invasive disease (A, C, Y, and W-135). Meningococcal vaccines do not protect against serotype B, which causes more than 50% of the cases of meningococcal meningitis in children younger than 2 years of age.[29] Either of the two available meningococcal vaccines can be used in outbreak situations, with protective antibodies measurable within 7 to 10 days. A possible advantage of the new conjugate vaccine is that it is believed to provide a longer duration of immunity than the older polysaccharide vaccine, although clinical studies to validate the duration of protection are not yet completed. The CDC Advisory Committee on Immunization Practices and the American Academy of Pediatrics recommend that all adolescents 11 to 12 years of age receive a dose of the new quadrivalent conjugate vaccine (currently approved by the Food and Drug Administration for patients 11–55 years of age). Until broader indications for the conjugate vaccine are licensed, the polysaccharide vaccine is available for patients 2 to 10 years of age, as well as patients over 55 years of age.

❼ *Close contacts of patients with meningococcal infections should be evaluated for antimicrobial prophylaxis.* Close contacts include members of the same household, individuals who share sleeping quarters, day-care contacts, and individuals exposed to oral secretions of meningitis patients. After consultation with the local health department, close contacts should receive prophylactic antibiotics to eradicate nasopharyngeal carriage of the organism. Household contacts of patients with meningococcal meningitis have a 400- to 800-fold increased risk of developing meningitis.[28] Prophylactic antibiotics should be started as soon as possible, preferably within 24 hours of exposure (and within 14 days, after which the benefit is significantly reduced). Recommended regimens, all of which are 90% to 95% effective, for adults include rifampin 600 mg orally every 12 hours for 2 days, ciprofloxacin 500 mg orally for one dose, or ceftriaxone 250 mg intramuscylarly for one dose. Regimens for children include rifampin 5 mg/kg orally every 12 hours for 2 days (less than 1 month of age), rifampin 10 mg/kg orally every 12 hours for 2 days (greater than 1 month of age), or ceftriaxone

125 mg intramuscularly for one dose (less than 12 years of age).[27,28] It is not known if close contacts who have been vaccinated will benefit from prophylaxis. Patients with meningococcal meningitis who are treated with antibiotics other than third-generation cephalosporins also should be considered for prophylaxis to eradicate the nasopharyngeal carrier state.[29]

Streptococcus pneumoniae Meningitis

S. pneumoniae is the most common cause of meningitis in adults and in children younger than 2 years of age. Pneumococcus is associated with the highest mortality observed with bacterial meningitis in adults (20% to 30%), and coma and seizures are more common in pneumococcal meningitis.[1–3] Patients at high risk for pneumococcal meningitis include the elderly, alcoholics, splenectomized patients, patients with sickle cell disease, and patients with cochlear implants. At least 50% of pneumococcal meningitis cases are due to a primary infection of the ears, sinuses, or lungs.

High-dose penicillin G traditionally has been the drug of choice for the treatment of pneumococcal meningitis. However, due to increases in pneumococcal resistance, the preferred empirical treatment now includes a third-generation cephalosporin in combination with vancomycin.[13] All CSF isolates should be tested for penicillin and cephalosporin resistance by methods endorsed by the CLSI. Once in vitro sensitivity results are known, therapy may be tailored (Table 67–3). Patients with a history of type I penicillin allergy or cephalosporin allergy may be treated with vancomycin. Treatment should be continued for 10 to 14 days, after which no further maintenance therapy is required. Antimicrobial prophylaxis is not indicated for close contacts.

Administration of vaccines to high-risk individuals is a key strategy to reduce the risk of invasive pneumococcal disease. The 23-valent pneumococcal vaccine targets serotypes that account for over 90% of invasive disease in high-risk patients. However, the 23-valent vaccine does not produce a reliable immunologic response in children younger than 2 years of age or nor does it reduce pneumococcal carriage. The 7-valent pneumococcal protein-polysaccharide conjugate vaccine introduced in 2000 targets the 7 most common serotypes in children and provides protection (94% reduction) against invasive pneumococcal disease (such as sepsis and meningitis) in children younger than 5 years of age.[30] Widespread administration of the 7-valent conjugate vaccine to children has also contributed to a 28% reduction in invasive pneumococcal disease in adults.[7] Unlike the 23-valent vaccine, the 7-valent vaccine reduces carriage and transmission.

Haemophilus influenzae Meningitis

Prior to the introduction of the Hib conjugate vaccine, *H. influenzae* type b was the most common cause of bacterial meningitis in the United States.[5] Routine inoculation of pediatric patients against Hib since 1991 has reduced the incidence of invasive Hib disease (i.e., meningitis and sepsis) in children younger than 5 years of age by 99%,[6] with mortality from Hib meningitis now less than 5%.[2] The Hib vaccine is also recommended for patients undergoing splenectomy. Hib meningeal disease often is associated with a parameningeal focus such as a sinus or middle ear infection. Increases in β-lactamase-mediated resistance have changed the empirical treatment of choice from ampicillin to third-generation cephalosporins (e.g., ceftriaxone and cefotaxime). Treatment should be continued for 7 days, after which no further maintenance therapy is required.

Close contacts of patients with H. influenzae *type B meningitis should be evaluated for antimicrobial prophylaxis.* The risk of Hib meningitis in close contacts may be up to 200- to 1000-fold higher than in the general population.[24] Invasive Hib disease, including meningitis, should be reported to the local health department and the Centers for Disease Control and Prevention (CDC). Prophylaxis to eliminate nasal and oropharyngeal carriage of Hib in exposed individuals should be initiated after consultation with local health officials. Rifampin (600 mg/day for adults; 20 mg/kg per day for children, maximum of 600 mg/day) is administered for 4 days.[12] Rifampin prophylaxis is not necessary for individuals who have received the full Hib vaccine series. Exposed, unvaccinated children between 12 and 48 months of age should receive one dose of vaccine, and unvaccinated children 2 to 11 months of age should receive three doses of vaccine, as well as rifampin prophylaxis.[12] Because of prior vaccine shortages, it cannot be assumed that all children have been vaccinated. Further, some children have not received all childhood vaccines because of parental fears regarding vaccine safety.

Listeria monocytogenes Meningitis

L. monocytogenes is an intracellular gram-positive bacillus that has been reported to contaminate certain foods, such as soft cheese, unpasteurized milk, raw meats and fish, processed meats, and raw vegetables. Bacteria from contaminated foods colonize the gastrointestinal tract, pass into the bloodstream, and overcome natural cellular immune responses to cause infection. *L. monocytogenes* meningitis, usually observed in patients at extremes of age and in immunocompromised patients with depressed cellular immunity (including patients with leukemia, solid-organ transplants, and HIV/AIDS), has an overall mortality rate of up to 30%.[31,32]

Only a limited number of antibiotics show bactericidal activity against *Listeria*. The combination of high-dose ampicillin or penicillin G and an aminoglycoside is synergistic and bactericidal against *Listeria*. A total treatment course of at least 3 weeks is required. Because of concerns about the risk of nephrotoxicity with an extended treatment course of aminoglycosides, patients are treated with combination therapy for 10 days and may finish out the remainder of their treatment with ampicillin or penicillin alone.[31] In penicillin-allergic patients, trimethoprim-sulfamethoxazole is the agent of choice due to documented in vitro bactericidal activity against *Listeria*, as well as good CNS penetration. Vancomycin and cephalosporins

are not effective treatments for *Listeria* meningitis. Prophylaxis is not needed for close contacts, nor is suppressive therapy indicated. Patients with severe depression of cell-mediated immunity should be advised to avoid foods that may be contaminated with *Listeria.*

Group B *Streptococcus* Meningitis

Infection with group B *Streptococcus* (such as *S. agalactiae*) is the most common cause of neonatal sepsis and meningitis. One of every 4 to 5 pregnant women is a carrier of group B *Streptococcus* in the vagina or rectum. Group B streptococci can be acquired during childbirth after exposure to infected secretions from the mother's birth canal or rectum. Neonates born to women who are carriers are at very high risk (1 of every 100–200 babies) of developing invasive group B streptococcal disease, including sepsis and meningitis.[33] Neonatal meningitis is associated with significant morbidity and mortality. Synergistic treatment with penicillin or ampicillin, plus gentamicin, for 14 to 21 days is recommended for the treatment of group B streptococcal meningitis.[13]

To reduce the risk of clinical group B streptococcal disease in neonates, pregnant women should be screened at 35 to 37 weeks' gestation to determine if they are carriers of group B streptococci.[33] Intrapartum antibiotics (e.g., penicillin or ampicillin) are recommended for pregnant women with the following characteristics: group B streptococcal carrier state detected at screening, history of group B streptococcal bacteriuria at any time during pregnancy, and history of delivery of infant with invasive group B streptococcal disease.[33]

Gram-Negative Bacillary Meningitis

Meningitis caused by enteric gram-negative bacilli is an important cause of morbidity and mortality in populations at risk, including those with diabetes, malignancy, cirrhosis, immunosuppression, advanced age, parameningeal infection, and/or a defect allowing communication from skin to CNS (such as neurosurgery, congenital defects, or cranial trauma).[24]

The optimal treatment for gram-negative bacillary meningitis is not well defined. The introduction of extended-spectrum cephalosporins has improved patient outcomes significantly. While the third-generation cephalosporins ceftriaxone and cefotaxime provide good coverage for most **Enterobacteriaceae,** these antibiotics are not active against *P. aeruginosa*. Ceftazidime, cefepime, and carbapenems have been shown to be effective in pseudomonal meningitis.[21,23] Addition of an aminoglycoside may improve treatment results; however, CNS penetration of aminoglycosides is extremely poor, even in the setting of inflamed **meninges.** Intrathecal or intraventricular administration of aminoglycosides may be useful, but intraventricular antibiotics have been associated with increased mortality in neonates.[21,34] Intrathecal therapy is accomplished by administering the antibiotic into the CSF via lumbar puncture, whereas intraventricular therapy is usually administered into a reservoir implanted in the ventricles of the brain.

Initial therapy of suspected or documented pseudomonal meningitis should include an extended-spectrum β-lactam (e.g., ceftazidime, cefepime, or meropenem) plus an aminoglycoside (preferably tobramycin or amikacin). Although the carbapenem imipenem-cilastatin has similar activity to these β-lactams, its use is not recommended in meningitis because of the risk of seizures. Aztreonam, high-dose ciprofloxacin, and colistin are alternative treatments for pseudomonal meningitis. Local therapy (i.e., intrathecal or intraventricular therapy) may be indicated in patients with gram-negative bacillary meningitis (especially infections caused by multidrug-resistant *P. aeruginosa*) or in patients who fail to improve on intravenous antibiotics alone. Given the differences in local hospital resistance patterns, administration of pathogen-directed treatment is very important after microbiology results become available. Therapy for gram-negative bacillary meningitis should be continued for at least 21 days.

Postoperative Infections in the Neurosurgical Patients and Shunt Infections

Patients who undergo neurosurgical procedures or have invasive or implanted foreign devices (such as CSF shunts, intraspinal pumps or catheters, or epidural catheters) are at risk for CNS infections. Key pathogens in postneurosurgical infections include coagulase-negative staphylococci, *S. aureus*, streptococci, propionobacteria, and gram-negative bacilli, including *P. aeruginosa*. Clinical signs and symptoms may be similar to those of other CNS infections, and there also may be evidence of malfunction of implanted hardware or visible signs of a postoperative wound infection.

Empirical therapy for postoperative infections in neurosurgical patients (including patients with CSF shunts) should include vancomycin in combination with either cefepime, ceftazidime, or meropenem. Linezolid has been reported to reach adequate CSF concentrations and resolve cases of meningitis refractory to vancomycin.[35] However, data with linezolid are limited. The addition of rifampin should be considered for treatment of shunt infections. When culture and sensitivity data are available, pathogen-directed antibiotic therapy should be administered. Removal of infected devices is desirable; aggressive antibiotic therapy (including high-dose intravenous antibiotic therapy plus intraventricular vancomycin and/or tobramycin) may be effective for patients in whom hardware removal is not possible. [36]

Brain abscesses are localized collections of pus within the cranium. These infections are difficult to treat due to the presence of walled-off infections in the brain tissue that are hard for some antibiotics to reach. In addition to appropriate antimicrobial therapy (a discussion of which is beyond the scope of this chapter), surgical debridement is often required as an adjunctive measure. Surgical debridement also may be required in the management of neurosurgical postoperative infections.

Viral Encephalitis and Meningitis

Viral encephalitis and meningitis may mimic bacterial meningitis on clinical presentation but often can be differentiated by CSF findings (Table 67–2). The most common viral pathogens are enteroviruses, which cause approximately 85% of cases of viral CNS infections.[24] Other viruses that may cause CNS infections include arboviruses, herpes simplex virus, cytomegalovirus, varicella-zoster virus, rotavirus, coronavirus, influenza viruses A and B, West Nile virus, and Epstein-Barr virus. Viral CNS infections are acquired through **hematogenous** or neuronal spread.[24] Most cases of enteroviral meningitis or encephalitis are self-limiting with supportive treatment.[37] However, arbovirus, West Nile virus, and Eastern equine virus infections are associated with a less favorable prognosis.

In contrast to other viral encephalitides, herpes simplex virus (HSV) type 1 and 2 encephalitis is treatable. Although rare (1 case per 250,000 population per year in the United States), HSV encephalitis is a serious, life-threatening infection.[38] Over 90% of HSV encephalitis in adults is due to HSV type 1, whereas HSV type 2 predominates in neonatal HSV encephalitis (greater than 70%).[39] HSV encephalitis is the result of reactivation of a latent infection (two-thirds of cases) or a severe case of primary infection (one-third). Without effective treatment, the mortality rate may be as high as 85%, and survivors often have significant residual neurologic deficits. High-dose intravenous acyclovir is the drug of choice, given for 2 to 3 weeks at a dose of 10 mg/kg intravenously every 8 hours in adults and for 3 weeks at a dose of 20 mg/kg intravenously every 8 hours in neonates.[39] Foscarnet 120 to 200 mg/kg per day divided every 8 to 12 hours for 2 to 3 weeks is the treatment of choice for acyclovir-resistant HSV isolates.[40]

Adjunctive Dexamethasone Therapy

❽ *The adjunctive agent dexamethasone has been shown to improve outcomes in selected patient populations with meningitis.* Dexamethasone inhibits the release of proinflammatory **cytokines** and limits the CNS inflammatory response stimulated by infection and antibiotic therapy.

Clinical benefit in reducing neurologic deficits (primarily by reducing hearing loss) has been observed in infants and children with *H. influenzae* meningitis, as well as other pathogens causing meningitis, if dexamethasone is initiated prior to antibiotic therapy.[1,13] The American Academy of Pediatrics recommends dexamethasone (0.15 mg/kg intravenously every 6 hours for 2 to 4 days) for infants and children at least 6 weeks of age with Hib meningitis and consideration of dexamethasone in pneumococcal meningitis.[13,41] Dexamethasone should be initiated 10 to 20 minutes before or no later than the time of initiation of antibiotic therapy; it is not recommended for infants and children who have already received antibiotic therapy because it is unlikely to improve treatment outcome in these patients. There are insufficient data to make a recommendation regarding the use of adjunctive dexamethasone therapy in neonatal meningitis.

In adults, a significant benefit was observed with dexamethasone over placebo in reducing meningitis complications, including death, particularly in patients with pneumococcal meningitis.[42] The IDSA recommends dexamethasone 0.15 mg/kg intravenously every 6 hours for 2 to 4 days (with the first dose administered 10 to 20 minutes before or with the first dose of antibiotics) in adults with suspected or proven pneumococcal meningitis.[13] Dexamethasone is not recommended for adults who have already received antibiotic therapy. Some clinicians would administer dexamethasone to all adults with meningitis pending results of laboratory tests.

There is concern regarding administration of dexamethasone to patients with pneumococcal meningitis caused by penicillin- or cephalosporin-resistant strains, for which vancomycin would be required. Animal models indicate that concurrent steroid use reduces vancomycin penetration into the CSF by 42% to 77% and delays CSF sterilization due to reduction in the inflammatory response.[23] Treatment failures have been reported in adults with resistant pneumococcal meningitis who were treated with dexamethasone, but the risk-benefit of using dexamethasone in these patients cannot be defined at this time. Animal models indicate a benefit of adding rifampin in patients with resistant pneumococcal meningitis whenever dexamethasone is used.[21,23]

OUTCOME EVALUATION

Monitor patients with CNS infections continuously throughout their treatment course to evaluate their progress toward achieving treatment goals, including relief of symptoms, eradication of infection, and reduction of inflammation to prevent death and the development of neurologic deficits. These treatment goals are best achieved by appropriate parenteral antimicrobial therapy, including empirical therapy to cover the most likely pathogens, followed by directed therapy after culture and sensitivity results are known. ❿ *Components of a monitoring plan to assess efficacy and safety of antimicrobial therapy of CNS infections include clinical signs and symptoms and laboratory data (such as CSF findings, culture, and sensitivity data).*

During the patient's treatment course, monitor clinical signs and symptoms at least three times daily. Trends are more important than one-time assessments. Expect fever, headache, nausea and vomiting, and malaise to begin to improve within 24 to 48 hours of initiation of antimicrobial therapy and supportive care. Evaluate the patient for resolution of neurologic signs and symptoms, such as altered mental status and nuchal rigidity, as the infection is eradicated and inflammation is reduced within the CNS. Expect improvement and subsequent resolution of signs and symptoms as the treatment course continues. At the time of hospital discharge, arrange outpatient follow-up for several weeks to months depending on the causative pathogen, clinical treatment course, and patient's underlying comorbidities. Specifically evaluate patients for the presence of residual neurologic deficits.

Monitoring of laboratory tests is important in patients receiving treatment for CNS infections. Monitor CSF and blood cultures so that antimicrobial therapy can be tailored to the etiologic organisms. Follow-up cultures may be obtained to prove

eradication of the organism(s) or treatment failure. Although repeat LP generally is not performed, consider repeat LP for patients who do not respond clinically after 48 hours of appropriate antimicrobial therapy, especially those with resistant pneumococcus who receive dexamethasone.[13] Other candidates for repeat LP include the following: those with infection with gram-negative bacilli, prolonged fever, and recurrent meningitis. Repeat the LP in neonates to determine the duration of therapy. Repeat LP also may be performed to relieve elevated intracranial pressure. Expect repeat blood cultures to become negative quickly during therapy and the serum WBC count to improve and normalize with appropriate antimicrobial therapy.

Evaluate antimicrobial dosing regimens to ensure efficacy of the treatment regimen. Trough vancomycin concentrations of 15 to 20 mg/L are recommended for the treatment of CNS infections.[13] Monitor patients for drug adverse effects, drug allergies, and drug interactions. The specific safety monitoring plan will depend on the antibiotic(s) used (Table 67–3). Play close attention to concomitant medications in patients on rifampin for treatment or prophylaxis. Rifampin is a potent inducer of hepatic metabolism and may reduce the efficacy of other drugs metabolized by the cytochrome P-450 3A enzyme pathway.



Patient Encounter

JD is a 17-year-old high school senior who visited her sister at her college dormitory for 1 week prior to her sister leaving for winter break. JD now presents to the emergency department with a 2-day history of headache and fever. Physical findings and laboratory values include temperature of 38.3°C (101°F) and WBC count of 14,400/mm^3 (14.4 × 10^9/L), with 90% PMNs. Examination reveals nuchal rigidity and a petechial truncal rash. JD reports light sensitivity and nausea with vomiting. She has tried over-the-counter analgesics and antipyretics with no relief from her headache or fever.

- What signs and symptoms consistent with meningitis are present in JD?
- What clues to causative pathogen are present in JD?
- What is the empirical regimen of choice for JD?
- How are laboratory data (including culture & sensitivity data) used to refine empirical antibiotic regimen?
- Which drugs are recommended for prophylaxis of close contacts of patients with meningitis?



Patient Care and Monitoring

1. Assess the patient's signs, symptoms, and risk factors for meningitis. Do these offer any clues to the offending pathogen?
2. Determine if the patient can undergo an immediate LP or if the LP should be delayed until a CNS mass lesion can be ruled out. If the LP is delayed, blood cultures should be drawn and appropriate empirical antimicrobial therapy initiated immediately.
3. Based on patient-specific data, local resistance patterns, and other relevant data, design an appropriate empirical antimicrobial regimen directed at the most likely pathogens; empirical regimens should consist of high-dose intravenous cidal therapy.
4. Determine if adjunctive dexamethasone therapy is indicated; if so, start steroid therapy 15 to 20 minutes before the first dose of antimicrobial therapy.
5. Provide supportive care for patients with CNS infections, including hydration, electrolyte replacement, antipyretics, analgesics, and antiepileptic drugs.
6. Monitor culture and sensitivity data from the microbiology laboratory to determine whether any refinements are needed in the patient's treatment regimen. Design a therapeutic plan to finish out the patient's course of therapy for acute meningitis.
7. Monitor the patient's response to therapy (i.e., clinical signs/symptoms and laboratory data), as well as the development of complications, including seizures and hearing loss. Dexamethasone therapy may reduce antibiotic penetration, so antimicrobial drug dosing may have to be increased (especially vancomycin) to achieve adequate CSF levels. Serum levels of vancomycin should be measured and doses titrated to ensure adequate CNS concentrations. Evaluate whether intraventricular or intrathecal antibiotics are indicated.
8. Perform ongoing surveillance for adverse drug reactions, drug allergies, and drug interactions.
9. Determine whether prophylaxis is indicated for close contacts of patients with CNS infections. Close contacts should be located for patients with suspected meningococcal or Hib meningitis. After consultation with the local health department, antibiotic prophylaxis should be provided promptly to these individuals to avoid secondary disease.
10. Evaluate whether the patient is a candidate for finishing out his or her course of parenteral treatment on an outpatient basis. If so, the importance of close medical follow-up and medication compliance should be stressed to the patient and his or her family.
11. Consider how to minimize the patient's risk of contracting the current (and other) CNS infections in the future; administer appropriate vaccines after recovery from the acute infection.
12. Arrange for patient follow-up after discharge from the hospital. Continue to monitor for neurologic sequelae for several months after completion of treatment, and educate the patient and family in this regard. Serious complications that may occur include, among others, hearing loss, **hemiparesis,** quadriparesis, muscular hypertonia, ataxia, seizure disorders, mental retardation, learning disabilities, and obstructive hydrocephalus.

ABBREVIATIONS

AIDS: acquired immune deficiency syndrome
CDC: Centers for Disease Control and Prevention
CLSI: Clinical and Laboratory Standards Institute
CNS: central nervous system
CSF: cerebrospinal fluid
CT: computed tomography
DIC: disseminated intravascular coagulation
FDA: Food and Drug Administration
Hib: *Haemophilus influenzae* type B
HIV: Human Immunodeficiency Virus
HSV: Herpes Simplex Virus
IDSA: Infectious Diseases Society of America
IL-2: interleukin 2
LP: lumbar puncture
MBC: minimum bactericidal concentration
MIC: minimum inhibitory concentration
MRI magnetic resonance imaging
MRSA: methicillin-resistant *Staphylococcus aureus*
MRSE: Methicillin *Staphylococcus epidermidis*
PCR: polymerase chain reaction
PMN: polymorphonuclear cell
TNF-α: tumor necrosis factor α
WBC: white blood cell

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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68 Lower Respiratory Tract Infections

Diane M. Cappelletty



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. List the common pathogens that cause community-acquired pneumonia, aspiration pneumonia, ventilator-associated pneumonia (early versus late onset), and health care–associated pneumonia.
2. Explain the host defenses that protect against infection.
3. Explain the pathophysiology of pneumonia.
4. Recognize the signs and symptoms associated with community-acquired pneumonia and ventilator-associated pneumonia.
5. Identify patient and organism factors required to guide the selection of a specific antimicrobial regimen for an individual patient.
6. Design an appropriate empirical antimicrobial regimen based on patient-specific data for an individual with community-acquired pneumonia, aspiration pneumonia, and ventilator-associated pneumonia or health care–associated pneumonia (early versus late onset).
7. Design an appropriate antimicrobial regimen based on both patient- and organism-specific data.
8. Develop a monitoring plan based on patient-specific information for a patient with community-acquired pneumonia and health care– or ventilator-associated pneumonia.
9. Formulate appropriate educational information to be provided to a patient with pneumonia.

Key Concept

❶ There are five classifications of pneumonia: community-acquired, aspiration, hospital-acquired, ventilator-associated, and health care–associated.
❷ The etiology of bacterial pneumonia varies in accordance with the type of pneumonia.
❸ *Streptococcus pneumoniae* is the most common bacterial pathogen associated with community-acquired pneumonia.
❹ The signs and symptoms and severity of pneumonia are needed not only to diagnose the patient but also to assess response to therapy.
❺ The goal of therapy is to eliminate the patient's symptoms, minimize or prevent complications, and decrease mortality.
❻ Treatment of community-acquired pneumonia is predominantly empirical.
❼ Empirical selection of antimicrobial therapy for ventilator-associated, health care–associated, and hospital-associated pneumonia is broad spectrum; however, once culture and susceptibility information are available, the therapy should be narrowed (deescalation) to cover the identified pathogen(s).
❽ Duration of therapy should be kept to the shortest amount of time possible.
❾ Monitoring response to therapy is essential for determining efficacy, identifying adverse reactions, and determining the duration of therapy.
❿ Prevention of pneumococcal disease through the use of vaccination is a national goal.

Pneumonia is inflammation of the lung with consolidation. The cause of the inflammation is infection, which can result from a wide range of organisms. ❶ *There are five classifications of pneumonia: community-acquired, aspiration, hospital-acquired, ventilator-associated, and health care–associated.* Patients who develop pneumonia in the outpatient setting and have not been in any health care facilities, which include wound care and hemodialysis clinics, have *community-acquired pneumonia* (CAP). *Aspiration* is of either oropharyngeal or gastrointestinal contents. *Hospital-acquired pneumonia* (HAP) is defined as pneumonia that occurs 48 hours or more after admission.[1,2] *Ventilator-associated pneumonia* (VAP) requires endotracheal intubation for at least 48 to 72 hours before the onset of

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pneumonia.[2,3] The newest category is *health care–associated pneumonia* (HCAP), which is defined as pneumonia occurring in any patient hospitalized for at least 2 days within 90 days of the onset of the infection; residing in a nursing home or long-term care facility; having received intravenous antibiotic therapy, wound care, or chemotherapy within the last 30 days of the onset of the infection; or having attended a hemodialysis clinic.[2,4,5]

EPIDEMIOLOGY AND ETIOLOGY

Etiology and Mortality Rates

❷ *The etiology of bacterial pneumonia varies in accordance with the type of pneumonia.* Table 68–1 lists the more common bacterial pathogens associated with the various types or classifications of pneumonia. *Streptococcus pneumoniae* is a component of the nasopharyngeal flora in up to 50% of healthy adults and may colonize the lower airways in individuals with chronic bronchitis.[6,7] It possesses many virulence factors that enhance its ability to cause infection in the respiratory tract. ❸ Therefore, *it is not surprising that S. pneumoniae is the predominant bacterial pathogen associated with CAP.* The second most common pathogen is one of the atypical organisms, *Mycoplasma pneumoniae*. Colonization with nontypeable *Hemophilus influenzae* comes and goes in about 80% of the population, and the incidence of permanent colonization increases in chronic obstructive pulmonary disease (COPD) patients and those with cystic fibrosis. Therefore, the likelihood of nontypeable *H. influenzae* causing pneumonia increases in COPD patients. *Moraxella catarrhalis* is a more common cause of pneumonia in the very young and the very old. *Chlamydia pneumoniae* and *Legionella pneumophila* are less frequent causes than the other bacterial and atypical organisms.

Viruses are a common cause of CAP in children (~65%) and much less common in adults (~15%).[8] Viruses often associated with pneumonia in adults include influenza A and B and adenoviruses, whereas less common causes include rhinoviruses, enteroviruses, cytomegalovirus, varicella-zoster virus, herpes simplex virus, and others. In children, viral pneumonia is caused more commonly by respiratory syncytial virus, influenza A virus, and parainfluenza virus. The viruses associated with CAP in adults are much less common causes of pneumonia in children.

Mortality associated with CAP depends on the severity of the illness and the age of the patient. In elderly patients admitted to the hospital with severe pneumonia, the mortality rate is up to 40%.[9–12] In the outpatient setting (mild to moderate disease), the mortality rate is less than 5%.[13]

Pneumonia owing to aspiration of oral contents is caused by a variety of anaerobes (*Bacteroides* spp., *Fusobacterium* spp., *Prevotella* spp., and anaerobic gram-positive cocci), as well as *Streptococcus* spp. *M. catarrhalis* and *Eikenella corrodens* may be involved, but much less frequently.[14,15] When gastric contents are aspirated, then enteric gram-negative bacilli and *Staphylococcus aureus* are more commonly the pathogens.[15]

HAP, VAP, and HCAP may be caused by a wide spectrum of organisms such as those listed earlier for CAP or enteric gram-negative bacilli, *Pseudomonas aeruginosa, Acinetobacter* spp., or *S. aureus* (both methicillin-susceptible and methicillin-resistant). Rarely are viruses or fungi a cause of these institution-associated pneumonias. The number of infections caused by multidrug-resistant bacteria is increasing significantly in hospitalized patients.[16–21]

TABLE 68–1. Common Bacterial Pathogens by Type of Pneumonia

Type of Pneumonia	Common Bacterial Pathogens
Community	Typical: *S. pneumoniae, H. influenzae, M. catarrhalis* Atypical: *M. pneumoniae, C. pneumoniae, Legionella pneumophila*
Aspiration	Oral contents: Anaerobes, *viridans* streptococci Gastrointestinal contents with pH increase: Enteric gram-negative bacilli
Hospital	(Early onset no risk factors for resistant pathogens)
Ventilator	*S. pneumoniae,* MSSA, *E. coli, K. pneumoniae, M. pneumoniae,*
Health care	*C. pneumoniae*
Hospital	(Late onset and/or risk factors for resistant
Ventilator	pathogens)
Health care	MRSA, extended-spectrum β-lactamase-producing *K. pneumoniae, P. aeruginosa, Acinetobacter* spp.

PATHOPHYSIOLOGY

Local Host Defenses

Local host defenses of both the upper and lower respiratory tract, along with the anatomy of the airways, are important in preventing infection. Upper respiratory defenses include the mucociliary apparatus of the nasopharynx, nasal hair, normal bacterial flora, IgA antibodies, and complement. Local host defenses of the lower respiratory tract include cough, mucociliary apparatus of the trachea and bronchi, antibodies (IgA, IgM, and IgG), complement, and alveolar macrophages. Mucus lines the cells of the respiratory tract, forming a protective barrier for the cells. This minimizes the ability of organisms to attach to the cells and initiate the infectious process. The squamous epithelial cells of the upper respiratory tract are not ciliated, but those of the columnar epithelium of the lower tract are. The cilia beat in a uniform fashion upward, moving particles up and out of the lower respiratory tract.

Particles larger than 10 microns are trapped efficiently by mechanisms of the upper airway and are removed from the nasopharynx either by swallowing or by expulsion. The mucociliary apparatus of the trachea and bronchi, along with the sharp angles of the bronchi, often are effective at trapping and eliminating particles that are 2 to 10 microns in size. Particles in the range of 0.5 to 1 micron may consistently reach the alveolar sacs of the lung. Microorganisms fall within this size range, and if they reach the alveolar sacs, then infection may result if alveolar macrophages and other defenses cannot contain the organisms.

Aspiration

Aspiration of the oropharyngeal or gastric contents may lead to aspiration pneumonia or chemical (acid) pneumonitis. Risk factors for aspiration include

- Dysphagia
- Change in oropharyngeal colonization
- Gastroesophageal reflux
- Decreased host defenses

Dysphagia can be caused by stroke or other neurologic disorders, seizures, alcoholism, and aging.[14] Oropharyngeal colonization may be altered by oral/dental disease, poor oral hygiene, tube feedings, or medications. This could result in a higher number of anaerobic organisms in the oral cavity or colonization with enteric gram-negative bacilli.[14] Gastroesophageal reflux (GER) occurs in all individuals to a degree, but those with GER disease (GERD) have it more frequently. Acid suppression is an important factor in the treatment of GERD, which may allow enteric gram-negative bacilli to colonize the gastric contents. Finally, impaired mucus production or cilia function, decreased immunoglobulin in secretions, and altered cough reflex may increase the likelihood of infection following aspiration. The infection can result in a necrotizing pneumonia or lung abscess.

HAP, VAP, HCAP

Risk factors for the development of HAP fall into four general categories:

- Intubation and mechanical ventilation
- Aspiration
- Oropharyngeal colonization
- Hyperglycemia

Intubation and mechanical ventilation increase the risk of HAP/VAP 6- to 21-fold.[2,22] VAP also may be related to colonization of the ventilator circuit.[23] Risk of aspiration is increased in these patients owing to the supine positioning of the patient, the presence of the endotracheal tube preventing closure of the epiglottis over the glottis, enteral feedings, gastroesophageal reflux, and medications.[23] Oropharyngeal colonization is affected by the use of antibiotics, oral antiseptics, and poor infection-control measures, which may decrease normal commensal flora and allow pathogenic organisms to colonize the oral cavity. Hyperglycemia may promote infection directly or indirectly; two proposed mechanisms are inhibiting phagocytosis and providing additional nutrients for bacteria.

Once breakdown of the local host defenses occurs and organisms invade the lung tissue, an inflammatory response in generated either by the organisms causing tissue damage or by the immune response to the presence of the organisms. This inflammatory response either can remain localized in the infected tissue or can become systemic. The role of the alveolar macrophages is twofold. First is to engulf the organisms



Patient Encounter 1, Part 1

A 73-year-old woman presents to your clinic complaining of difficulty breathing and shortness of breath. Her physical examination reveals that she is alert and oriented × 3, has decreased breath sounds on the left side compared with the right, and has rales in the left lower lobe. Her temperature is 37.4ºC, respiratory rate is 20 breaths per minute, and blood pressure is 110/76 mm Hg.

- What are her signs and symptoms of pneumonia?
- What are the top two organisms that could be causing the pneumonia?
- What additional information do you need to know before creating a treatment plan for this patient?



Patient Encounter 2, Part 1

A 52-year-old man was admitted to the hospital for abdominal surgery. He developed complications postoperatively and was intubated 6 days ago. The nurses note an increase in the amount and purulence of his sputum. Attempts yesterday and today to wean the patient off the ventilator have failed. He is sedated but does respond to commands. His temperature is 38.4ºC, his blood pressure is 120/84 mm Hg, and his white blood cell (WBC) count is 14.2/mm^3 with a cell differential of 76% neutrophils, 4% bands, 16% lymphocytes, and 4% monocytes.

- What are his signs and symptoms of pneumonia?
- What are the top three organisms that could be causing the pneumonia?
- What additional information do you need to know before creating a treatment plan for this patient?

and contain the infection. Second is to process the antigens for presentation in order to generate a specific immune response by either the cell-mediated system or the humoral system or both. The macrophages release cytokines in the area of the infection, which results in an increase in mucus production, constriction of the local vasculature and lymphatic vessels, and attraction of other immune cells to the site. The increase in mucus is associated with symptoms such as cough and sputum production. If tumor necrosis factor α (TNF-α) and interleukins 1 (IL-1), and IL-6 are released systemically, then the symptoms become more severe and include hypotension, organ dysfunction, and/or a septic or septic-shock clinical presentation.

CLINICAL PRESENTATION AND DIAGNOSIS

Several scoring systems are available for assessing the severity of the pneumonia: the Pneumonia Severity Index (PSI), Confusion, Urea, Respiratory Rate, and Blood Pressure (CURB), and CURB-65 (those 65 years and older).[9,24] Some of the characteristics evaluated with these models include but are not limited to age, comorbidities, blood pressure, mental status, respiratory rate, and organ function. These models are used by physicians to help determine the severity of illness, prognosis (mortality risk), and need for hospitalization and then to help guide the selection of antimicrobial therapy along with the use of published guidelines.[9,13,24]

TREATMENT

Desired Outcomes

❺ *The goal of antibiotic therapy is to eliminate the patient's symptoms, minimize or prevent complications, and decrease mortality*. Potential complications secondary to pneumonia include further decline in pulmonary function in patients with underlying pulmonary disease, prolonged mechanical ventilation, bacteremia/sepsis/septic shock, and death. In addition, using an agent with the narrowest spectrum of activity that covers the suspected pathogen without having activity against organisms not involved in the infection is preferred. This is to minimize the development of resistance.



Presentation of Community-Acquired or Aspiration Pneumonia

General

Patients may experience nonrespiratory symptoms in addition to respiratory symptoms. With increasing age, both respiratory and nonrespiratory symptoms decrease in frequency.

❹ Symptoms

- Respiratory: cough (productive or nonproductive), shortness of breath, difficulty breathing
- Nonrespiratory: fever, fatigue, sweats, headache, myalgias, mental status changes

❹ Signs

- Temperature may increase or decrease from baseline, but most often it is elevated. The temperature may be sustained or intermittent.
- Respiratory rate is often increased. Cyanosis, increased respiratory rate, and use of accessory muscles of respiration are suggestive of severe respiratory compromise.
- Breath sounds may be diminished. Rales or rhonci may be heard.
- Confusion, lethargy, and disorientation are relatively common in elderly patients.

Diagnostic Tests

- Chest x-ray should reveal single or multiple infiltrates.
- Oxygen saturation should be over 90%, as determined by pulse oximetery.
- Arterial blood gases are beneficial primarily in patients with severe pneumonia.

Laboratory Tests

- The WBC count may or may not be elevated. In elderly patients, a drop in WBCs also can be a sign of infection. The differential should show a predominance of neutrophils if a bacterial infection is present. The presence of bands also could be an indicator of bacterial infection. Elevated lymphocytes are an indication of viral infection.
- Blood urea nitrogen (BUN) and serum creatinine are needed to dose antibiotics appropriately and to minimize or prevent drug toxicity (especially in the elderly patient).

Microbiology Tests

- Sputum Gram stain should demonstrate the presence of WBCs and the absence of squamous epithelial cells. It may or may not show a predominance of one type of organism.
- Sputum culture and susceptibility are not obtained in the outpatient setting. The value of culturing is debated owing to the rapidity in which *S. pneumoniae* dies in transport media and the inability to reliably or routinely culture atypical organisms.
- **Bronchoscopy** may be performed to improve the ability to diagnose pneumonia. Tracheal secretions often are better specimens than sputum owing to the lack of oral contamination.
- Serology (IgM and IgG) is useful in determining the presence of atypical organisms such as *Mycoplasma* and *Chlamydia*.
- Urinary direct fluorescence antigen (DFA) is used to diagnose *L. pneumophila*.
- Polymerase chain reaction (PCR) is being used more frequently to detect the DNA of respiratory pathogens.
- Blood cultures must be obtained in all patients hospitalized with pneumonia to comply with Joint Commission on Accreditation of Healthcare Organizations (JCAHO) pneumonia guidelines. Positive blood cultures are present in about 1% to 20% of patients with CAP.



Presentation of Severe Community-Acquired or Aspiration Pneumonia

General

In approximately 10% of patients, community-acquired pneumonia will be severe enough to require intensive care or mechanical ventilation.

❹ Symptoms

- Respiratory: cough (productive or nonproductive), shortness of breath, difficulty breathing
- Nonrespiratory: fever, fatigue, sweats, headache, myalgias, mental status changes

❹ Signs

- Temperature may increase or decrease from baseline, but most often it is elevated. The temperature may be sustained or intermittent.
- Respiratory rate greater than 30 breaths per minute. Cyanosis and use of accessory muscles of respiration along with the increased respiratory rate are suggestive of severe respiratory compromise.
- Hypotension (systolic blood pressure less than 90 mm Hg or diastolic blood pressure less than 60 mm Hg)
- Requirement for vasopressors
- Breath sounds may be diminished. Rales or rhonci may be heard.
- Urine output less than 20 mL/hour or less than 80 mL over 4 hours.
- Confusion, lethargy, and disorientation are relatively common in elderly patients.

Diagnostic Tests

As stated in the clinical presentation of community-acquired or aspiration pneumonia.

Laboratory Tests

As stated in the clinical presentation of community-acquired or aspiration pneumonia.

Microbiology Tests

As stated in the clinical presentation of community-acquired or aspiration pneumonia.

General Approach to Treatment

Designing a therapeutic regimen for any patient with any type of pneumonia begins with three general categories of consideration:

1. Patient-specific factors that will affect therapy
2. The top one to three organisms likely causing the infection and resistance issues associated with each organism
3. What antimicrobials will cover these organisms and not be too broad or narrow in spectrum, will penetrate into the site of infection, and what they cost

Patient factors that need to be considered include age, renal function, drug allergies and/or drug intolerances, immune status (e.g., diabetes, neutropenia, or immunocompromised host), cardiopulmonary disease, pregnancy, medical insurance and prescription coverage, and prior antibiotic exposure(s) (what agents and when).

The most common pathogens vary with the type of pneumonia, and they are listed in Table 68–1. *M. pneumoniae* lacks a cell wall; therefore, β-lactam drugs have no activity against



Diagnosis of Ventilator-Associated Pneumonia

Clinical Strategy

- Chest x-ray should reveal a new infiltrate *plus* two of the following:
  - Temperature greater than 38ºC
  - Leukocytosis or leukopenia
  - Purulent secretions
- Semiquantitative cultures are obtained to identify the pathogen(s).
  - **Tracheal aspirates** grow more organisms than invasive quantitative cultures and often result in overuse of antibiotics.
- The major limitation of the clinical strategy is the consistent overprescribing of antibiotics.

Bacteriologic Strategy

- Uses quantitative culture of endotracheal aspirates, **bronchoalveolar lavage** (BAL), or **protected specimen brush** (PSB).
  - Greater than or equal to 10^6 cfu/mL for endotracheal aspirates
  - Greater than or equal to 10^4 to 10^5 cfu/mL for BAL
  - Greater than or equal to 10^3 cfu/mL for PSB
- The advantage of this method is that it separates colonization from infection better than culturing tracheal aspirates.
- The limitation is the potential misinterpretation of negative culture results. These samples should be obtained prior to antibiotics being started.

Recommended Diagnostic Strategy

- Combination of the preceding two methods.
- Obtain either a quantitative or semiquantitative culture of a lower respiratory sample. Initiate empirical broad-spectrum antibiotic therapy.
- Days 2 and 3: Check culture results, and assess clinical response to therapy: temperature, WBCs, chest x-ray, oxygenation, purulent sputum, hemodynamic changes, and organ function.
- Assess clinical improvement at 48 to 72 hours:
  - Improvement and culture negative—stop antibiotics.
  - Improvement and culture positive—narrow antibiotic therapy.
  - No improvement and culture negative—consider other pathogens, complications, or other diagnosis.
  - No improvement and culture positive—change antibiotic therapy and consider other pathogens, complications, or other diagnosis.



Patient Encounter 1, Part 2: Medical History, Physical Examination, and Diagnostic Tests

The 73-year-old woman presents again to your clinic complaining of difficulty breathing and shortness of breath. Her daughter also states that she is easily confused and that this is not normal for her.

PMH
- Chronic obstructive pulmonary disease (COPD) for 15 years
- Hypertension for 4 years, currently controlled

FH
Father died of lung cancer at the age of 68 years; mother died of natural causes.

SH
Smoked 2 packs per day for 23 years, quit 15 years ago. Does not drink alcohol. She lives with her daughter.

Allergies: NKDA

Meds
- Lisinopril 10 mg PO qd
- Ipratropium bromide 4 puffs 4 times per day
- Flunisolide 3 puffs 2 times per day
- Albuterol 2 puffs prn

ROS
(+) difficulty breathing and shortness of breath; (–) chest pain, N/V/D, weight loss, change in appetite.

PE
- **VS:** BP 110/76, P 82, RR 22, T 37.4°C
- **CV:** RRR, normal S_1, S_2; no murmurs, rubs, or gallops
- **Lungs:** Decreased breath sounds on the left side compared with the right and rales in the left lower lobe
- **Abd:** Soft, nontender, nondistended; (+) bowel sounds, no hepatosplenomegaly, heme (–) stool
- **Neuro:** Oriented to name and place but not to date. She is easily confused by questions asked of her.

Diagnostic Tests
- Chest x-ray: left lower lobe infiltrates
- Oxygen saturation 92% on room air

Labs
Unavailable in the clinic.

- Given this additional information, what is your assessment of the patient's condition?
- Identify your treatment goals for the patient.



Patient Encounter 2, Part 2: Medical History, Physical Examination, and Diagnostic Tests

The 52-year-old man who developed complications after abdominal surgery was intubated 6 days ago. The nurses note an increase in the amount and the purulence of his sputum. Attempts yesterday and today to wean the patient off the ventilator have failed. He is sedated, but he does respond to commands.

PMH
- Small bowel obstruction, surgery 8 days ago
- Hypertension for 15 years, currently controlled

FH
Father died of acute MI at the age of 68 years; mother, age 72, years is alive, with hypertension and hypothyroid

SH
No tobacco use; drinks 2 beers per night. He lives with his wife; occupation—carpenter.

Allergies: Penicillin—hives

Meds
Lisinopril 40 mg PO qd

PE
- **VS:** BP 120/84, P 78, T 38.4°C
- **CV:** RRR, normal S_1, S_2; no murmurs, rubs, or gallops
- **Abd:** Soft, nontender, nondistended; (+) bowel sounds, no hepatosplenomegaly, incision looks good and is healing.

Diagnostic Tests
- Chest x-ray: left middle and lower lobe infiltrates
- Oxygen saturation 98% on ventilator

Labs
- WBCs 18.2 cells/mm^3 with a cell differential of 72% neutrophils, 8% bands, 16% lymphocytes, and 4% monocytes
- BUN 10 mg/dL (3.57 mmol/L), SCr 0.9 mg/dL (79.56 µmol/L)
- Sputum Gram stain: many gram-negative bacilli, many WBCs
- Sputum culture is pending.

- Given this additional information, what is your assessment of the patient's condition?
- Identify your treatment goals for the patient.

this organism. The atypical organisms have not changed in recent years with respect to antibiotic resistance. β-Lactamase production in *H. influenzae* has remained relatively steady over the last 5 to 10 years, and the rate is approximately 35%.[25] *S. pneumoniae* is developing resistance mechanisms against many classes of antimicrobials, and these mechanisms include

- Alteration of the penicillin-binding proteins (PBPs) inactivating β-lactams
- Efflux or methylation of the ribosome inactivating macrolides
- Ribosome protection (*tetM* gene) inactivating tetracyclines
- Alteration of DNA gyrase or topoisomerase IV inactivating fluoroquinolones

Resistance to commonly prescribed antimicrobials such as the penicillins and macrolides/azalides increased dramatically in the late 1980s through the middle to late 1990s. Table 68–2 provides resistance information collected nationally from 1999 to 2004 using the Tracking Resistance in the US Today (TRUST) surveillance database.[26] In 2004, the average national rate of resistance to penicillin and macrolides was approximately 18% and 25%, respectively. Susceptibility results alone do not account for clinical success or failures when treating pneumonia.

TABLE 68–2. Percentage of Resistance for Various Antimicrobials Against S. pneumoniae

Antimicrobial	1999	2000	2001	2002[a]	2003	2004
Penicillin	14.7	16.0	16.9	18.4	17.3	18.6
Azithromycin	22.7	23.4	27.5	27.5	27.5	25.0
Ceftriaxone[a]	3.4	3.8	3.0	1.7	1.5	1.4
Levofloxacin	0.6	0.5	0.8	0.9	0.9	1.1
Trimeth-sulfa	NA	NA	NA	26.1	23.9	21.2
Tetracycline	NA	NA	NA	NA	NA	13.5

[a]Separation of ceftriaxone into nonmeningitis interpretation versus meningitis. Numbers presented are nonmeningitis.
NA, not available.

Therefore, despite the 18% and 25% resistance to penicillin and macrolides, the clinical failure rate is less than this. Owing to the empirical treatment of CAP in the outpatient setting, establishing a meaningful clinical failure rate with any therapy is difficult to do. No studies have been performed that established a correlation between clinical failure rates with a particular antimicrobial agent and the percentage of resistant bacterial pathogens.

For HCAP, HAP, and VAP, the risk of infection from a multidrug-resistant (MDR) pathogen is relatively high. The number and type of organisms that are MDR vary from hospital to hospital, making it more difficult to generate guidelines for treatment. Therefore, the treatment recommendations may be too broad or too narrow for any given institution. Treating patients with HCAP, HAP, or VAP is more complex than treating patients with CAP. There are many factors to consider, and one of these relates the timing of infection to the most likely pathogens. Early-onset infection is less likely to be caused by MDR pathogens than late-onset infection. In early-onset infection, community pathogens such as pneumococcus, *Legionella*, and *Mycoplasma* need to be considered, as well as some of the hospital pathogens. Patients developing late-onset pneumonia are at increased risk of having a resistant pathogen or MDR pathogen such as staphylococci, enteric gram-negative bacilli, *Pseudomonas*, and *Acinetobacter*. Another issue is how HCAP and HAP are studied compared with VAP. Most of the studies were performed using patients who were intubated. Therefore, the body of literature supporting the treatment recommendations is greatest for VAP and not for HCAP or HAP. The evidence-based guidelines generated by the American Thoracic Society were derived from VAP and applied to HCAP and HAP.

Risk factors for developing an infection caused by a resistant pathogen generally are related to the prior use of antibiotics, insertion of catheters or other invasive devices, and hospitalization in a unit contaminated/colonized with resistant organisms. The following is a more complete list of factors influencing infection from a resistant organism:

- Antimicrobial therapy in preceding 90 days
- Current hospitalization of at least 5 days
- High occurrence of antibiotic resistance in the community or in the specific hospital unit
- Presence of risk factors for HCAP:
  - Hospitalization for 2 days or more in the preceding 90 days
  - Residence in a nursing home or extended-care facility
  - Home infusion therapy (including antibiotics)
  - Peritoneal or hemodialysis within 30 days
  - Home wound care
  - Close contact family member with MDR pathogen
- Immunosuppressive disease and/or therapy

Once these issues are addressed, antimicrobial therapy can be selected and initiated. The patient- and drug-related categories are common to all types of pneumonia, but the organisms vary with the type of pneumonia. Guidelines have been generated by experts in the field for all types of pneumonia. These guidelines were generated to provide practitioners with evidenced-based therapeutic options for the management of patients with pneumonia.

Pharmacologic Therapy for Community-Acquired Pneumonia (CAP)

❻ *Treatment of community-acquired pneumonia is predominantly empirical.* As a way of incorporating an evidence-based approach to antibiotic selection, several different organizations have generated guidelines for the treatment of bacterial or atypical CAP in adults. Two of the most commonly used or cited guidelines are from the Infectious Diseases Society of America (IDSA), and the American Thoracic Society (ATS).[27,28] These two guidelines are similar in their organization and slightly different with respect to recommended therapies. Both differentiate patients into two broad categories of outpatient and inpatient and then further divide the groups by comorbid conditions and location in the hospital, respectively. These guidelines use patient-specific data along with predominant pathogen information to design appropriate empirical antimicrobial regimens. Table 68–3 summarizes these therapeutic options. If influenza virus is the cause, supportive care is the best medical intervention available; antiviral agents against influenza are not very effective.

Adult Outpatient Previously Healthy

First-line therapeutic options for treating previously healthy adults include use of a macrolide (e.g., erythromycin or clarithromycin) or an azalide (e.g., azithromycin) or doxycycline or a respiratory fluoroquinolone (e.g., levofloxacin, gatifloxacin, or moxifloxacin).[27,28] The issue with using a respiratory fluoroquinolone as first-line therapy in these patients is the broad-spectrum activity of these agents beyond *S. pneumoniae, M. pneumoniae, C. pneumoniae,* and *H. influenzae,* which are the predominant pathogens associated with CAP. If a patient has failed therapy with a macrolide, azalide, or doxycycline, one has to consider why the patient failed. The most common reasons are either medication adherence issues or the presence of resistant organisms. If a resistant organism is suspected, then use of one of the respiratory fluoroquinolones is warranted.

TABLE 68–3. Summary of Community-Acquired Pneumonia Treatment

Adult outpatient otherwise healthy	***Monotherapy:***
Empirical coverage against *S. pneumoniae, M. pneumoniae, C. pneumoniae,* & *H. influenzae*	azithromycin, clarithromycin, erythromycin, doxycycline, telithromycin, gatifloxacin, levofloxacin, moxifloxacin
Adult outpatient comorbidities	***Combination therapy:***
Empirical coverage against *S. pneumoniae, M. pneumoniae, C. pneumoniae,* & *H. influenzae*	high-dose amoxicillin, high-dose amoxicillin-clavulanate, or cefpodoxime, or cefprozil, or cefuroxime *plus* azithromycin or clarithromycin or telithromycin
	Monotherapy:
	gatifloxacin, levofloxacin, moxifloxacin
Adult inpatient (non-ICU)	***Combination therapy:***
Empirical coverage against *S. pneumoniae, H. influenzae M. pneumoniae,* & *C. pneumoniae*	cefotaxime, or ceftriaxone, or ampicillin-sulbactam, or ertapenem *plus* azithromycin or clarithromycin or telithromycin
	Monotherapy:
	gatifloxacin, levofloxacin, moxifloxacin
Adult inpatient ICU (no Pseudomonas)	***Combination therapy:***
Empirical coverage against *S. pneumoniae, L. pneumophila, H. influenzae,* enteric GNB, & *S. aureus*	cefotaxime or ceftriaxone *plus* azithromycin, or clarithromycin or gatifloxacin, or levofloxacin, or moxifloxacin
Adult inpatient ICU (Pseudomonas is a concern)	***Combination therapy:***
Empirical coverage against *P. aeruginosa, S. pneumoniae, L. pneumophila, H. influenzae,* enteric GNB, & *S. aureus*	cefepime, or ceftazidime, or piperacillin-tazobactam, or imipenem, or meropenem *plus* or ciprofloxacin levofloxacin or an aminoglycoside
	If an aminoglycoside is chosen, then add azithromycin or levofloxacin or gatifloxacin or moxifloxacin.
Pediatric outpatient	***Monotherapy:***
Empirical coverage against *S. pneumoniae, M. pneumoniae,* & *C. pneumoniae*	high-dose amoxicillin, or high-dose amoxicillin-clavulanate, or intramuscular ceftriaxone, or azithromycin, or clarithromycin
Pediatric inpatient (non-ICU)	***Combination therapy:***
Empirical coverage against *S. pneumoniae, H. influenzae, M. pneumoniae,* & *C. pneumoniae*	intravenous cefuroxime, or cefotaxime, or ceftriaxone or ampicillin-sulbactam plus azithromycin, or clarithromycin
Pediatric inpatient ICU	***Combination therapy:***
Empirical coverage against *S. pneumoniae, L. pneumophila, H. influenzae,* enteric GNB, & *S. aureus*	cefotaxime, or ceftriaxone plus azithromycin, or clarithromycin

Adult Outpatient with Comorbid Conditions

The comorbid conditions that can affect therapy and outcomes in patients with CAP include diabetes mellitus, COPD, congestive heart failure, and renal failure.[27,28] If the patient has not received antibiotics in the past 3 months, then clarithromycin or azithromycin is the recommended first-line therapy by the IDSA. If the patient has received antibiotics in the last 3 months, then the IDSA recommends using either a respiratory fluoroquinolone alone or a combination of an oral β-lactam and an advanced macrolide/azalide (e.g., clarithromycin/azithromycin). The ATS recommends combination therapy or monotherapy with a respiratory fluoroquinolone for all patients with comorbidities. The β-lactam agents recommended include high-dose amoxicillin, high-dose amoxicillin-clavulanate, cefpodoxime, cefprozil, and cefuroxime.

Missing from the recommendations for treating any outpatient is telithromycin, which is a ketolide antibiotic. Telithromycin was approved after the guidelines were generated. Telithromycin is similar in spectrum of activity to clarithromycin and azithromycin in that it covers primarily the respiratory pathogens and not gram-negative bacilli. At present, it is maintaining activity against macrolide-resistant *S. pneumoniae*. It is approved for the treatment of mild to moderate CAP and is a viable option in the treatment of pneumonia in these patients.

Adult Inpatient Not in the ICU

In patients admitted to the hospital with CAP, the severity of illness generally is increased (caused either by the organism itself or by underlying comorbidities in the patient), and the pathogens are essentially the same as in the outpatient setting. Recommendations by both organizations include using either a respiratory fluoroquinolone alone or a combination of an intravenous β-lactam and either an advanced macrolide/azalide (e.g., clarithromycin/azithromycin) or doxycycline. The recommended β-lactams include cefotaxime, ceftriaxone, ampicillin-sulbactam, and ertapenem.[27,28] Therapy should be initiated within the 4 hours of presentation to the emergency room or hospital. Conversion to oral therapy should occur within 48 to 72 hours for most patients, and discharge from the hospital should be within 5 days if there are no complications.

Adult Inpatient in the ICU

Patients admitted to the intensive-care unit (ICU) have severe pneumonia, and the etiology includes *S. pneumoniae* and *H. influenzae* as in the other categories; however, the incidence of *Legionella pneumophila* increases in this setting and should be included in the organism differential. In addition, enteric gram-negative bacilli and *S. aureus* are more frequently the cause of the pneumonia. The recommendations are to treat with an

intravenous third-generation cephalosporin plus either clarithromycin or azithromycin or a respiratory fluoroquinolone. This combination therapy minimizes the risk of treatment failure owing to a resistant pathogen and also provides coverage against all the potential pathogens.[27,28]

If *P. aeruginosa* is suspected (e.g., patient comes from a long-term care facility or has had a recent hospitalization), then the antimicrobial treatment must include *P. aeruginosa* as well as the organisms listed earlier. Recommended regimens double-cover the *Pseudomonas* and include the use of an antipseudomonal β-lactam (e.g., cefepime, ceftazidime, piperacillin-tazobactam, imipenem, or meropenem) plus either ciprofloxacin/levofloxacin or an aminoglycoside. If an aminoglycoside is chosen, then either intravenous azithromycin or a respiratory fluoroquinolone should be added to cover *S. pneumoniae* and the atypical organisms.[27,28]

Influenza

Influenza viruses A and B can cause pneumonia in pediatric and adult patients. Amantidine and rimantidine are available oral agents with activity against influenza virus type A. If started within 48 hours of the onset of the first symptoms, they reduce the duration of the illness by about 1.3 days. Oseltamivir and zanamivir also are oral agents and are active against both type A and B viruses. These agents also reduce the duration of the illness by about 1.3 days if initiated within 40 to 48 hours of the first symptoms.[29] For active infection beyond the first 48 hours, none of these agents is effective in treating the infection, and supportive care is the best treatment for these patients.

Aspiration

If a patient aspirates his or her oral contents and pneumonia develops, then anaerobes and *Streptococcus* spp. are the primary pathogens. Antibiotics active against these organisms include penicillin G, ampicillin/sulbactam, clindamycin, and metronidazole.

Pediatric Outpatient

If viral pneumonia is diagnosed, then treatment is often supportive (i.e., maintaining hydration and administration of antipyretics) because we have very few effective antiviral agents. The bacterial pathogens are the same as for adults with *S. pneumoniae* as the predominant pathogen, then *M. pneumoniae*, and then the other organisms. Resistance issues with these organisms are similar to those seen in adult patients. Fluoroquinolones and tetracyclines should not be used in children. High-dose amoxicillin, amoxicillin-clavulanate, intramuscular ceftriaxone, azithromycin, and clarithromycin all are potential agents for use in children.

Pediatric Inpatient

If the child is not admitted to the ICU, then the CDC recommends the use of intravenous cefuroxime, cefotaxime, ceftriaxone, or ampicillin-sulbactam plus a macrolide or azalide. If the child is admitted to the ICU, then only the third-generation cephalosporins (e.g., cefotaxime and ceftriaxone) plus a macrolide or azalide should be administered.[30]



Patient Encounter 1, Part 3: Creating a Care Plan

Based on the information presented, create a care plan for this patient's pneumonia. Your plan should include (1) the goals of therapy, (2) a patient-specific detailed therapeutic plan, and (3) a plan for follow-up to determine whether the goals have been achieved and adverse effects avoided.

Pharmacologic Therapy for HCAP/HAP/VAP

Nosocomial pneumonia is the term used to describe patients who developed pneumonia in an institutional setting. This has since been replaced by the terms *health care–associated pneumonia, hospital-associated pneumonia,* and *ventilator-associated pneumonia.* ❼ *Empirical selection of antimicrobial therapy for ventilator-associated, health care–associated, and hospital-associated pneumonia is broad spectrum; however, once culture and susceptibility information are available, the therapy should be narrowed (deescalation) to cover the identified pathogen(s).* Two factors important to the empirical selection of antibiotics for these types of pneumonia are onset time after admission and risk factors for MDR organisms. If it is early onset (less than or equal to 5 days since admission) and there are no risk factors for MDR organisms, then the most frequent pathogens include *S. pneumoniae, H. influenzae*, MSSA, and enteric gram-negative bacilli. Recommendations for therapy include third-generation cephalosporins such as ceftriaxone or cefotaxime; a respiratory fluoroquinolone such as gatifloxacin, levofloxacin, or moxifloxacin; ampicillin-sulbactam, or ertapenem.[31] If it is late-onset pneumonia and/or there are risk factors for MDR organisms, then the pathogen list includes *P. aeruginosa*, extended-spectrum β-lactamase-producing *Klebsiella pneumoniae, Acinetobacter* spp., and MRSA. Empirical antibiotic selection must cover *P. aeruginosa*, which often then covers the other gram-negative pathogens. Available antibiotics include cefepime, ceftazidime, imipenem, meropenem, piperacillin- tazobactam, ticarcillin-clavulanate, levofloxacin, ciprofloxacin, gentamicin, tobramycin, and amikacin. Empirical therapy could include any of the β-lactams, carbapenems, or fluoroquinolones alone or in combination with one of the aminoglycosides. If MRSA is suspected, then either vancomycin or linezolid should be added to the empirical regimen.

Currently, there is debate over whether or not double coverage for *Pseudomonas* is required. In vitro studies have shown that aminoglycosides exhibit synergistic killing against gram-negative bacilli when combined with β-lactams. Dosing of the aminoglycosides depends on the patient's renal function.

TABLE 68–4. Empirical Therapy for Late-Onset HAP, HCAP, or VAP

Antibiotic	Dosage Based on Normal Renal and Hepatic Function
Cefepime	1 g IV q8hours or 2 g IV q12hours
Ceftazidime	2 g IV q8hours
Imipenem	500 mg IV q6hours or 1 g IV q8hours
Meropenem	1 g IV q8hours
Piperacillin-tazobactam	4.5 g IV q6hours or 3.375 g IV q4hours
Ticarcillin-clavulanate	3.1 g IV q6hours
Levofloxacin	750 mg IV/PO q24hours
Ciprofloxacin	400 mg IV q8hours or 750 mg PO q8hours
Gentamicin or Tobramcyin[a]	5–7 mg/kg IV q24hours
Amikacin[a]	20 mg/kg IV q24hours
Vancomycin[b]	15–20 mg/kg q12hours
Linezolid	600 mg IV/PO q12hours

[a]Trough concentrations ideally should be nondetectable; less than 1 mcg/mL (2.09 µmol/L) for gentamicin and tobramycin and less than 4–5 mcg/mL (6.84–8.55 µmol/L) for amikacin are potentially acceptable.
[b]Trough concentrations should be between 5 and 20 mcg/mL.

A high-dose once-daily regimen (e.g., 4–7 mg/kg gentamicin or tobramycin or 15–20 mg/kg amikacin) can be used in patients with good renal function. Most of the studies enrolled patients with estimated creatinine clearances of at least 70 mL/minute (1.17 mL/s). Meta-analyses have shown high-dose once-daily regimens to be as efficacious and less toxic than divided daily dosing.[32–36] Divided daily dosing (e.g., 1–2 mg/kg gentamicin or tobramycin or 7.5 mg/kg amikacin) has been used since the 1970s, and the dosing interval is based on the patient's renal function so that the trough concentration is less than 1 mcg/mL.

In addition to obtaining a synergistic effect, another reason for double coverage when treating VAP, HAP, or HCAP is to broaden the coverage empirically to increase the likelihood of covering the majority of resistant pathogens. VAP is the most studied of these types of pneumonias and is often the most severe. Studies have demonstrated an increase in mortality when inadequate therapy is initiated for VAP. Crude mortality ranges from 35% to 92% with inadequate therapy compared with 25% to 47% with adequate therapy.[16]

❼ *Once a pathogen or pathogens have been identified, therapy should be narrowed to cover only those pathogens.* Use of broad-spectrum antibiotics for prolonged durations increases the risk of colonization with MDR pathogens.



Patient Encounter 2, Part 3: Creating a Care Plan

Based on the information presented, create a care plan for this patient's pneumonia. Your plan should include (1) the goals of therapy, (2) a patient-specific detailed therapeutic plan, and (3) a plan for follow-up to determine whether the goals have been achieved and adverse effects avoided.

Duration of Therapy

❽ *The duration of therapy for pneumonia should be kept as short as possible* and depends on several factors: type of pneumonia, inpatient or outpatient status, patient comorbidities, bacteremia/sepsis, and the antibiotic chosen. If the duration of therapy is too prolonged, then it can have a negative impact on the patient's normal flora in the respiratory and gastrointestinal tracts, vaginal tract of women, and the skin. This can result in colonization with resistant pathogens, *Clostridium difficile* colitis, or overgrowth of yeast. In addition, the longer antibiotics are administered, the greater is the chance for toxicity from the agent as well as an increase cost.[16]

For treating outpatient CAP, two antibiotics are approved for a 5-day duration of therapy, levofloxacin (the 750-mg dose) and azithromycin. The duration of therapy for all other therapies is 7 to 10 days. For treatment of CAP in patients admitted to the hospital, the duration depends on whether or not blood cultures were positive. In the absence of positive blood cultures, the duration of therapy is 7 to 10 days. If blood cultures were positive, then the duration of therapy should be 2 weeks from the day blood cultures first became negative.

The duration of therapy cited in the literature for HCAP, HAP, or VAP ranges from 10 to 21 days. Shortening the duration of therapy is acknowledged as beneficial because of the colonization, toxicity, and cost issues. The Clinical Pulmonary Infection Score (CPIS) has been used to determine when to end therapy for VAP. Luna and colleagues used the CPIS and found that patients who survived VAP and were treated with adequate therapy improved clinically within 3 to 5 days.[37] This was support for shortening the duration of therapy to 6 days. Another study found that when the CPIS was 6 or less, patients were at low risk of VAP or resistant pathogens, and treatment only needed to be for 3 days.[38]

OUTCOME EVALUATION

For CAP, outcomes include preventing hospitalization, shortening the duration of hospitalization, and minimizing mortality. For patients admitted to the hospital, if antibiotics are initiated within 4 hours of presentation, the duration of hospitalization is decreased compared with when antibiotics are started after 4 hours.[39]

Improvement in symptoms should occur within 48 to 72 hours after initiation of therapy for most patients with CAP. Response to therapy could be slowed in patients with underlying pulmonary disease such as moderate to severe asthma, COPD, or emphysema. In patients not responding to therapy with no underlying factors that would suggest a slowed response to therapy, then other infectious and noninfectious reasons must be considered. The infection could be caused by a pathogen not covered by the initial therapy, a drug-resistant isolate could be present, or more severe infection could be present (nonpulmonary), and the patient should be

reevaluated. Noninfectious reasons to consider include pulmonary embolus, congestive heart failure, carcinoma, lymphoma, intrapulmonary hemorrhage, and certain inflammatory lung diseases.

Outcome parameters for VAP, HAP, and HCAP are similar to those with CAP. Clinical improvement should occur within 48 to 72 hours of the start of therapy. If a patient is not responding to therapy, then, again, consider infectious and noninfectious reasons. Infectious explanations are the same as for CAP, but noninfectious reasons are not. They include atelectasis, acute respiratory distress syndrome (ARDS), pulmonary embolism or hemorrhage, cancer, empyema, or lung abscess.

PREVENTION

⑩ *Prevention of pneumococcal disease by use of vaccination is a national goal.* Vaccination is used to prevent or minimize the severity of pneumonia caused by *S. pneumoniae* or the influenza virus.

The influenza vaccine is available in two forms, injectable and nasal inhalation. The injectable is an inactivated vaccine (containing killed virus). The flu shot is approved for use in people older than 6 months of age, including healthy people and people with chronic medical conditions. The nasal-spray flu vaccine is made with live, weakened flu viruses that do not cause the flu (live attenuated influenza vaccine). This formulation is approved for use in healthy people 5 to 49 years of age who are not pregnant. The ability of the flu vaccine to protect a person depends on two key factors: the age and health status of the person getting the vaccine and the similarity or "match" between the virus strains in the vaccine and those in circulation. Given these factors, the vaccine has been shown to be effective. The influenza vaccine is recommended for the following groups of people[40]:

1. *People at high risk for complications from the flu:*
   - People 65 years of age and older
   - People who live in nursing homes and other long-term care facilities that house those with long-term illnesses
   - Adults and children 6 months of age and older with chronic heart or lung conditions, including asthma
   - Adults and children 6 months of age and older who needed regular medical care or were in a hospital during the previous year because of a metabolic disease (such as diabetes), chronic kidney disease, or weakened immune system (including immune system problems caused by medicines or by infection with HIV/AIDS)
   - Children 6 months to 18 years of age who are on long-term aspirin therapy
   - Women who will be pregnant during the influenza season
   - All children 6 to 23 months of age
   - People with any condition that can compromise respiratory function or the handling of respiratory secretions (i.e., a condition that makes it hard to breathe or swallow, such as brain injury or disease, spinal cord injuries, seizure disorders, or other nerve or muscle disorders)
2. *People 50 to 64 years of age.* Comorid conditions are present in nearly one-third of people 50 to 64 years of age in the United States, and this places them at increased risk for serious flu complications. Therefore, vaccination is recommended for all persons aged 50 to 64 years.
3. *People who can transmit flu to others at high risk for complications.* Any person in close contact with someone in a high-risk group should get vaccinated. This includes all health care workers, household contacts, and out-of-home caregivers of children 0 to 23 months of age and adults 65 years of age and older.

There are two pneumococcal vaccines, a 7-valent conjugated vaccine for children younger than 6 years of age and a 23-purified-capsular polysaccharide antigen vaccine for adults. The 23 capsular types in the vaccine represent at least 85% to 90% of the serotypes that cause invasive pneumococcal infections among children and adults in the United States.[41] After vaccination, an antigen-specific antibody response, indicated by a twofold or greater rise in serotype-specific antibody, develops within 2 to 3 weeks in 80% or more of healthy young adults.[42]



Patient Care and Monitoring

⑨ *Monitoring response to therapy is essential for determining efficacy, identifying adverse reactions, and determining the duration of therapy.*

1. Assess the patient's symptoms and status (i.e., inpatient, outpatient, or intubated) to determine the type of pneumonia and comorbid conditions. Does the patient have moderate to severe asthma, COPD, or emphysema or is a current smoker?
2. Review any available diagnostic data to determine severity of the disease.
3. Obtain a history of prescription and nonprescription medication use, as well as allergies and drug intolerances, noting the severity of the reaction.
4. What are the top two to three organisms associated with the type of pneumonia the patient has?
5. Select an appropriate empirical antibiotic regimen for the patient, ensuring that the doses are correct for renal function.
6. Develop a plan to assess the effectiveness of the antibiotic therapy after 24 to 72 hours. If the patient is not improving, then reevaluate the diagnosis and pathogen list, and make appropriate changes to therapy. Develop a plan to assess the effectiveness of the antibiotic therapy again at the end of therapy. When can conversion from intravenous to oral therapy occur?
7. Evaluate the patient for the presence of adverse drug reactions, drug allergies, and drug interactions.
8. For patients who meet the qualifications, discuss the value of vaccination against *S. pneumoniae*.

However, immune responses may not be consistent among all 23 serotypes in the vaccine.[42] Those who should receive the polysaccharide vaccine include

1. *All adults 65 years of age or older.*
2. *Anyone over 6 years of age who has a long-term health problem such as*
   - Heart disease
   - Lung disease
   - Sickle cell disease
   - Diabetes
   - Alcoholism
   - Cirrhosis
   - Leaks of cerebrospinal fluid
3. *Anyone over 6 years of age who has a disease or condition or is taking any drug that lowers the body's resistance to infection, such as*
   - Hodgkin's disease
   - Lymphoma, leukemia
   - Kidney failure
   - Multiple myeloma
   - Nephrotic syndrome
   - HIV infection or AIDS
   - Damaged spleen, or no spleen
   - Organ transplant
   - Long-term steroids
   - Certain cancer drugs
   - Radiation therapy
4. *Alaskan Natives and certain Native American populations.*

The conjugated pneumococcal vaccine is recommended for all children aged 2 to 23 months and for certain children aged 24 to 59 months. If there are underlying health issues such as diabetes mellitus or cardiopulmonary disease, then children 24 to 59 months should receive this vaccine as well. The seven capsular types in the vaccine represent at least 85% to 90% of the serotypes that cause invasive pneumococcal infections among children in the United States.[41]

ABBREVIATIONS

ATS:	American Thoracic Society
CAP:	community-acquired pneumonia
CDC:	Centers for Disease Control and Prevention
COPD:	chronic obstructive pulmonary disease
CPIS:	Clinical Pulmonary Infection Score
DFA:	direct fluorescence antigen
GER(D):	gastroesophageal reflux (disease)
HCAP:	health care–associated pneumonia
HAP:	hospital-associated pneumonia
IDSA:	Infectious Diseases Society of America
MSSA:	methicillin-susceptible *Staphylococcus aureus*
MRSA:	methicillin-resistant *Staphylococcus aureus*
PCR:	polymerase chain reaction
TNF-α:	tumor necrosis factor α
TRUST:	Tracking Resistance in the US Today
VAP:	ventilator-associated pneumonia

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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69 Upper Respiratory Tract Infections

Heather L. VandenBussche



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. List the most common bacterial pathogens that cause acute otitis media, acute bacterial rhinosinusitis, and acute pharyngitis.
2. Explain the pathophysiologic causes of and risk factors for acute otitis media, bacterial rhinosinusitis, and acute pharyngitis.
3. Identify clinical signs and symptoms associated with acute otitis media, bacterial rhinosinusitis, and streptococcal pharyngitis.
4. List treatment goals for acute otitis media, bacterial rhinosinusitis, and streptococcal pharyngitis.
5. Develop an appropriate antibiotic regimen for each infection based on patient-specific data.
6. Recommend appropriate adjunctive therapy for a patient with acute otitis media, acute bacterial rhinosinusitis, or streptococcal pharyngitis.
7. Create a monitoring plan for a patient being treated for each infection using patient-specific information and prescribed therapy.
8. Educate patients about upper respiratory tract infections and proper use of antibiotic therapy.

Key Concepts

❶ Antibiotic resistance patterns affect treatment options for bacterial upper respiratory tract infections.

❷ The majority of uncomplicated acute otitis media infections resolve spontaneously without significant morbidity.

❸ Antibiotic therapy for acute otitis media should be reserved for children who are most likely to benefit from therapy: those under 2 years of age and those with severe disease.

❹ Proper diagnosis of bacterial upper respiratory tract infections is crucial to identify patients who require antibiotics to avoid unnecessary antibiotic use.

❺ Amoxicillin and amoxicillin-clavulanate are first-line antibiotics for acute otitis media.

❻ Antibiotic therapy for sinusitis should be reserved for patients with moderate persistent symptoms, clinical decompensation, or severe symptoms.

❼ Empirical antibiotic selection for acute bacterial rhinosinusitis should incorporate patient risk factors for bacterial resistance.

❽ Amoxicillin and amoxicillin-clavulanate are first-line antibiotics for acute bacterial rhinosinusitis.

❾ The goals of therapy for streptococcal pharyngitis are to eradicate infection, reduce symptoms and infectivity, and prevent complications.

❿ Penicillin is the drug of choice for streptococcal pharyngitis, but cephalosporins may be appropriate alternative first-line agents owing to increasing failure rates after penicillin therapy.

Upper respiratory tract infection (URI) is a term that refers to various upper airway infections, including otitis media, sinusitis, pharyngitis, and rhinitis. Most URIs are viral and often self-limited. Over 1 billion viral URIs occur annually in the United States, resulting in millions of physician office visits each year.[1] Excessive antibiotic use for URIs has contributed to the significant development of bacterial resistance. Guidelines have been established to reduce inappropriate antibiotic use for viral URIs.[2] This chapter will focus on acute otitis media, sinusitis, and pharyngitis because they are frequently caused by bacteria and require appropriate antibiotic therapy to minimize complications.

OTITIS MEDIA

Otitis media, or inflammation of the middle ear, is the most common reason for prescribing antibiotics in children. It usually occurs after a viral infection of the nasopharynx and can be subclassified as acute otitis media or otitis media with

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Patient Encounter 1, Part 1

A 15-month-old girl presents to the pediatric clinic with 2 days of fever (38.9°C), runny nose, and fussiness. Her mother states that she is more irritable than usual and cries many times throughout the night. She is not as interested in eating today. She attends day care and has a 5-year-old brother who recently had a cold. Physical examination reveals erythema and bulging of the right tympanic membrane and the presence of middle ear fluid. The left tympanic membrane is obscured with cerumen.

- What information is suggestive of AOM?
- Does the child have risk factors for AOM?
- Is there any additional information you need to know before recommending a treatment plan?

effusion. **Acute otitis media** (AOM) is a symptomatic middle ear infection that occurs rapidly along with effusion, or presence of fluid. **Otitis media with effusion** (OME) is the presence of fluid in the middle ear without symptoms of acute illness. It is important to distinguish between AOM and OME because antibiotics are only useful for treatment of AOM. Effusions can be present for up to 6 months after an acute episode.

Epidemiology and Etiology

Otitis media is most common in children between 6 months and 2 years of age but can occur in all age groups, including adults. By 12 months of age, 75% of children have had at least one episode of otitis media, and up to 20% have recurrent infections.[3,4] At least 13 million antibiotic prescriptions are written annually in the United States for otitis media, resulting in $2 billion in direct costs.[5] Many risk factors (Table 69–1) predispose children to otitis media and can be associated with microbial resistance, such as day-care attendance, prior antibiotic exposure, and age younger than 2 years.[3,4,6]

Bacteria frequently are isolated from middle ear fluid in children with AOM, but viruses also play a predominant role.

TABLE 69–1. Risk Factors for Otitis Media[3,4,6]

Viral respiratory tract infection/ winter season	Native American or Inuit ethnicity
Day-care attendance[a]	Low socioeconomic status
Siblings	Pacifier use
Male gender	Lack of breastfeeding
Tobacco smoke exposure	Young age at first diagnosis[a]
Allergies	Immunodeficiency
Anatomic defects such as cleft palate	Gastroesophageal reflux
Positive family history/genetic predisposition	

[a]Risk factors for infection with a resistant pathogen (day-care attendee, age under 2 years, recent antibiotic use in previous 3 months).

Streptococcus pneumoniae traditionally has been the most common organism, responsible for 25% to 50% of cases.[5,7] Nontypeable *Hemophilus influenzae* and *Moraxella catarrhalis* cause 15% to 30% and 3% to 20% of cases, respectively. Recent data suggest that the microbiology of AOM is shifting toward a prevalence of *H. influenzae* owing to routine childhood immunization with pneumococcal conjugate vaccine.[8] Bacteria that are less frequently associated with AOM include *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. Viruses such as respiratory syncytial virus, influenza virus, rhinovirus, and adenovirus are isolated from middle ear fluid with or without concomitant bacteria in over half of AOM cases.[9,10] Lack of improvement with antibiotic therapy is often a result of viral infection and subsequent inflammation rather than antibiotic resistance.

❶ *Bacterial resistance has significantly affected treatment guidelines for AOM.* Penicillin-resistant *S. pneumoniae* (PRSP) encompasses both intermediate resistance (minimum inhibitory concentrations between 0.1 and 1.0 mcg/mL) and high-level resistance (minimum inhibitory concentration of 2.0 mcg/mL and higher). Approximately 35% of respiratory pneumococcal isolates are penicillin-resistant owing to altered penicillin-binding proteins, and almost half are highly penicillin-resistant.[11] PRSP are also commonly resistant to other drug classes, including sulfonamides, macrolides, and clindamycin, and increasingly resistant to fluoroquinolones. Although inappropriate use of antibiotics for URIs has led to increased resistance rates, treatment for pneumococcal AOM is necessary because infection caused by *S. pneumoniae* is unlikely to resolve spontaneously. β-Lactamase production occurs in 30% and nearly 100% of *H. influenzae* and *M. catarrhalis*, respectively.[12] Although infections caused by these organisms are more likely to resolve without treatment, they must be considered in cases of treatment failure.

Pathophysiology

Multiple factors play a role in the development of AOM. Viral infection of the nasopharynx impairs eustachian tube function and causes mucosal inflammation, impairing mucociliary clearance and promoting bacterial proliferation and infection. Children are predisposed to AOM because their eustachian tubes are shorter, more flaccid, and more horizontal than adults, which make them less functional for drainage and protection of the middle ear from bacterial entry. Clinical signs and symptoms of AOM are the result of host immune response and damage to cells caused by inflammatory mediators such as tumor necrosis factor and interleukins that are released from bacteria.[4]

❷ *The majority of uncomplicated AOM cases resolve spontaneously without significant morbidity.* Untreated AOM improves by day 2 or 3 of illness in 80% of children without increasing the risk of complications.[13] Antibiotics improve ear pain in only 7% of children between days 2 and 7 of therapy and significantly improve recovery in children younger than

2 years of age and in those with severe AOM symptoms.[5,14,15] ❸ *Therefore, antibiotics should be reserved for children most likely to benefit from therapy.* Delayed antibiotic therapy in older children and those with less severe disease does not result in more infectious complications, such as mastoiditis or meningitis, when compared with routine initial antibiotic treatment.[14] Use of this approach or use of a safety-net antibiotic prescription that parents fill 2 days later only if the child is not better can reduce antibiotic use for AOM dramatically without increasing complications.[16]

Viscous middle ear effusions caused by allergy or irritant exposure may contribute to impaired mucociliary clearance and AOM in susceptible individuals.[4] OME occurs chronically in atopic children, and effusion can persist for months after an episode of AOM. Children with chronic OME usually require **tympanostomy tube** placement to reduce complications such as hearing and speech impairment and recurrent otitis media.



Clinical Presentation and Diagnosis

It is important to differentiate AOM from OME because they are treated dramatically differently. Patients with AOM usually have cold symptoms, including rhinorrhea, cough, or nasal congestion before or at diagnosis.

Symptoms

- Young children: ear tugging, irritable, poor sleeping and eating habits
- Older patients: ear pain (mild, moderate, or severe), ear fullness, hearing impairment

Signs[5,7]

- Fever: present in less than 25% of patients; often in younger children
- Middle ear effusion
  - Otorrhea (middle ear perforation with fluid drainage): uncommon
  - Bulging tympanic membrane
  - Limited or absent mobility of tympanic membrane
- Distinct erythema of tympanic membrane
- Opaque or cloudy tympanic membrane obscuring or reducing visibility of middle ear

Laboratory Tests

Gram stain, culture, and sensitivities of ear fluid if draining spontaneously or obtained via **tympanocentesis** (not performed routinely in practice)

Complications

- Infectious: mastoiditis, meningitis, osteomyelitis, intracranial abscess
- Structural: perforated eardrum, **cholesteatoma**
- Hearing and/or speech impairment

Diagnosis[5]

- Certain AOM: Requires *all* the following:
  - Rapid onset of signs and symptoms
  - Middle ear effusion findings with **pneumatic otoscopy** (as above)
  - Inflammation indicated by either otoscopic evidence (distinct erythema) or otalgia
- Uncertain AOM: Not all three criteria are present.
- Severe AOM: Moderate to severe ear pain or fever of 39°C or greater.
- Nonsevere AOM: Mild ear pain and fever of less than 39°C in past 24 hours.



Patient Encounter 1, Part 2

On further questioning, you discover that the child is allergic to penicillin. She developed a nonurticarial rash last year during treatment for pharyngitis. She has not received antibiotics since that time, and this is her first ear infection.

Immunizations: Up to date

Meds

Acetaminophen drops 120 mg PO every 4 to 6 hours as needed for fever or pain

ROS

(+) nasal congestion and rhinorrhea, (–) vomiting, diarrhea, or cough

PE

- **Gen:** Irritable child but consolable
- **VS:** Blood pressure 100/60 mm Hg, pulse 120 beats per minute, respiratory rate 18 breaths per minute, temperature 38.6°C
- **HEENT:** As noted before

- Identify your treatment goals for this child.
- Given this information, what nonpharmacologic and pharmacologic therapy do you recommend?

Treatment

Desired Outcomes

Therapy for AOM focuses on symptom relief and prevention of complications. The goals of treatment are to alleviate ear pain and fever, if present; eradicate infection; prevent sequelae; and minimize unnecessary antibiotic use.

General Approach to Treatment

❸ ❹ *Treatment of AOM depends on patient age, illness severity, and the certainty of diagnosis.* Children younger than 2 years of age have a higher incidence of penicillin-resistant pneumococcal infections and have higher clinical and bacteriologic failure rates and complications when not treated initially with antibiotics as compared with older children.[5,15] Patients with severe illness, defined by degree of fever and

pain severity, have lower spontaneous recovery rates than those with nonsevere disease.[14,15] Current guidelines recommend stratifying patients based on these criteria, along with certainty of diagnosis, in order to identify those most likely to benefit from antibiotic therapy.[5]

Nonpharmacologic Therapy

Watchful waiting and safety-net antibiotic prescriptions are approaches being used more frequently to attenuate microbial resistance and avoid unnecessary adverse events and costs of antibiotics. Observation is practiced extensively in Europe and involves monitoring for 48 to 72 hours after diagnosing AOM to see if spontaneous resolution will occur. Observation or delayed antibiotic therapy should be considered only in otherwise healthy children without recurrent disease (Fig. 69–1) and only if proper follow-up and good communication exist between clinicians and the parent/caregiver.[4,5,16]

Other nondrug approaches include the use of external heat or cold to reduce postauricular pain and surgery. Tympanostomy tubes are most useful for patients with recurrent disease or chronic OME with impaired hearing or speech. Adenoidectomy may be necessary for children with chronic nasal obstruction, but tonsillectomy is rarely indicated.

Pharmacologic Therapy

Antibiotic Therapy

When antibiotic therapy is needed, many factors influence initial drug selection. Clinicians must consider drug factors such as antimicrobial spectrum, likelihood of clinical response, incidence of side effects, drug interactions, and cost, as well as patient factors, including risk factors for bacterial resistance, allergies, ease of dosing regimen, medication palatability, and presence of other medical conditions. Studies in uncomplicated AOM have not revealed significant differences between antibiotics in clinical response rates that can be confounded by spontaneous resolution. Bacteriologic response varies among antibiotics and does not always correlate with clinical response. Two recent well-designed trials that performed tympanocentesis at baseline and at days 4 to 6 of treatment found significantly less clinical improvement with azithromycin than with amoxicillin-clavulanate (p less than 0.05) with even larger differences in bacteriologic eradication (p less than 0.01).[17,18] These studies are important because they only included patients with bacteriologically proven AOM and assessed bacteriologic cure separately from clinical resolution, highlighting that clinical success does not equal bacteriologic success.

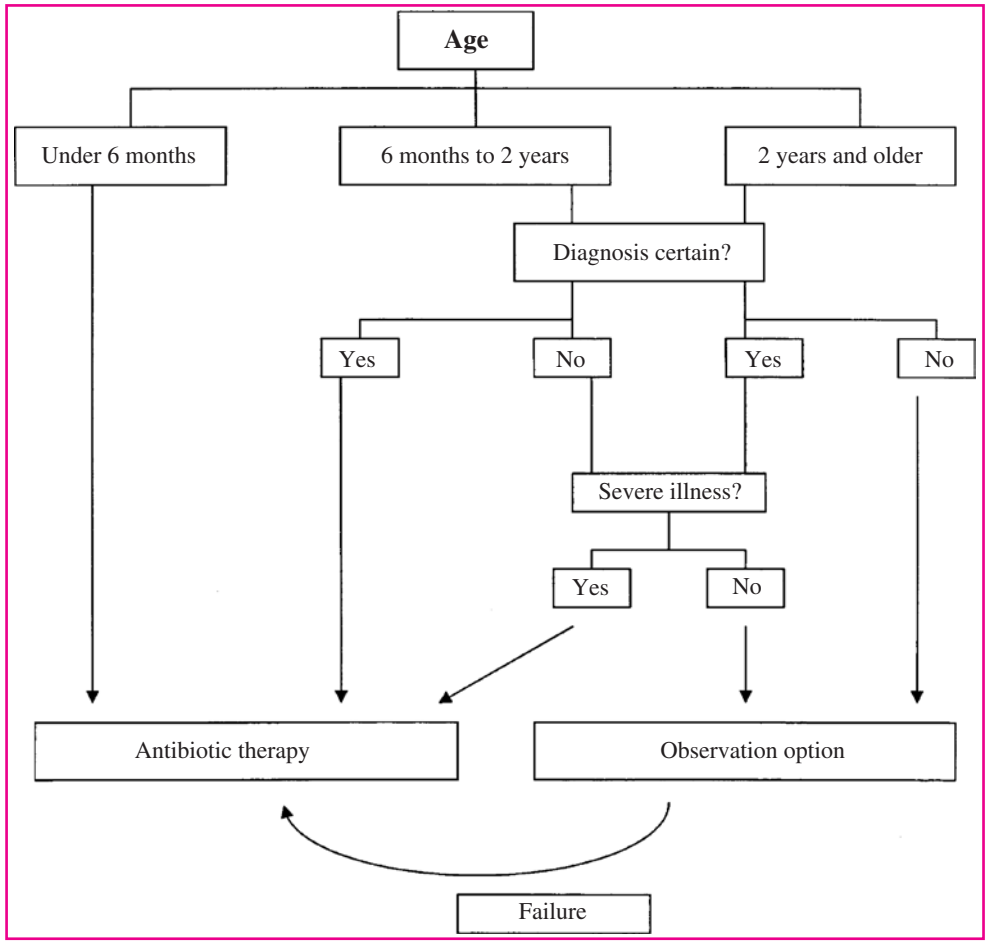


FIGURE 69–1. Treatment algorithm for initial antibiotics or observation in children with suspected or certain uncomplicated AOM.[5]

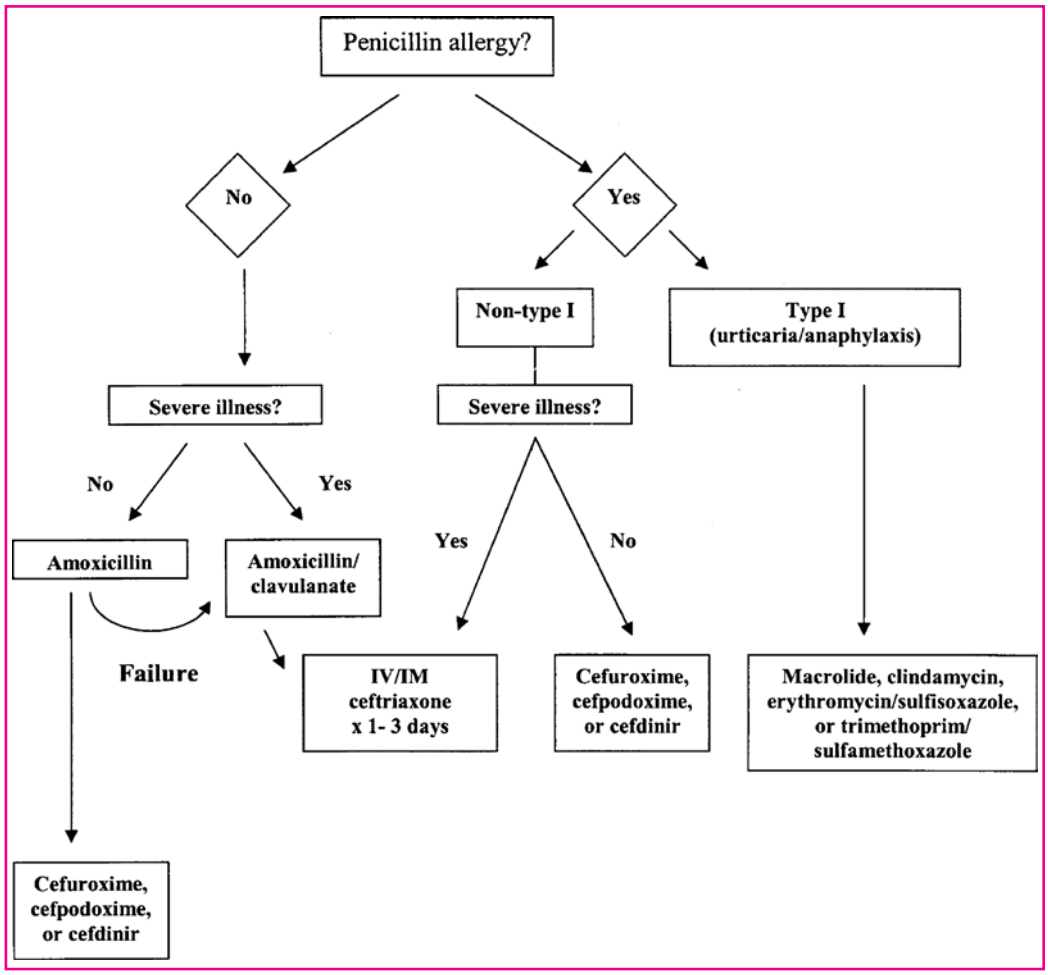


FIGURE 69–2. Treatment algorithm for uncomplicated AOM in children 2 months to 12 years of age.[5,6]

Guidelines from the American Academy of Pediatrics and the American Academy of Family Physicians are available for children between 2 months and 12 years of age with uncomplicated AOM (Fig. 69–2) and are based on published trials and expert opinion.[5] ❺ *Amoxicillin remains the drug of choice in most patients because of its proven effectiveness in AOM when used in sufficient doses for PRSP, as well as its excellent safety profile, low cost, good-tasting suspension, and relatively narrow spectrum of activity* (Table 69–2). High-dose amoxicillin (80–90 mg/kg per day) is preferred over conventional doses because higher drug levels are achieved in middle ear fluid to overcome pneumococcal resistance without substantially increasing adverse effects.[19] ❺ *In cases of severe illness or when coverage for β-lactamase-producing organisms is desired, high-dose amoxicillin-clavulanate is the preferred agent.* Pneumococcal resistance to trimethoprim-sulfamethoxazole and macrolides is problematic and strikingly common in PRSP, making these agents less desirable for most patients.[6,20,21] Patients with penicillin allergies require alternative first-line therapy (see Fig. 69–2). Children who have received an antibiotic in the previous month are more likely to harbor resistant organisms and also should receive alternative therapy.[6] A single dose of intramuscular ceftriaxone is effective for children who cannot tolerate oral medications, but a 3-day course may be preferred because of increasing pneumococcal resistance and failure of single doses.[22] Ototopic antibiotics are an alternative to systemic agents for AOM in patients with tympanostomy tubes.[23]

If there is a lack of improvement or worsening with initial therapy during the first 48 to 72 hours, antibiotic selection must be reassessed, and other contributing diseases must be excluded[5,6] (see Fig. 69–2). Tympanocentesis can help to guide therapy in difficult cases.

Duration of therapy, like drug selection, depends on patient age and disease severity. Standard 10-day oral therapy is more effective than shorter courses for uncomplicated AOM in children younger than 2 years of age and those with recurrent infections, as well as in older patients with severe illness.[5,24] Exceptions to the 10-day regimen are for azithromycin and ceftriaxone. In older children with mild or moderate illness, antibiotic therapy is needed only for 5 to 7 days.

TABLE 69–2. Antibiotics[a] for the Treatment of AOM[5,7]

Drug	Usual Dose and Schedule	Common Adverse Effects	Relative Cost[b]	Comments
Amoxicillin	80–90 mg/kg per day in 2–3 doses (adult: 875 mg twice daily)	Nausea, vomiting, diarrhea, rash	$	Drug of choice for AOM; experts recommended high-dose over conventional doses (40–45 mg/kg per day)
Amoxicillin-clavulanate	80–90 mg/kg per day in 2–3 doses (adult: 875 mg twice daily)	Nausea, vomiting, diarrhea, rash, diaper rash	$$$–$$$$	More diarrhea than amoxicillin, Augmentin ES formulation preferred owing to lower daily clavulanate component
Cefuroxime axetil	30 mg/kg per day in 2 doses (max 1 g/day with suspension; adult: 250 mg twice daily)	Nausea, vomiting, diarrhea, rash, diaper rash	$$$	Suspension gritty and bitter tasting, not interchangeable with tablets (less bioavailable)
Cefdinir	14 mg/kg per day in 1–2 doses (adult: 300 mg twice daily or 600 mg once daily)	Diarrhea, rash, vomiting, diaper rash, yeast infections	$$$	Preferred oral cephalosporin (good taste); separate from Al or Mg antacids and Fe supplements by 2 hours
Cefpodoxime proxetil	10 mg/kg per day in 2 doses (adult: 200 mg twice daily)	Diarrhea, diaper rash, vomiting, rash, yeast infections	$$$	Suspension is bitter tasting
Ceftriaxone	50 mg/kg IM or IV for 1–3 days (max 1 g/dose)	Injection site pain, swelling, or erythema, diarrhea, rash	$$$–$$$$	3-day regimen preferred for PRSP; avoid in children under 2 months
Azithromycin	10 mg/kg × 1 day, 5 mg/kg per day × 4 days; 10 mg/kg per day × 3 days; or 30 mg/kg single dose (adult dose 500 mg × 1,250 mg × 4 days; 500 mg/day × 3 days)	Nausea, vomiting, diarrhea, abdominal pain	$$	Separate from Al or Mg antacids by 2 hours; diarrhea/vomiting more common with single-dose regimen; 3- or 5-day courses preferred; increasing pneumococcal resistance; many failures with *H. influenzae* infection
Clarithromycin	15 mg/kg per day in 2 doses (adult: 250 mg twice daily)	Diarrhea, vomiting, rash, abnormal taste, abdominal pain	$$	Many drug interactions (inhibits cytochrome P-450 3A4); suspension cannot be refrigerated and has metallic taste; same microbiologic issues as azithromycin
Erythromycin-sulfisoxazole	50 mg/kg per day of erythromycin component in 3–4 doses	Nausea, vomiting, abdominal pain, diarrhea, rash	$$	Many drug interactions (like clarithromycin), contraindicated in children under 2 months; increasing pneumococcal resistance
Trimethoprim-sulfamethoxazole	8–10 mg/kg per day of trimethoprim component in 2 doses	Nausea, vomiting, anorexia, rash, urticaria	$	Increasing pneumococcal resistance; contraindicated in children under 2 months
Clindamycin	20–30 mg/kg per day in 3–4 doses (adult: 300 mg four times daily or 450 mg three times daily)	Nausea, diarrhea, *C. difficile* colitis, anorexia	$	Oral liquid has very poor taste; only for pneumococcal infection

[a]Other FDA-approved antibiotics for AOM not included in AAP/AAFP guidelines: cefaclor, cephalexin, cefprozil, cefixime, loracarbef, and ceftibuten.
[b]Approximate cost per course: $ (under $25), $$ ($25–$50), $$$ ($50–$100), $$$$ (over $100).

Adjunctive Therapy

Pain is a central feature of AOM but is often overlooked in disease management. If pain is present on presentation, analgesics or topical anesthetics can be used to alleviate otalgia. Acetaminophen and ibuprofen are commonly used over-the-counter agents for mild to moderate pain. While studies have not demonstrated superior therapeutic advantages of one agent over the other,[25] ibuprofen has a longer duration of effect but is not used routinely in children younger than 6 months of age because of increased toxicity concerns. Alternating ibuprofen with acetaminophen is not recommended owing to a lack of safety and efficacy data on combination therapy and the potential for dosing confusion and error. Topical anesthetic drops such as benzocaine (Auralgan®) provide pain relief within 30 minutes of administration and may be preferred over systemic analgesics when fever is absent. **Myringotomy** provides immediate relief but is performed rarely. Other medications such as decongestants, antihistamines, and corticosteroids have no role in the treatment of AOM and can, in some cases, prolong effusion duration.[26,27] Data are lacking on the safety and efficacy of complementary and alternative treatments.

Prevention

Immunizations may prevent AOM in certain patients, but data are conflicting. Influenza vaccine is more effective in preventing AOM in children older than 2 years of age than in younger patients perhaps owing to impaired immune response and immature host defense in infants and toddlers.[28,29] Pneumococcal conjugate vaccine is protective against infection by vaccine serotypes only with a limited overall benefit for AOM.[30] Antibiotic prophylaxis is no longer recommended for otitis-prone children because of increasing resistance. Avoidance or minimization of risk factors associated with otitis media, such as tobacco smoke and bottle feeding, is advised, but the effects of these interventions remain unproven.

Outcome Evaluation

Improvement of signs and symptoms (i.e., pain, fever, and tympanic membrane inflammation) should be evident by 72 hours of therapy. Children can appear clinically worse during the first 24 hours of treatment but often stabilize during the second day with defervescence and improved eating and sleeping patterns. If clinical improvement is not seen, or if the patient worsens, reevaluation must occur to determine the proper diagnosis and treatment. Counsel patients and caregivers regarding common antibiotic adverse events such as rash, diarrhea, and vomiting that may prompt additional medical attention.

Presence of middle ear effusion in the absence of symptoms is not an indicator of treatment failure. Children who complete therapy and are otherwise healthy should be reevaluated after 3 months for the presence of effusion that requires a hearing evaluation. Preschool-aged and younger children may need reexamination 3 to 6 weeks after therapy because speech and hearing impairment is more difficult to assess in this age group.



Patient Care and Monitoring

1. Assess the patient's signs and symptoms. Are they consistent with acute otitis media?
2. Review diagnostic information to determine if acute infection is present. Are all three diagnostic criteria present? Was the proper method used for diagnosis (pneumatic otoscopy)?
3. Does the patient require antibiotic therapy, or is observation an appropriate option?
4. Obtain a complete medication history, including prescription drugs, nonprescription drugs, and natural product use, as well as allergies and adverse effects.
5. Determine what medication should be used for pain, if present.
6. If applicable, determine which antibiotic to use and the duration of therapy.
7. Develop a plan to assess effectiveness of the chosen therapy and course of action to take if the patient does not improve or worsens.
8. Provide patient education on
   - What to expect from prescribed medication, including potential adverse effects
   - Avoidance of antihistamines and decongestants
   - Signs of treatment failure
9. Stress the importance of adherence to therapy, including antibiotic resistance concerns.
10. Determine the need for influenza and pneumococcal vaccinations.
11. Educate the family regarding risk factors for otitis media.

SINUSITIS

Sinusitis, or inflammation of the paranasal sinuses, is better described as **rhinosinusitis** that also involves inflammation of contiguous nasal mucosa, which occurs in virtually all cases of viral respiratory infections. Acute rhinosinusitis is characterized by symptoms that resolve completely in less than 4 weeks, whereas chronic rhinosinusitis typically persists as cough, rhinorrhea, or nasal obstruction for more than 90 days. Acute bacterial rhinosinusitis (ABRS) refers to an acute bacterial infection of the sinuses that can occur independently or be superimposed on chronic sinusitis. The focus of this section will be on ABRS and appropriate treatment.

Epidemiology and Etiology

Rhinosinusitis is one of the most common medical conditions in the United States, affecting about 1 billion people annually.[1] It is caused mainly by respiratory viruses such as rhinovirus, influenza virus, and respiratory syncytial virus but also can be due to allergies or environmental irritants. Only 0.5% to 2% of

TABLE 69–3. Risk Factors for Acute Bacterial Rhinosinusitis[31,33]

Viral respiratory tract infection/winter season	Anatomic defects (e.g., septal deviation)
Allergic or nonallergic rhinitis	Intranasal medications or illicit drugs
Tobacco smoke exposure	Immunodeficiency
Dental infections or procedures	Swimming/diving
Cystic fibrosis or ciliary dyskinesia	Mechanical ventilation
Nasogastric tubes	Traumatic head injury
Aspirin allergy, nasal polyps, and asthma	Female gender

viral rhinosinusitis in adults is complicated by secondary bacterial infection, but this occurs in 5% to 13% of children.[31,32] Upper respiratory infections of less than 7 days' duration usually are of viral etiology, whereas more prolonged disease or disease with severe symptoms often is caused by bacteria. Risk factors for ABRS include prior viral respiratory infection, allergic rhinitis, anatomic defects, and certain medical conditions[31,33] (Table 69–3). Clinicians often inappropriately prescribe antibiotics for clinically suspected rhinosinusitis that usually is self-limiting and infrequently is complicated by bacterial disease. Antibiotics are useful only in shortening the course of ABRS.

Bacterial pathogens that cause sinusitis are similar to those that cause acute otitis media. *S. pneumoniae* and *H. influenzae* are responsible for 50% to 60% of cases in all patients, with an additional 20% of cases caused by *M. catarrhalis* in children.[31,33] Risk factors for drug-resistant pathogens are also similar to those in AOM.[1] Other pathogens that cause sinusitis include *Streptococcus pyogenes* (up to 5%), anaerobic bacteria such as *Bacteroides* and *Peptostreptococcus* spp. (up to 9% of adults), and *Staphylococcus aureus* (up to 5% of adults).[31] Chronic infections are commonly polymicrobial with a higher incidence of anaerobes, gram-negative bacilli, and fungi.

Pathophysiology

Rhinosinusitis is caused by mucosal inflammation and local damage to mucociliary clearance mechanisms usually as a result of viral infection or allergy. Increased mucus production and reduced clearance of secretions can lead to blockage of the sinus ostia, or the opening of the sinuses to the upper airway. This environment is ideal for bacterial growth and promotes a cycle of local inflammatory response and mucosal injury characterized by increased concentrations of interleukins, histamine, and tumor necrosis factor.[31,33] Factors that contribute to bacterial invasion include nose blowing, reduced local immunity, viral virulence, and nasopharyngeal colonization with bacteria.[31] Damage to the host defense system perpetuates bacterial overgrowth and persistence of infection. Despite bacterial illness, there is a 50% to 70% spontaneous resolution rate for ABRS.[34–36]



Clinical Presentation and Diagnosis

Sinusitis symptoms typically last 7 to 10 days after a viral infection and are caused by activation of the immune system and parasympathetic nervous system.

Acute Signs and Symptoms[31,32]

- *Adults:* Nasal congestion or obstruction, nasal/postnasal discharge or purulence, facial pain or pressure (especially unilateral in a sinus area), diminished sense of smell, fever, cough, maxillary dental pain, fatigue, ear fullness or pain
- *Children:* Nasal/postnasal drainage, congestion, persistent cough (particularly at night), fever, pharyngitis, ear discomfort, halitosis, morning periorbital edema or facial swelling, fatigue, facial or tooth pain

Complications

Orbital cellulitis or abscess, periorbital cellulitis, meningitis, cavernous sinus thrombosis, ethmoid or frontal sinus erosion, chronic sinusitis, and exacerbation of asthma or bronchitis

❹ Diagnosis[31,34]

- *Clinical diagnosis:* Most common method; a viral URI that has not resolved after 10 days or worsens after 5 to 7 days *and* with signs and symptoms of acute infection (as above).
- *Radiographic studies:* Useful for assessing presence of abscess or intracranial complication.
- *Paranasal sinus puncture:* "Gold standard"; not performed routinely but can be useful in complicated or chronic cases.
- *Laboratory studies/nasopharyngeal cultures:* Not recommended for routine diagnosis.

Treatment

Desired Outcomes

The goals of treatment for ABRS are to eradicate bacteria and prevent serious sequelae. Specific aims are to relieve symptoms, normalize the nasal environment, use antibiotics when appropriate, select effective antibiotics that minimize resistance, and prevent development of chronic disease or complications.

General Approach to Treatment

Initial management of rhinosinusitis focuses on symptom relief for patients with mild disease lasting less than 10 days. Routine antibiotic use is not recommended for all patients because viral sinusitis is self-limiting and bacterial infection resolves spontaneously in many cases. ❻ *Antibiotic therapy should be reserved for persistent, worsening, or severe ABRS: patients with mild to moderately severe symptoms based on clinical judgment that have persisted for greater than 10 days or worsened after 5 to 7 days and patients with severe disease regardless of duration.*[31,34] Empirical selection is often employed and should target likely pathogens because sinus cultures are rarely obtained.

Nonpharmacologic Therapy

Ancillary treatments such as humidifiers, vaporizers, and saline nasal sprays or drops are used to moisturize the nasal canal and impair crusting of secretions along with promoting ciliary function. Although many patients report benefit from such therapies, there are no controlled studies that support their use.[32,34,36]

Pharmacologic Therapy

Adjunctive Therapy

Supportive medications that target symptoms of viral URIs are used widely in patients with rhinosinusitis, particularly in the early stage of infection. There is a lack of evidence supporting their use in ABRS, but they may provide temporary relief in certain patients.[32,36,37] Analgesics can be used to treat fever and pain from sinus pressure. Oral decongestants relieve congested nasal passages but should be avoided in children younger than 2 years of age and patients with ischemic heart disease or uncontrolled hypertension. Intranasal decongestants can be used for severe congestion in most patients 6 years of age or older, but use should be limited to 3 days or less to avoid rebound nasal congestion. Antihistamines should be avoided because they thicken mucus and impair its clearance, but they may be useful in patients with predisposing allergic rhinitis or chronic sinusitis. Similarly, intranasal corticosteroids usually are reserved for patients with allergies or chronic sinusitis, but they may be beneficial as monotherapy or with antibiotics in ABRS.[38,39]

Antibiotic Therapy

Although many clinical studies have been performed evaluating antibiotics for ABRS, no randomized, double-blind, placebo-controlled studies have used pre- and posttreatment sinus aspirate cultures as an outcome measure. Despite this, antibiotics appear to resolve symptoms more quickly and reduce failure rates and complications compared with no treatment.[35–37] Since diagnosis usually is based on clinical presentation and not sinus aspirate cultures, clinicians must attempt to differentiate ABRS from viral rhinosinusitis. ❻ *Therefore, it is important to limit antibiotic use to cases where infection is unlikely to resolve without causing prolonged disease: patients with mild to moderate symptoms that persist for 10 days or worsen over 5 to 7 days and patients with severe symptoms.*[31,34]

Treatment guidelines developed by the Sinus and Allergy Health Partnership reflect antibiotic choices that are likely to result in favorable clinical and bacteriologic outcomes based on pathogen distribution, spontaneous resolution rates, and nationwide resistance patterns.[31] ❼ *These guidelines (Figs. 69–3 and 69–4) stratify therapy based on severity of disease and risk of infection with resistant organisms, defined as mild disease in patients with prior antibiotic use within 4 to 6 weeks. Other risk factors for resistance include day-care attendance or frequent*

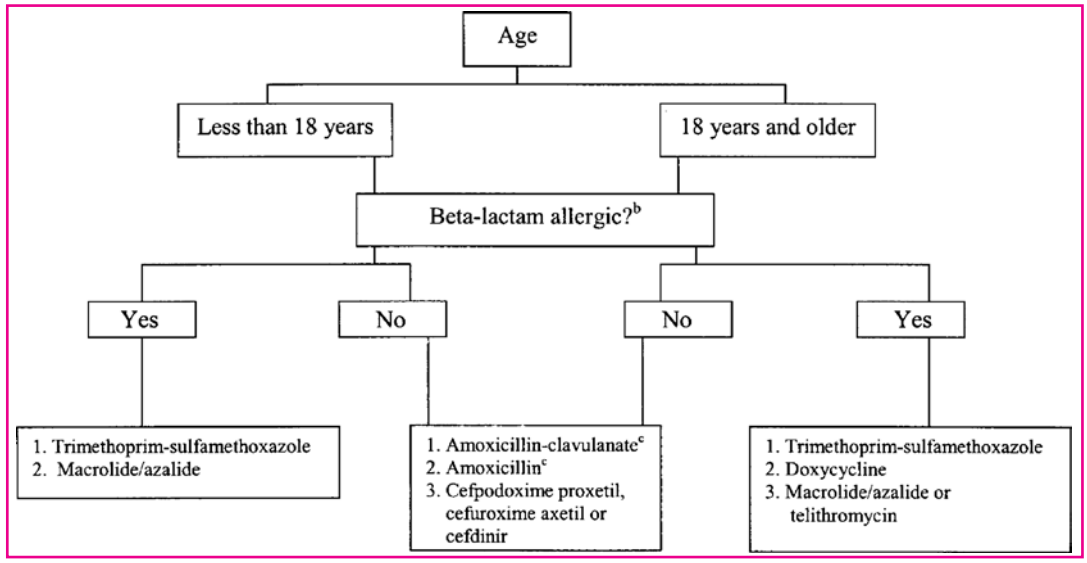


FIGURE 69–3. Treatment algorithm[a] for acute bacterial rhinosinusitis in patients with mild disease without recent antibiotic exposure.[31] [a]Antibiotics are listed in order of predicted efficacy based on predicted clinical and bacteriologic efficacy rates, clinical studies, safety, and tolerability. Doses can be found in Table 69–4. [b]Cephalosporins should be considered for patients with non-type I hypersensitivity to penicillins; they are more likely to be effective than the alternative agents. [c]High doses (90 mg/kg per day) are recommended for most children, especially those with day-care contacts or frequent infections.

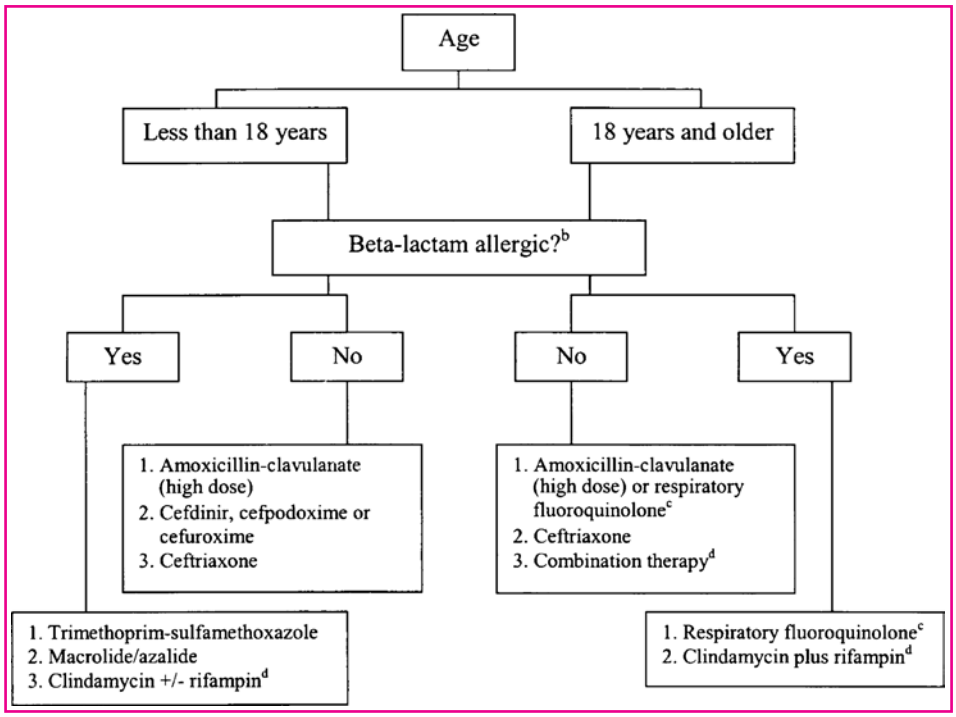


FIGURE 69–4. Treatment algorithm[a] for acute bacterial rhinosinusitis in patients with mild disease and recent antibiotic exposure or moderate disease.[31] [a]Antibiotics are listed in order of predicted efficacy based on predicted clinical and bacteriologic efficacy rates, clinical studies, safety, and tolerability. Doses can be found in Table 69–4. [b]Cephalosporins should be considered for patients with non-type I hypersensitivity to penicillins; they are more likely to be effective than the alternative agents. [c]Respiratory fluoroquinolone = gatifloxacin, levofloxacin, moxifloxacin. [d]Combination therapy should provide gram-positive and gram-negative coverage. Examples are high-dose amoxicillin or clindamycin plus rifampin or cefixime. There are no published clinical studies to support such combinations.

exposure to children in day care and recurrent disease. Severe disease requires evaluation and treatment in conjunction with specialized physicians such as otolaryngologists.

Antibiotic therapy (Table 69–4) is targeted against *S. pneumoniae,* but consideration must be given to other pathogens such as *H. influenzae*, *M. catarrhalis*, and PRSP. ❽ *Patients with mild disease and no prior antibiotic exposure should receive initial therapy with amoxicillin or amoxicillin-clavulanate.* Amoxicillin is effective for most mild infections and can be used in high doses to cover PRSP. It is less expensive and better tolerated than amoxicillin-clavulanate, which provides expanded coverage against β-lactamase-producing bacteria. Patients who are allergic to penicillins can be treated with an appropriate cephalosporin; severe penicillin allergies require treatment with alternative agents that may be less effective based solely on microbial resistance trends and not clinical data[11,20,31,36] (see Fig. 69–3). Initial therapy for patients with moderate symptoms or those with recent antibiotic exposure includes high-dose amoxicillin-clavulanate or a respiratory fluoroquinolone[31,32] (see Fig. 69–4).

Failure to respond to initial therapy after 3 days requires patient reevaluation to consider changing therapy to cover pathogens not treated with the initial choice. Antibiotics traditionally have been given for at least 10 to 14 days, with up to 21 days needed for resolution in some patients.[31] Recent data suggest that 5-day treatment courses of some fluoroquinolones and telithromycin are as effective as longer courses in adults with uncomplicated acute maxillary sinusitis.[40] Treatment success is influenced by medication adherence to the prescribed regimen, where once- or twice-daily agents are preferred over multiple daily doses.

Outcome Evaluation

Clinical improvement should be evident by 72 hours of therapy, as demonstrated by defervescence, reduction in nasal congestion and discharge, and improvements in facial pain or pressure and other symptoms. Patients should be monitored for common adverse events and referred to a specialist if clinical response is not obtained with first- or second-line therapy. Referral is also important for recurrent or chronic sinusitis or acute disease in immunocompromised patients. Surgery may be indicated in complicated cases.

PHARYNGITIS

Pharyngitis is an acute throat infection caused by viruses or bacteria. Other conditions, such as gastroesophageal reflux, postnasal drip, or allergies, also can cause sore throat and must be distinguished from infectious causes. Acute pharyngitis is responsible for 1% to 2% of adult physician visits and 6% to 8% of pediatric visits but generally is self-limited without serious sequelae.[41,42] Antibiotics are prescribed in 50% to 70% of cases in adults and children because of the inability to

TABLE 69–4. Antibiotics[a,b] for the Treatment of Acute Bacterial Rhinosinusitis[31,32]

Drug	Adult Dose	Pediatric Dose[c]	Comments
Amoxicillin	1.5–4 g/day in 2–3 doses	90 mg/kg per day in 2 doses	Lacks coverage against β-lactamase producers
Amoxicillin-clavulanate	1.75–4 g/day in 2–3 doses	90 mg/kg per day in 2 doses	Broad coverage particularly with high doses; Augmentin XR (2 g every 12 hours) targeted toward PRSP
Cefdinir	600 mg/day in 1–2 doses	14 mg/kg per day in 1–2 doses	Preferred oral liquid cephalosporin owing to palatability
Cefpodoxime proxetil	200 mg twice daily	10 mg/kg per day in 2 doses	
Cefuroxime axetil	250–500 mg twice daily	15–30 mg/kg per day in 2 doses	
Ceftriaxone	1 g IM/IV every 24 hours	50 mg/kg IM/IV every 24 hours	Experts recommend a 5-day treatment course
Trimethoprim-sulfamethoxazole	160/800 mg (1 DS tablet) twice daily	8–10 mg/kg per day of trimethoprim component in 2 doses	Considerable pneumococcal resistance limits use of this agent
Azithromycin	500 mg × 1 day, 250 mg/day × 4 days; 500 mg/day × 3 days; 2 g × 1 dose	10 mg/kg × 1 day, 5 mg/kg per day × 4 days; 10 mg/kg per day × 3 days	Increasing pneumococcal resistance and limited *H. influenzae* activity; single-dose regimen has high incidence of nausea, vomiting, and diarrhea
Clarithromycin	500 mg twice daily or 1 g once daily (XL only)	15 mg/kg per day in 2 doses	XL tablets reported to have fewer gastrointestinal problems and taste disturbances than twice-daily preparation
Telithromycin	800 mg once daily × 5 days	Not available	Improved pneumococcal coverage over macrolides; can cause blurred or double vision and difficulty focusing; cost and other side effects similar to clarithromycin-azithromycin
Doxycycline	100 mg twice daily	Avoid in children under 8 years	Can cause photosensitivity, gastrointestinal problems, tooth staining in young children; many drug-drug interactions (antacids, iron, calcium)
Gatifloxacin	400 mg once daily	Not available	Common fluoroquinolone side effects are nausea, vaginitis, diarrhea, dizziness; many drug-drug interactions (antacids, iron, calcium); tendon rupture, photosensitivity, QT prolongation possible; cost similar to amoxicillin/clavulanate
Levofloxacin	500–750 mg once daily (750 mg × 5 days)	Not available	
Moxifloxacin	400 mg once daily	Not available	
Clindamycin	150–450 mg 3–4 times daily	20–40 mg/kg per day in 3–4 doses	No gram-negative coverage; use in combination

[a]Refer to Table 69–2 for more information on antibiotics.
[b]Other FDA-approved antibiotics for ABRS not included in the Sinus and Allergy Health Partnership or AAP guidelines: cefaclor, cefprozil, cefixime, ciprofloxacin, erythromycin, loracarbef.
[c]Maximum dose not to exceed adult dose.



Patient Care and Monitoring

1. Assess the patient's signs and symptoms. Are they consistent with ABRS?
2. How long have the patient's symptoms been present? If symptoms are mild and present for fewer than 10 days, viral sinusitis is likely. Persistent moderate or acute severe symptoms are more indicative of bacterial infection.
3. Does the patient require antibiotic therapy? Avoid antibiotic use in viral disease.
4. Obtain a complete medication history, including prescription drugs, nonprescription drugs, and natural product use, as well as allergies and adverse effects.
5. Determine what adjunctive therapies should be used for symptoms, such as pain and congestion.
6. If applicable, determine which antibiotic to use and the duration of therapy.
7. Develop a plan to assess effectiveness of the chosen therapy and course of action to take if the patient does not improve or worsens.
8. Provide patient education on
   - What to expect from the antibiotic and other medications, including potential adverse effects
   - Avoidance of antihistamines, if appropriate
   - Signs of treatment failure
   - Role of viral infections in sinusitis and how to prevent disease transmission
9. Stress the importance of adherence to therapy, including antibiotic resistance concerns.

easily distinguish between viral and bacterial pathogens and fear of untreated streptococcal illness.[42,43]

Epidemiology and Etiology

Viruses most commonly cause pharyngitis, usually as part of an upper respiratory infection, and include rhinovirus, coronavirus, adenovirus, influenza virus, parainfluenza, and Epstein-Barr virus. *S. pyogenes*, or group A *Streptococcus,* is the most common bacterial cause of acute pharyngitis, responsible for 15% to 30% of cases in children and 5% to 10% of adult infections.[41,44] Infection is most common in late winter and early spring and is spread easily through direct contact with contaminated secretions. Clusters of infection are common within families, classrooms, and other crowded areas. Less common causes of bacterial pharyngitis are *Corynebacterium diphtheriae*, groups C and G streptococci, and *Neisseria gonorrhoeae*. This section will focus on group A streptococcal disease in which antibiotic therapy is indicated.

Pathophysiology

Pharyngeal colonization with group A streptococci occurs in up to 20% of children and is a risk factor for developing streptococcal pharyngitis after a break in mucosal integrity.[45] Clinicians should recognize that the symptoms of streptococcal pharyngitis usually are self-limited and resolve within 2 to 4 days of onset without treatment.[44] Historically, untreated or inappropriately treated disease caused acute **rheumatic fever,** potential permanent heart valve damage, and complications such as peritonsillar abscesses. Delayed antibiotic therapy given up to 9 days after symptom onset can prevent these sequelae, so proper diagnosis is important to minimize unnecessary antibiotic use for viral disease and complications of untreated streptococcal infection.[44,45]



Patient Encounter 2

A 7-year-old boy presents to the pediatrician with a sore throat and fever of 39.2°C for 24 hours. His mother reports that other children in his class have had "strep throat" recently. He also complains of pain on swallowing and is not eating or drinking very much. He does not have any other symptoms and has no known drug allergies. Physical examination reveals pharyngeal and tonsillar erythema with exudates and painful cervical lymphadenopathy.

- Does this child have streptococcal pharyngitis?
- Is antibiotic therapy indicated? If so, what agent should be initiated and for how long?
- What education should be provided to his mother regarding treatment?



Clinical Presentation and Diagnosis

Children between 5 and 15 years of age have the highest incidence of streptococcal pharyngitis. Parents and adults with significant pediatric contact are also at increased risk.

Signs and Symptoms of Streptococcal Pharyngitis[44,45]

- Sudden onset of sore throat with severe pain on swallowing
- Fever
- Headache, abdominal pain, nausea, or vomiting (especially in children)
- Pharyngeal and tonsillar erythema with possible patchy exudates
- Tender, enlarged anterior cervical lymph nodes
- Swollen and red uvula
- Soft palate petechiae
- Scarlatiniform rash
- General absence of conjunctivitis, hoarseness, cough, rhinorrhea, discrete ulcerations, and diarrhea (suggestive of viral etiology)

Diagnosis[41,45]

- Throat swab and culture: "Gold standard"; results within 24 to 48 hours
- Rapid antigen detection test: 80% to 90% sensitivity; results within minutes
- These tests should be performed *only* if there is a clinical suspicion of streptococcal pharyngitis.

Treatment

Desired Outcomes

❾ *The goals of therapy for streptococcal pharyngitis are to eradicate infection in order to prevent complications, shorten the disease course, and reduce infectivity and spread to close contacts*. Sequelae that can be prevented by antibiotic use are peritonsillar or retropharyngeal abscess, cervical lymphadenitis, and rheumatic fever. There is no evidence that antibiotic use has an impact on the incidence of poststreptococcal **glomerulonephritis.**

Pharmacologic Therapy

❹ *Antibiotics should be used only in cases of laboratory-documented streptococcal pharyngitis associated with clinical symptoms in order to avoid overtreatment*[45,46] (Fig. 69–5). Effective therapy (Table 69–5) reduces the infectious period from approximately 10 days to 24 hours and shortens symptom duration by 1 to 2 days.[41] ❿ *Treatment guidelines recommend penicillin as the drug of choice owing to its narrow antimicrobial spectrum, documented safety and efficacy in eradicating streptococci from the nasopharynx, and low cost.*[41,45] Historical studies proving that antibiotics prevent rheumatic fever used intramuscular procaine penicillin, but other antibiotics can eradicate nasopharyngeal streptococci and presumably are effective for

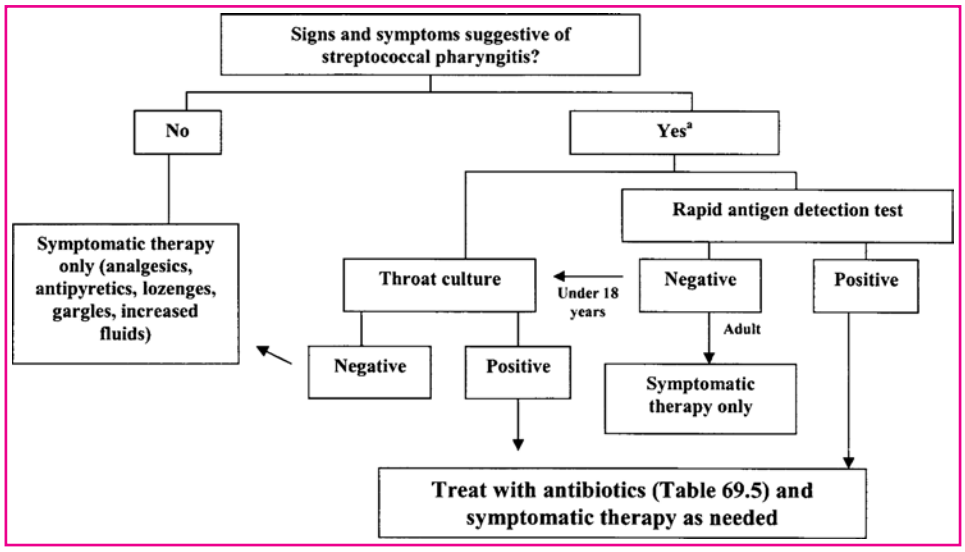


FIGURE 69–5. Treatment algorithm for management of pharyngitis in children and adults.[45,46] [a]Rapid antigen detection tests (RADTs) are preferred if the test sensitivity exceeds 80%.

preventing rheumatic heart disease.[45] ⑩ *Recent data suggest that cephalosporins are more effective than penicillin in producing bacteriologic and clinical cure and can be considered as first-line therapy alternatives in children and adults.*[47,48] Possible reasons for improved cephalosporin efficacy include the copresence of β-lactamase-producing organisms that inactivate penicillin, improved eradication of commensal streptococci by penicillin that are protective against group A streptococcal disease, and improved pharyngeal tissue penetration of cephalosporins. Usual duration of therapy is 10 days, but evidence is mounting that 5-day courses of certain cephalosporins are just as effective for bacterial eradication as 10 days of penicillin.[49,50]

Antibiotic resistance plays a smaller role in pharyngitis therapy compared with other URIs. ❶ *Penicillin resistance has not yet been documented in group A streptococci, but resistance and clinical failures occur more frequently with tetracyclines, trimethoprim-sulfamethoxazole, and to a lesser degree macrolides.* As such, patients with penicillin allergies should be treated with a first-generation cephalosporin (if non-type I allergy), a macrolide/azalide, or clindamycin. Recurrent infections caused by reinfection, poor adherence to therapy, or true penicillin failure can be treated with amoxicillin-clavulanate, clindamycin, or penicillin G benzathine.[45]

Outcome Evaluation

Antibiotics relieve symptoms over 3 to 5 days, and after the first 24 hours of therapy, patients can return to work or school if improved clinically. Follow-up cultures are not recommended to test for bacterial eradication. Lack of improvement or worsening of symptoms after 72 hours of therapy requires reevaluation. Recurrent symptoms following an appropriate treatment course should prompt reevaluation for possible retreatment.

TABLE 69–5. Antibiotics[a] for the Treatment of Streptococcal Pharyngitis[44,45]

Drug	Adult Dose	Pediatric Dose	Duration	Comments
Penicillin V	250 mg 3–4 times daily or 500 mg twice daily	250 mg 2–3 times daily 500 mg twice daily (over 12 years)	10 days	Drug of choice but increasing reports of treatment failures
Penicillin G benzathine	1.2 million units	600,000 units (if under 27 kg)	1 IM dose	Useful for nonadherence or emesis; painful injection
Amoxicillin	250–500 mg 3 times daily 750 mg daily being studied	40–50 mg/kg per day in 3 doses	10 days	Preferred over penicillin V for young children (more palatable)
Cephalexin	250–500 mg 4 times daily	25–50 mg/kg per day in 4 doses	10 days	Consider in penicillin allergy (if non-type I reaction)
Cefadroxil	500 mg twice daily	30 mg/kg per day in 2 doses	10 days	
Cefuroxime axetil	250 mg twice daily	20 mg/kg per day in 2 doses	10 days	
Cefdinir	300 mg twice daily or 600 mg once daily	14 mg/kg per day in 1–2 doses	5–10 days	Broad spectrum; expensive
Azithromycin	500 mg once daily	12 mg/kg once daily	5 days	Increasing resistance
Clindamycin	150 mg 4 times daily	20–30 mg/kg per day in 3 doses	10 days	Useful for recurrent infections

[a]Other FDA-approved agents include amoxicillin-clavulanate, cefixime, cefaclor, cefprozil, cefpodoxime, erythromycin, clarithromycin, and others.



Patient Care and Monitoring

1. Assess the patient's signs and symptoms. Are they consistent with streptococcal pharyngitis? Are symptoms of viral infection present?
2. Perform laboratory testing to confirm the presence of group A streptococci.
3. Does the patient require antibiotic therapy? Avoid antibiotic use in viral disease.
4. Obtain a complete medication history, including prescription drugs, nonprescription drugs, and natural product use, as well as allergies and adverse effects.
5. Recommend antipyretic or analgesic therapy, if needed.
6. If applicable, determine which antibiotic to use and the duration of therapy.
7. Develop a plan to assess effectiveness of chosen therapy and course of action to take if the patient does not improve or worsens.
8. Provide patient education on
   - What to expect from the antibiotic, including potential adverse effects
   - Avoidance of close contacts for 24 hours
   - Signs of treatment failure
9. Stress the importance of adherence to therapy, including antibiotic resistance concerns.

ABBREVIATIONS

ABRS: acute bacterial rhinosinusitis
AOM: acute otitis media
OME: otitis media with effusion
PRSP: penicillin-resistant *Streptococcus pneumoniae*
URI: upper respiratory tract infection

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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70 Skin and Soft Tissue Infections

A. Christie Graham and Randy Wesnitzer



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Discuss characteristics of the skin that render it resistant to infection.
2. Describe the epidemiology, etiology, pathogenesis, clinical manifestations, diagnostic criteria, and complications associated with skin and soft tissue infections.
3. Identify the desired therapeutic outcomes for patients with skin and soft tissue infections.
4. Recommend appropriate empirical and definitive antimicrobial regimens when given a diagnosis, physical examination, and laboratory findings.
5. Monitor chosen antimicrobial therapy for safety and efficacy.

Key Concepts

❶ Impetigo is a skin infection that most commonly afflicts young children. It is caused by group A streptococci or *Staphylococcus aureus* and is characterized by the development of numerous blisters that rupture and form crusts. Dicloxacillin, cephalexin, and topical mupirocin are considered the antibiotics of choice for treatment of impetigo.

❷ Folliculitis, furuncles, and carbuncles refer to the inflammation of one or more hair follicles, often attributed to infection with *S. aureus.* Treatment depends on severity and may involve local heat, incision and drainage, and/or oral or topical antibiotic therapy.

❸ Erysipelas is a superficial infection of the upper dermis and superficial lymphatics. It is distinguished clinically from cellulitis by its well-defined borders and slightly raised lesions. It is usually caused by β-hemolytic streptococci and treated with penicillin.

❹ Cellulitis is a bacterial infection of the dermis and subcutaneous tissue. *S. aureus* and β-hemolytic streptococci are the most common causes of acute cellulitis in otherwise healthy hosts. Persons who are immunocompromised, have vascular insufficiency, or use injection drugs are at risk for polymicrobial cellulitis.

❺ The antibiotics of choice for treating methicillin-sensitive *S. aureus* (MSSA) infections are penicillinase-stable penicillins and first-generation cephalosporins.

❻ Community-acquired methicillin-resistant *S. aureus* (CA-MRSA) is becoming an increasingly common pathogen in cellulitis. CA-MRSA can be distinguished from health care–associated MRSA (HA-MRSA) by its genetic dissimilarity, host population, drug susceptibility patterns, and toxin production.

❼ Immediate surgical débridement and intravenous broad-spectrum antibiotics are key to reducing the mortality associated with necrotizing fasciitis.

❽ The pathogenesis of diabetic foot infection stems from three key factors: neuropathy, angiopathy, and immunopathy. Aerobic gram-positive cocci, such as *S. aureus* and β-hemolytic streptococci, are the predominant pathogens in acutely infected diabetic foot ulcers. However, chronically infected wounds are subject to polymicrobial infection and require treatment with broad-spectrum antibiotics.

❾ Prevention is key in the management of pressure sores. Mild superficial pressure sore infections may be treated with topical antimicrobial agents. Systemic antibiotics are indicated for pressure sores associated with spreading cellulitis, osteomyelitis, or bacteremia.

❿ Every patient receiving antimicrobial therapy for skin and soft tissue infections must be monitored for efficacy and safety. Efficacy typically is manifested by reductions in temperature, white blood cell count, erythema, edema, and pain that begin within 48 to 72 hours. To ensure safety, dose antibiotics according to renal and hepatic function as appropriate, and monitor for and minimize adverse drug reactions, allergic reactions, and drug interactions.

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Infections of the skin and soft tissues are encountered frequently in both acute- and ambulatory-care settings. They can range in severity from mild, superficial, and self-limiting to life-threatening deep tissue infections that require intensive care, surgical intervention, and intravenous (IV) broad-spectrum antibiotics. They are sometimes associated with severe complications, including osteomyelitis, glomerulonephritis, and septic shock. This chapter will cover the epidemiology, pathogenesis, clinical manifestations, and pharmacologic management of the more common and severe bacterial skin and soft tissue infections (SSTIs).

PATHOPHYSIOLOGY

Intact skin generally is resistant to bacterial, fungal, and viral infection. In addition to providing a mechanical barrier, its relative dryness, slightly acidic pH, colonizing bacteria, frequent desquamation, and sweat (which contains IgG and IgA) prevent invasion by various microorganisms.[1] Conditions that predispose a patient to SSTIs include (1) high bacterial load (greater than 10^5 microorganisms), (2) excessive skin moisture, (3) decreased skin perfusion, (4) availability of bacterial nutrients, and perhaps most important, (5) damage to the corneal layer of the skin.[2]

IMPETIGO

Epidemiology and Etiology

Impetigo, which stems from the Latin word for "attack," is a common skin infection worldwide. ❶ *It predominately afflicts children between 2 and 5 years of age but may occur in any age group.*[3] *β-Hemolytic streptococci and Staphylococcus aureus are the most common causative pathogens.*[3,4] It is a superficial infection and is spread easily, especially in settings of poor hygiene and crowding and particularly during the summer months. The offending microorganisms colonize the skin surface and then invade through abrasions, insect bites, or other small traumas. The scabby, crusty eruption of impetigo ensues. These lesions may occur anywhere on the body but are most common on the face and extremities.

Clinical Presentation and Diagnosis

Impetigo lesions are numerous, well localized, and **erythematous.** They develop either as small, thin-walled blisters (impetigo contagiosum) or as larger blisters (bullous impetigo).[3–5] The blisters rupture easily, leaving behind a **friable** crust reminiscent of cornflakes. The lesions of impetigo are rarely painful but are **pruritic**. Scratching the lesions can spread the infection to other areas of the body.

Treatment

Desired Outcomes

The primary goal of therapy for impetigo is resolution of infection. A secondary goal is prevention of glomerulonephritis (although extremely rare) secondary to group A *Streptococcus* (GAS).

Nonpharmacologic Treatment

Because impetigo is rarely painful, there is often a delay in seeking medical attention. However, the lesions will resolve with time and increased hygiene. Soaking the lesions with soap and water and the use of skin emollients to dry skin areas may reduce spread of the lesions.

Pharmacologic Treatment

Because GAS historically has been the primary causative organism, penicillin has been the mainstay of therapy. ❶ *However, the incidence of S. aureus impetigo is increasing, so oral penicillinase-stable penicillins or first-generation cephalosporins are now preferred.*[3] Erythromycin is an alternative choice when penicillin allergy is a concern. *Topical mupirocin may be used alone when there are few lesions.*[3]

FOLLICULITIS, FURUNCLES, AND CARBUNCLES

See Table 70–1.

LYMPHANGITIS

Epidemiology and Etiology

Simply stated, lymphangitis is an inflammation of a lymphatic channel. Lymphangitis begins when a local skin infection is not contained. The infection spreads into the lymphatic channel and is carried to the regional lymph nodes. Most cases are attributed to GAS.

Clinical Presentation and Diagnosis

Lymphangitis is characterized by red linear streaks that extend from the infection site toward the regional lymph nodes.[5,7] The lymph nodes become tender and swollen. If left unchecked, lymphangitis may lead to a complicating bacteremia.

Treatment

Pharmacologic Treatment

In uncomplicated cases, prompt oral antibiotic therapy with amoxicillin or a first-generation cephalosporin halts the progression of lymphangitis. Clindamycin may be used if the patient has a significant β-lactam allergy. Intravenous antibiotics (penicillinase-stable penicillins, first-generation cephalosporins,

TABLE 70–1. Folliculitis, Furuncles, and Carbuncles[3,5,6]

	Folliculitis	Furuncles	Carbuncles
Epidemiology/ etiology	❷ *Folliculitis is a superficial inflammatory reaction involving the hair follicle.* The most familiar form of folliculitis is acne. It can be infectious, caused by microorganisms such as *Staphylococcus aureus, Pseudomonas,* and *Candida*. It is also sometimes chemically induced.	*Also known as boils, furuncles might be described as a deep form of folliculitis. A furuncle is a bacterial infection that has spread into the subcutaneous skin layers but still only involves individual follicles.* Furuncles occur primarily in young men. DM and obesity are other predisposing factors. *Staphylococci are the most common cause.*	*Carbuncles share all the characteristics of furuncles. However, a carbuncle is larger and involves several adjacent follicles and may extend into the subcutaneous fat.* Carbuncles are most common in diabetics and tend to from on the neck and back.
Presentation and diagnosis	Folliculitis presents as small, pruritic, erythematous **papules**. Location of the lesions and a good patient history are often all that are required in the diagnosis of folliculitis. While the papules may be cultured and Gram stains or potassium hydroxide stains done to help determine causative agent, it is not generally required because folliculitis often resolves spontaneously within a few days.	Furuncles most commonly develop on the face, neck, axilla, and buttock. A furuncle typically starts as a small, red, tender nodule. Within in a few days, the nodule becomes painful and pustular. Typically, a furuncle will spontaneously discharge pus, heal, and leave a small scar.	These are larger than a furuncle and exquisitely painful. All carbuncles and furuncles that are large or associated with cellulitis or fever require incision and drainage in order to resolve.
Desired outcomes	The goals of therapy for folliculitis, furuncles, and carbuncles are resolution of infection with no or minimal scaring. A secondary goal of therapy for larger furuncles and all carbuncles is to minimize the risk of endocarditis or osteomyelitis by reducing bloodstream invasion.		
Non-pharmacologic treatment	❷ *Warm compresses are generally sufficient.*	*Moist heat is indicated to facilitate drainage. Large furuncles require incision and drainage.*	*Incision and drainage are indicated.*
Pharmacologic treatment	❷ Often resolves spontaneously. *A topical antibiotic or antifungal may be used to control the spread of infection but generally is unnecessary.* For staphylococcal or streptococcal folliculitis, antibiotic ointments such as mupirocin might be administered three times daily. Antifungal shampoo can be used for **dermatophytes.**	*Carbuncles and furuncles that have surrounding cellulitis and fever or are located midline on the face must be treated systemically with an antibiotic that will cover Staphylococcus, such as dicloxacillin, cephalexin, or erythromycin.* Treatment should continue until acute inflammation has resolved, usually a 5–10-day course.	

or clindamycin) and hospitalization are warranted for patients displaying signs of systemic illness or bacteremia.[7]

CELLULITIS AND ERYSIPELAS

Epidemiology and Etiology

Cellulitis and erysipelas are bacterial infections of the skin. Although separate entities, there is some clinical difficulty in distinguishing the two. ❸❹ *Cellulitis is a bacterial infection of the dermis and subcutaneous tissue, whereas erysipelas is a more superficial infection of the upper dermis and superficial lymphatics.* Although both can occur on any part of the body, about 90% of infections involve the leg.[8,9] Another 7.5% of cases involve the arm or face. Erysipelas is most common in the young and the elderly. Typically, both infections develop after a break in skin integrity, resulting from trauma, surgery, ulceration, burns, tinea infection, or other skin disorder. However, they may occur after an inapparent break in the skin, and the skin may appear previously intact.[3,10] In rare cases, cellulitis develops from blood-borne or contiguous (from adjacent tissues) spread of pathogens.[5,10]

Etiologic microorganisms vary according to the area involved, host factors, and exposures. ❹ *In otherwise healthy adults, S. aureus and GAS are the most common causative bacteria.* ❸ *GAS is the causative pathogen in approximatey 65% of erysipelas cases.*[9] ❹*Persons who are immunocompromised, have vascular insufficiency, or use injection drugs are at risk for polymicrobial cellulitis.*[3]

Clinical Presentation and Diagnosis

The manifestations of and diagnostic criteria for erysipelas and cellulitis are presented in Table 70–2. Once diagnosed, cellulitis is grouped into uncomplicated or complicated presentations depending on patient characteristics and severity of

TABLE 70–2. Presentation of Erysipelas and Cellulitis[3,9–12]

Symptoms

The infected area is described as painful or tender. In the case of erysipelas, the patient may complain of "burning pain" at the lesion site.

Signs

Both erysipelas and cellulitis are manifested by rapidly spreading areas of redness, edema, and heat. Vesicles containing clear fluid may appear on the skin. Lymphangitis and regional lymphadenopathy may be observed.

Important clinical differences between erysipelas and cellulitis exist:

- In erysipelas, low-grade fever and flulike illness are common prior to development of the lesion. The lesion is fiery red, raised above the level of surrounding skin, and has well-defined borders.
- In cellulitis, the lesion is not raised and has poorly defined margins.

Laboratory Tests

Leukocytosis may be present.

Cultures and sensitivities:

- Blood cultures are only positive about 4% of the time but should be obtained for complicated cases. Cultures aspirated from the lesion have an organism isolation rate of less than 20% but also may be considered.
- Abscess drainage and débrided tissue, if obtainable, can be cultured and will yield the causative organism(s) up to 90% of the time.

Imaging Studies

Imaging studies may identify abscess formation, gas in the soft tissues, or osteomyelitis.

infection. Complicated infections are those in which there are systemic signs and symptoms of infection (i.e., fever, chills, leukocytosis, and hypotension); the patient is immunocompromised, bacteremic, or has vascular insufficiency; polymicrobial infection is suspected; or the cellulitis is spreading rapidly, involves a large area of the body, or is chronic. Persons with complicated cellulitis often are hospitalized and require IV antibiotics. Otherwise, cellulitis is classified as uncomplicated and treated with oral antibiotics on an outpatient basis.[12]

Complications of Cellulitis

The causative pathogen(s) of cellulitis can enter the circulation, causing a bacteremia and occasionally sepsis. The mortality rate associated with complicated cellulitis requiring hospitalization is approximately 5%. Patients with multiple comorbid conditions, congestive heart failure, or severe obesity tend to be at higher risk. If the circumference of an extremity is cellulitic, compartment syndrome becomes a concern, and a surgical consult may be required. Infrequently, cellulitis can progress to necrotizing fasciitis, a life-threatening condition that will be discussed later in this chapter.[13]

Recurrent cellulitis can be problematic as well. About 30% of patients hospitalized with cellulitis will develop a recurrent episode within 3 years. Vascular and lymphatic insufficiencies increase the risk of recurrences.[10,11,13]

Treatment

Desired Outcomes

The goals of therapy for cellulitis and erysipelas are rapid and successful eradication of the infection and prevention of related complications.

Nonpharmacologic Treatment

Nonpharmacologic treatment includes elevating and immobilizing the involved limb to decrease associated swelling. For cellulitis, sterile saline dressings should be placed on any open lesions to cleanse them of **purulent** materials. Surgical débridement is indicated occasionally for severe infection. If an abscess is present, drainage is imperative to achieving clinical cure.[10]

Pharmacologic Treatment

❸ *Penicillin is the treatment of choice for erysipelas.* In uncomplicated cases, a 5-day course is as effective as a 10-day course.[3] Other agents that are acceptable for treatment include clindamycin, erythromycin, cephalexin, and dicloxacillin.

❺ *Currently, β-lactams active against penicillinase-producing strains of S. aureus (commonly known as methicillin-sensitive S. aureus, or MSSA) are the drugs of choice for acute bacterial cellulitis in otherwise healthy individuals.*[10] ❻ *However, there is a rapidly increasing prevalence of cellulitis caused by community-acquired methicillin-resistant S. aureus (CA-MRSA) in this population.* Treatment of these infections is problematic secondary to the organism's resistance to many antibiotics and the lack of well-studied, orally administered agents active against it.[14]

❻ *CA-MRSA can be distinguished from health care–associated MRSA (HA-MRSA) by its genetic dissimilarity, host population, drug susceptibility patterns, and toxin production.* While acquisition of HA-MRSA is associated with well-defined risk factors (i.e., history of prolonged hospital or nursing home stay, past antimicrobial use, indwelling catheters, pressure sores, surgery, or dialysis), risk factors for acquisition of CA-MRSA are not well established.[14]

CA-MRSA is susceptible to more antibiotics than HA-MRSA. Like HA-MRSA, CA-MRSA typically is sensitive to vancomycin, linezolid, daptomycin, tigecycline, and quinupristin/dalfopristin, but it also may be sensitive to clindamycin, doxycycline, minocycline, and/or trimethoprim-sulfamethoxazole (TMP-SMX).[14]

Of the latter four agents, clindamycin has the most data supporting its use. However, the clinician must be aware of inducible clindamycin resistance. For CA-MRSA isolates determined to be resistant to erythromycin but sensitive to clindamycin, an additional laboratory analysis, known as the *erythromycin-clindamycin D-zone test,* is conducted to assess for inducible clindamycin resistance.[15] Isolates for which the D-zone test indicates inducible resistance should not be treated with clindamycin.

With regard to the clinical effectiveness of TMP-SMX and the tetracyclines, anecdotal evidence and small trials support their use in the treatment of CA-MRSA cellulitis. However, large randomized, controlled trials are needed to confirm their place in therapy.[16,17]

Finally, CA-MRSA produces the virulent Panton-Valentine leukcocidin toxin. It destroys leukocytes, causes severe tissue damage and necrosis, and has been associated with both necrotizing skin infections and pneumonia.[14]

In addition to being at risk for staphylococcal and streptococcal cellulitis, immunocompromised patients are also at risk for disease caused by resistant gram-negative, anaerobic, and low-virulence organisms (i.e., *S. epidermidis*). Empirical broad-spectrum antimicrobial coverage, including coverage for resistant organisms such as HA-MRSA and *Pseudomonas* spp., is appropriate for severe cellulitis and/or systemic illness. The clinician should be diligent in attempting to isolate a causative pathogen in these individuals.[3]

Injection drug use also predisposes individuals to polymicrobial cellulitis. The antecubital region of the arm is usually the site of infection. *S. aureus,* the most common isolate, is frequently associated with abscess formation. Because some injection drug users lick their needles to "clean" them, antibiotics with anaerobic coverage should be used. Occasionally, *Candida* spp. are isolated, and the patient may require antifungal therapy.[18]

Table 70–3 lists some recommended antibiotic regimens for the treatment of cellulitis. The duration of therapy for uncomplicated cellulitis typically ranges from 7 to 10 days. For complicated cellulitis, begin therapy with IV antibiotics and switch to oral once the patient is afebrile and skin findings begin to resolve. Typically, this is done after 3 to 5 days. The complete duration of therapy can range from 10 to 14 days and longer in cases where abscess, tissue necrosis, underlying skin wounds, or delayed response to therapy are involved.[10]

TABLE 70–3. Empirical Antimicrobial Therapy for Cellulitis[3,6,10]

Host Factors	Probable Etiologic Bacteria	Mild Infection or Step-Down Therapy[a] (Oral Antibiotic Therapy)	Moderate–Severe Infection[a] (IV Antibiotic Therapy)
Previously healthy	MSSA GAS CA-MRSA	Dicloxacillin 500 mg every 6 hours Cephalexin 500 mg every 6 hours CA-MRSA suspected or allergy to PCNs: TMP-SMX DS 1–2 tabs every 12 hours[b] Clindamycin 300 mg every 6 hours[c] Doxycycline 100 mg every 12 hours[b]	Nafcillin 1–2 g every 4 hours Cefazolin 1–2 g every 8 hours CA-MRSA suspected or allergy to PCNs: Vancomycin 15 mg/kg every 12 hours Clindamycin 600 mg every 8 hours[c] TMP-SMX 2.5 mg/kg (TMP component) every 12 hours[b] Doxycycline 100 mg every 12 hours[b] Linezolid 600 mg every 12 hours Daptomycin 4 mg/kg daily
Injection drug use	MSSA GAS Gram-negatives Anaerobes CA-MRSA[d]	Amoxicillin-clavulanate 500 mg every 8 hours Fluoroquinolone + clindamycin 300 mg every 6 hours TMP-SMX DS 1–2 tabs every 12 hours + clindamycin 300 mg every 6 hours	Ampicillin-sulbactam 3 g every 6 hours Piperacillin-tazobactam 3.375 g every 6 hours Ceftriaxone 1 g daily + clindamycin 600 mg every 8 hours Ertapenem 1 g daily
Immune compromise, DM	MSSA HA-MRSA[e] Gram-negatives *Pseudomonas* spp.	Amoxicillin-clavanate 500 mg every 8 hours Fluoroquinolone[f] + clindamycin 300 mg every 6 hours	Piperacillin-tazobactam 3.375–4.5 g every 6 hours[g] Imipenem-cilastatin 500 mg every 6 hours[g] Cefepime 2 g every 8–12 hours[g] + metronidazole 500 mg every 8 hours Cefatazidime 2 g every 8 hours[g] + clindamycin 600 mg every 8 hours Fluoroquinolone[f] + clindamycin 600 mg every 8 hours Tigecycline 100 mg load, then 50 mg every 12 hours

[a]Doses given are for adults with normal renal function. IV therapy can be switched to oral therapy (as for mild infection) when the patient is afebrile and signs of infection are resolving.
[b]Limited clinical data exist for the treatment of MRSA infections.
[c]CA-MRSA isolates resistant to erythromycin should be evaluated for inducible clindamycin resistance.
[d]If CA-MRSA suspected, regimen must include an agent with activity against this organism.
[e]If HA-MRSA suspected, regimen must include vancomycin, daptomycin, linezolid, or tigecycline.
[f]Ciprofloxacin and levofloxacin exhibit activity against *Pseudomonas aeruginosa*.
[g]*Pseudomonas aeruginosa* generally is susceptible to this agent.



Patient Encounter, Part 1

A 56-year-old man presents to the emergency room with complaints of right lower leg pain and redness. Examining his leg, you notice that he has erythema and edema extending from his ankle to proximal tibia. The area feels warm. On questioning, the patient states that the redness started approximately 2 days ago. He has felt feverish over the previous 48 hours but did not check his temperature. He has had no other symptoms. He states that he bumped his shin on the bed frame last week and sustained a bruise but no apparent breaks in the skin. His vital signs at the clinic reveal a temperature of 38.3°C, pulse 102 beats per minute, blood pressure 110/72 mm Hg, and respiratory rate 20 breaths per minute. The physician diagnoses this patient with cellulitis.

- What clinical manifestations are suggestive of cellulitis?
- What additional information do you need before developing a therapeutic plan for this patient?

NECROTIZING FASCIITIS

Epidemiology and Etiology

Necrotizing fasciitis (NF) is an uncommon, rapidly progressive, life-threatening infection of the subcutaneous tissue and fascia. Its associated mortality rate is approximately 25% and is nearly 70% in patients who present with septic shock.[3,19] NF can affect any age group. Although the risk of NF is higher in patients with underlying diseases (specifically diabetes, alcoholism, cardiac disease, and peripheral vascular disease), healthy hosts can become infected as well.[20]

NF typically erupts after an initial trauma, which can range from a small abrasion to a deep penetrating wound. The infection begins in the fascia, where bacteria replicate and release toxins that facilitate their spread.[21]

There are two types of NF, distinguishable by microbiology, source, and severity of illness. Type I (~70% of cases) is polymicrobial and typically involves anaerobes (i.e., *Bacteroides* or *Peptostreptococcus*), **facultative anaerobes** (i.e., β-hemolytic streptococci), and Enterobacteriaceae (e.g., *Escherichia coli*, *Enterobacter*, or *Klebsiella*).[5] Type I infections develop in the following clinical settings: after surgery or deep penetrating wounds involving the bowel; from decubitous ulcer, perianal, or vulvovaginal infection; or from the injection site in an injection drug user (IDU).[3,5]

Type II NF is generally a monomicrobial infection caused by invasive GAS. Occasionally *S. aureus* is implicated. Type II often occurs after minor trauma, such as an insect bite or abrasion.[3] It is more severe than type I because invasive strains of GAS produce toxins that induce erythema, systemic toxicity, multiorgan failure, and shock.[22]



Patient Encounter, Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH
Hypertension. He is not aware of any other illnesses.

FH
Father died of stroke at age 72. Mother, age 79, is alive with diabetes and a history of breast cancer. One brother, age 59, is alive and healthy.

SH
Works as a college professor. Married. Three grown children. Denies tobacco use. Drinks approximately 4 glasses of wine on weekends. Denies illicit drug use.

Meds
Atenolol 100 mg by mouth daily, multiple vitamin 1 tablet by mouth daily

Allergies: No known drug allergies

ROS
(+) pain and swelling in the right lower extremity; (–) headache, chest pain, shortness of breath, cough, nausea, vomiting, diarrhea, and weight loss

PE
- **General:** Patient is in no acute distress. He weighs 72 kg (158 lbs) and is 5 ft, 9 in tall.
- **Chest:** Lungs bilaterally clear to auscultation.
- **CV:** Regular rate, rhythm. No murmurs/rubs/gallops.
- **Exts:** Right lower extremity with erythema and edema from the ankle to just below the knee. Warm to the touch. LLE within normal limits.

Labs
White blood cell count 17.3 × 10^3/μL, serum creatinine 0.8 mg/dL (70.7 μmol/L)
The patient is diagnosed with cellulitis and admitted to the medical floor.

- What are the most likely causative organisms in this case of cellulitis?
- What are the goals of therapy for this patient?
- What nonpharmacologic interventions would you recommend for him?
- What antimicrobial therapy would you recommend? Include drug, dosage, route, interval, and duration of therapy.
- How would you monitor your selected regimen for safety and efficacy?
- If the MRSA rate at your hospital is 75% (mostly CA-MRSA), would you change your pharmacologic recommendation? If so, how?

Clinical Presentation and Diagnosis

Patient outcomes rely on the clinician's ability to recognize NF early in the course of disease. This is often difficult because early disease tends to be indistinguishable clinically from cellulitis. The clinical presentation of NF is presented in Table 70–4.

Complications

NF is perhaps the most devastating SSTI. Left untreated, it can invade the muscles and circulation, resulting in myonecrosis and septic shock, respectively. Half the NF cases caused by GAS are accompanied by GAS toxic shock-like syndrome. The syndrome is endotoxin-mediated, manifested by hypotension and multiorgan dysfunction, and is fatal in 30% to 70% of those afflicted.[5,19] Amputation is required in up to 50% of patients with extremity infections.[23] Once the patient recovers from acute NF, he or she often requires skin and/or muscle grafting and consequent physical rehabilitation depending on the amount and types of tissue removed during surgical intervention and the duration of hospital stay.[24]

Treatment

Desired Outcomes

The goals of therapy for NF include eradication of infection and reduction of related morbidity and mortality.

Nonpharmacologic Treatment

After resuscitation and hemodynamic stabilization, *prompt surgical intervention is key in the treatment of NF. Delayed operative débridement increases mortality.*[21] Some clinicians recommend hyperbaric oxygen (HBO) as an adjunct treatment of NF, although its use is controversial. Clinical data supporting the use of HBO in NF are inconsistent, with some trials showing reduced mortality rates and others showing no benefit.[25]

TABLE 70–4. Presentation of Necrotizing Fasciitis[3,21]

Symptoms
Early: Severe pain that is disproportionate to clinical signs and extends beyond the margins of the infected area.
Late: Area may become numb secondary to muscle and nerve involvement.
Signs
Early: Skin is erythematous, edematous, and warm; the clinical presentation is similar to that of cellulitis.
Intermediate (within 24–48 hours): Blisters and bullae indicate severe skin and tissue ischemia.
Late: The skin becomes violaceous and progressively gangrenous; hemorrhagic bullae may be present. Septic shock may ensue.
Laboratory Tests
Leukocytosis, thrombocytopenia, and elevated serum creatinine may be present.
Deep tissue specimens obtained during surgical irrigation and débridement should be sent for Gram stain, culture, and sensitivity.[3]
Imaging Studies
MRI and CT scans may reveal fluid and gas along fascial planes.
Typically, imaging studies are avoided when making a diagnosis because they may delay surgical intervention and increase mortality.

Pharmacologic Treatment

Broad-spectrum IV antibiotic therapy should be initiated immediately in patients with NF regardless of suspected type. Often a high-dose β-lactam/β-lactamase inhibitor or carbapenem is used in combination with clindamycin. Although the latter agents are active against gram-positive aerobes and anaerobes, clindamycin still should be added to decrease bacterial toxin production, thereby limiting tissue damage.[3]

If GAS is identified as the sole causative organism from deep tissue culture, antimicrobial therapy can be narrowed to high-dose IV penicillin G plus clindamycin. Antibiotic therapy should be continued until further operative débridements are unnecessary, the patient displays substantial clinical improvement, and fevers have abated for at least 48 to 72 hours.[3]

CLOSTRIDIAL MYONECROSIS

Another important necrotizing skin and soft tissue infection is clostridial myonecrosis (gas gangrene). Clostridial myonecrosis can develop spontaneously but most often occurs after trauma. *Clostridium perfringens* is the most common causative pathogen.

The infected area initially may be tense, painful, and pale. The color changes rapidly, becoming bronze and then purplish red. Bullae filled with reddish blue fluid appear. Gas in the tissue is uniformly present and detected by imaging studies or as crepitus. The infection quickly becomes systemic, and the patient may present with shock and multiple-organ failure. The management of clostridial myonecrosis, like NF, requires aggressive surgical débridement and appropriate antibiotics, generally high-dose penicillin plus clindamycin.[5]

DIABETIC FOOT INFECTIONS

Epidemiology and Etiology

Foot ulcers and related infections are among the most common, severe, and costly complications of diabetes mellitus (DM). Fifteen percent of all patients with DM develop at least one foot ulcer, resulting in direct health care expenditures of approximately $9 billion annually in the United States.[26,27] Diabetic foot ulcers and wounds are highly susceptible to infection. Related skin, soft tissue, and bone infections account for 25% of all diabetes-related hospitalizations.[28] More than half of all nontraumatic lower extremity amputations (LEAs) performed each year in Western nations are linked to diabetic foot infection; 80,000 LEAs are performed annually in the United States alone.[29,30]

Pathophysiology

❽ *The pathogenesis of diabetic foot infection stems from three key factors:* ***neuropathy,*** *angiopathy, and immunopathy.*[29,30] Neuropathy, the most prominent risk factor for diabetic foot ulcers, develops when continuously high blood glucose levels damage motor, autonomic, and sensory nerves. Damage to motor neurons that supply the small intrinsic muscles of the foot causes deformation, resulting in altered muscular balance, abnormal areas of pressure on the tissues and bones, and repetitive injuries. Damage to autonomic neurons results in the shunting of blood through direct arteriole-venous communications, thereby decreasing capillary flow. The secretion of sweat and oil is also diminished, producing dry, cracked skin that is more prone to infection. Finally, damage to sensory neurons produces a loss of protective sensation so that the patient becomes unaware of injury or ulceration.

Angiopathy of large (macroangiopathy) and small (microangiopathy) vessels is also the result of high blood glucose concentrations. Angiopathy results in ischemia and skin breakdown.

Finally, persons with diabetes have altered immune function that predisposes them to infection. Although their humoral immune responses remain intact, leukocyte function and cell-mediated immunity are compromised in poorly controlled disease. Achieving and maintaining tightly controlled blood glucose levels can wholly or partially reverse diabetic immunopathy.

Infected diabetic foot ulcers typically contain a multitude of microorganisms. ❽ *Aerobic gram-positive cocci, such as S. aureus and β-hemolytic streptococci, are the predominant pathogens in acutely infected diabetic foot ulcers. However, chronically infected wounds are subject to polymicrobial infection.* The clinician should suspect the involvement of gram-negative (Enterobacteriaceae and *P. aeruginosa*) and possibly low-virulence pathogens (including enterococci and *S. epidermidis*) in chronic or necrotic wounds. Foul-smelling, necrotic or gangrenous wounds are also commonly infected with anaerobic bacteria. Patients recently hospitalized or treated with broad-spectrum antibiotics are at risk for infection with antibiotic-resistant organisms, including MRSA and vancomycin-resistant enterococci (VRE).[31]

Clinical Presentation and Diagnosis

Not all diabetic foot ulcers are infected. However, infection is often difficult to detect when perfusion and the inflammatory response are limited in the diabetic patient. The common signs and symptoms (i.e., pain, erythema, and edema) of infection may be absent.[32] Still, the diagnosis of diabetic foot infection depends mostly on clinical evaluation.

Purulent drainage from the ulcer is indicative of infection. When pus and inflammatory symptoms are not present, the clinician must be astute to more subtle findings. These include delayed healing, increase in lesion size, prolonged exudate production, malodor, and tissue friability. Abnormal granulation tissue also may be present, as evidenced by color change (from bright red to dark red, brown, or gray) and increased bleeding. The ability to probe the ulcer to the underlying bone is highly indicative of osteomyelitis.[32]

Diabetic foot infections are classified into four categories based on clinical presentation using the PEDIS scale (perfusion, extent/size, depth/tissue loss, infection, sensation). Grade 1 signifies no infection; grade 2, involvement of skin and subcutaneous tissue only; grade 3, extensive cellulitis or deeper infection; and grade 4, systemic inflammatory response syndrome.[33] Grade 2 infections are classified as non-limb-threatening infections, whereas grades 3 and 4 infections are limb-threatening.[30,31] Table 70–5 provides detailed information regarding the grades.

Imaging studies, such as x-ray and magnetic resonance imaging (MRI), can identify osteomyelitis. Blood cultures should be obtained from all patients with signs and symptoms of systemic illness. Deep tissue cultures may help to direct therapy. Bone also may be sent for culture in cases of osteomyelitis. Superficial cultures are unreliable and should be avoided.

Complications

Spreading soft tissue infection and osteomyelitis are often the first complications that develop from diabetic foot infection. Some patients develop bacteremia and sepsis.

TABLE 70–5. Clinical Classification of a Diabetic Foot Infection

Infection Severity	PEDIS Grade	Clinical Manifestations of Infection
Uninfected	1	Wound lacking purulence or any manifestations of inflammation
Mild	2	Presence of at least two manifestations of inflammation (purulence or erythema, pain, tenderness, warmth or **induration**), but any cellulitis/erythema extends no more than 2 cm around the ulcer, and infection is limited to the skin or superficial subcutaneous tissues; no other local complications or systemic illness
Moderate	3	Infection (as above) in a patient who is systemically well and metabolically stable but who has at least 1 of the following characteristics: cellulitis extending greater than 2 cm, lymphangitic streaking, spread beneath the superficial fascia, deep tissue abscess, gangrene, and involvement of muscle, tendon, joint, or bone
Severe	4	Infection in a patient with systemic toxicity or metabolic instability (e.g., fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycemia, or **azotemia**).

From ref. 31, with permission.

The most feared complication of infected diabetic foot ulcers is LEA. Diabetic patients are approximately 40 times more likely to require an amputation than nondiabetics.[34] Morbidity and mortality rates are high following amputation. Mortality ranges from 40% to 80% after 5 years, generally secondary to comorbid conditions, including heart and renal disease.[28,30]

Treatment

Desired Outcomes

The goals of therapy for diabetic foot infection are eradication of the infection and avoidance of soft tissue loss and amputation.

Prevention

Comprehensive foot care programs can reduce the rate of diabetic foot ulcers and associated LEAs by 45% to 85%.[29] Periodic foot examinations with monofilament testing and patient education regarding proper foot care, optimal glycemic control, and smoking cessation are key preventative strategies. Custom orthotic footwear and prophylactic reconstructive foot surgeries also may be effective in reducing the incidence of foot ulcers.[26]

Nonpharmacologic Treatment

The nonpharmacologic treatment of diabetic foot ulcers may include **off-loading,** chemical or surgical débridement of necrotic tissue, wound dressings, hyperbaric oxygen, vascular or orthopedic surgery, and the use of human skin equivalents.[30]

Pharmacologic Treatment

The severity of a patient's infection, based on the PEDIS scale, guides the selection of empirical antimicrobial therapy. While most patients with grade 2 diabetic foot infections can be treated as outpatients with oral antimicrobial agents, all grade 4 and many grade 3 infections require hospitalization, stabilization of the patient, and broad-spectrum IV antibiotic therapy.[31]

Multiple antibiotic options exist for the treatment of diabetic wound infections. Table 70–6 provides both general treatment strategies and specific, though not all-inclusive, antibiotic recommendations. The duration of therapy correlates with infection severity. Grade 2 infections require 7 to 14 days of therapy, whereas grade 3 to 4 wounds necessitate treatment durations of 14 to 28 days. If osteomyelitis is present, treatment should continue for at least 6 weeks.[31]

TABLE 70–6. Empirical Pharmacologic Treatment of Diabetic Foot Infection[31]

Infection Severity	PEDIS Grade	General Approach to Empirical Pharmacologic Treatment	Examples of Empirical Regimens[a]
Uninfected	1	None. Avoid treating uninfected diabetic foot ulcers.	Not applicable.
Mild	2	Oral, narrow-spectrum antibiotic therapy with activity against *Staphylococcus aureus* and streptococcal species. Include coverage for MRSA (HA- or CA-MRSA) according to patient history and resistance patterns in the area.	MRSA not suspected: Cephalexin 500 mg by mouth every 6 hours Dicloxacillin 500 mg by mouth every 6 hours HA-MRSA suspected: Linezolid 600 mg by mouth every 12 hours Vancomycin 1 g IV every 12 hours Daptomycin 4 mg/kg IV daily CA-MRSA suspected: Clindamycin 300 mg by mouth every 6 hours[b] TMP-SMX DS 1–2 tablets by mouth every 12 hours[c] Doxycycline 100 mg by mouth every 12 hours[c]
Moderate to severe	3–4	Parenteral, broad-spectrum antibiotic therapy. Generally select drugs with activity against gram-positive, gram-negative, and anaerobic bacteria (especially if wound is malodorous). Include coverage for MRSA (HA- or CA-MRSA) according to patient history and resistance patterns in the area.	Ceftriaxone 2 g IV daily + clindamycin 600 mg IV every 8 hours Piperacillin-tazobactam 3.375–4.5 g IV every 6 hours Imipenem-cilastatin 500 mg IV every 6 hours Ceftazidime 2 g IV + clindamycin 600 mg IV every 8 hours Fluoroquinolone[d] + clindamycin 600 mg IV every 8 hours Tigecycline 100 mg IV load, then 50 mg every 12 hours[e] If MRSA suspected: vancomycin, linezolid, daptomycin, dalfopristin/quinupristin are indicated, in addition to gram-negative and anaerobic coverage as required. Tigecycline is appropriate as monotherapy in polymicrobial SSTI that involves MRSA.[e]

[a]Doses given are for adults with normal renal function.
[b]CA-MRSA isolates resistant to erythromycin should be evaluated for inducible clindamycin resistance.
[c]Limited clinical data exist for the treatment of MRSA infections.
[d]Ciprofloxacin and levofloxacin exhibit activity against *Pseudomonas aeruginosa*.
[e]Tigecycline is not currently approved for the treatment of diabetic foot infections.

INFECTED PRESSURE SORES

Epidemiology and Etiology

Pressures sores, also known as *decubitous ulcers* or *bedsores,* affect 1.5 to 3 million Americans annually.[35] The cost of healing pressure sores can be substantial, with current estimates ranging from $2000 to $70,000 per wound.[35] Although the prevalence of pressure sores is highest in long-term care facilities, 57% to 60% of *new* pressure sores actually develop in the hospital, most commonly in intensive-care and orthopedic patients. Elderly patients and those with spinal cord injuries are most at risk.[36]

A pressure sore is a chronic wound that results from continuous pressure on the tissue overlying a bony prominence. This pressure impedes blood flow to the dermis and subcutaneous fat, resulting in tissue damage and necrosis.[37,38]

Pressure sore infections develop from breaks in skin integrity and contamination from dirty areas of close proximity. Pressure sore infections generally are polymicrobial.[39]

Clinical Presentation and Diagnosis

Approximately two-thirds of all pressure sores occur on the sacrum and heels. The remaining third occur predominately on the elbows, ankles, trochanters, ischia, knees, scapulas, shoulders, or occiput.[35] Pressure sores are classified according to the extent of tissue destruction.[40] The staging of pressure sores is presented in Table 70–7.

Bacterial colonization of pressure sores is common. Because infection impairs wound healing and may require systemic antimicrobial therapy, the clinician must be able to distinguish it from colonization. Table 70–8 describes the clinical presentation of infected pressure sores.

TABLE 70–7. Staging of Pressure Sores[40]

Stage I
Affected area of skin may feel warm (or cool) and boggy (or firm) when compared with the skin on an opposing area of the body. The patient may complain of pain or itching in the area.
Lightly pigmented skin: Persistent area of reddened skin.
Heavily pigmented skin: Persistent area of red-, blue-, or purple-toned skin.
Stage II
Partial-thickness skin loss of the epidermis and/or dermis.
Superficial ulceration presents clinically as an abrasion, blister, or shallow crater.
Stage III
Full-thickness skin loss involving damage to, or necrosis of, subcutaneous tissue that may extend down to underlying fascia.
The ulcer presents clinically as a deep crater with or without undermining of adjacent tissue.
Stage IV
Full-thickness skin loss with extensive damage or necrosis of muscle, bone, or supporting structures (e.g., tendon, joint, or capsule). Undermining and sinus tracts also may be present.

TABLE 70–8. Presentation of Infected Pressure Sores

Symptoms
Because many high-risk patients lack sensation, pain may not be a primary symptom.
Signs
Infection generally is diagnosed when erythema and edema of the surrounding skin, purulent drainage, malodor, or delayed wound healing are present.
Patients with bacteremia develop fever, chills, confusion, and/or hypotension.
Laboratory Tests
Deep tissue cultures may help to direct therapy. Bone also may be sent for culture in cases of osteomyelitis. Superficial cultures are unreliable and should be avoided.
Imaging Studies
Imaging studies, such as CT, MRI, or bone scan, can be used to detect osteomyelitis and to determine the depth and extent of tissue destruction.

Complications

Tens of thousands of Americans, including 1 of every 12 persons with spinal cord injury, die each year as a result of complications relating to pressure sores.[41] Most complications are infectious. The most common is osteomyelitis, which is present in approximately 38% of infected pressure sores.[37] Less frequently, NF, clostridial myonecrosis, and sepsis can occur.

Treatment

Desired Outcomes

The goals of therapy for infected pressure sores include resolution of infection, promotion of wound healing, and establishment of effective infection control.[38]

Prevention

❾ *Prevention is the most humane and cost-effective component in the management of pressure sores.* Key prevention strategies include monitoring of high-risk patients, reducing skin exposure to pressure and moisture, and promoting good nutritional status.

Careful monitoring and preventative care of high-risk patients can begin once these patients are identified. Intrinsic, or host-related, risk factors for the development of pressure sores include age greater than 75 years, limited mobility, loss of sensation, unconsciousness or altered sense of awareness, and malnutrition. Extrinsic, or environmental, risk factors include pressure, **friction, shear stress,** and moisture.[37,42]

Turning and repositioning the patient at least every 2 hours can reduce skin pressure and prevent pressure sores. However, because this level of care is unattainable in most hospital and nursing-home environments, multitudes of pressure-reducing mattresses have been manufactured. Although these can help to decrease pressure on susceptible areas, they do not negate the need for position changes.[37,42]

Maintaining a clean, dry environment can prevent skin **maceration** and subsequent tissue damage. This can be

TABLE 70–9. Antimicrobial Therapy for Infected Pressure Sores[36–38]

Mild Infection (Topical or Oral Antibiotics)[a]	Moderate to Severe Infection (Parenteral Antibiotics)[a]
Topical	Cefoxitin 1–2 g every 8 hours
Silver sulfadiazine 1% cream	Piperacillin-tazobactam 3.375–4.5 g every 6 hours[b]
Combination antibiotic ointments	Imipenem-cilastatin 500 mg every 6 hours[b]
Oral	Ertapenem 1 g daily
Amoxicillin-clavulanate 500 mg every 8 hours	Fluoroquinolone[c] + clindamycin 600 mg every 8 hours
Fluoroquinolone[c] + clindamycin 300 mg every 6 hours	
MRSA suspected:	
Regimen should include vancomycin, daptomycin, quinupristin/dalfopristin or linezolid.	

[a]Doses given are for adults with normal renal function.
[b]*Pseudomonas aeruginosa* is generally susceptible to this agent.
[c]Ciprofloxacin and levofloxacin exhibit activity against *Pseudomonas aeruginosa*.

accomplished with frequent changes of bed sheets and clothing, thorough drying of skin after bathing, and prompt disposal of incontinent stool or urine.[37]

Malnutrition is a significant but reversible risk factor. High-protein diets have been shown in multiple studies to improve wound healing in patients with pressure sores.[37]

Nonpharmacologic Treatment

Pressure relief, adequate nutrition (high-protein diet), and surgical débridement or abscess drainage are the mainstays of nonpharmacologic treatment.[38]

Pharmacologic Treatment

❾ *Systemic antibiotics are indicated for pressure sores associated with spreading cellulitis, osteomyelitis, or bacteremia.* Because the infections usually are polymicrobial, antibiotic therapy should target gram-positive, gram-negative, and anaerobic bacteria. The duration of treatment is generally 10 to 14 days, unless osteomyelitis is present.[38]

Mild superficial infections, such as those that present clinically with delayed wound healing or minimal cellulitis, may be treated with topical antimicrobial agents.[37] Table 70–9 lists some frequently used systemic and topical antibiotics.

INFECTED BITE WOUNDS

Epidemiology and Etiology

Fifty percent of Americans will be bitten by an animal at least once during their lifetimes. Although most of these injuries are minor, approximately 20% will require medical treatment.[3]

Dogs cause approximately 80% of all bites. These bites most commonly involve the extremities, and young children are particularly at risk.[43,44] Approximately 15% to 25% of dog bites become infected.[44]

Cat bites are the second most common animal bite, most often occurring in women and elderly individuals. Most involve the hand. Because cats have long, thin teeth that cause puncture wounds, their bites are more likely to become infected than a dog bite. Approximately 50% of cat bites become infected.[43,44]

Human bites are third most common and the most serious.[44] Before the availability of antibiotics, up to 20% resulted in amputation. Currently, human bite–associated amputation rates remain at 5%, secondary to vascular compromise and infectious complications.[43]

There are two types of human bite injuries. Occlusal injuries are inflicted by actual biting, whereas clenched-fist injuries are sustained when a person's closed fist hits another's teeth. Of the two, clenched-fist injuries typically are more prone to infectious complications.[43,44]

Bite-wound infections generally are polymicrobial. On average, five different bacterial species can be isolated from an infected animal bite wound.[3] Both the normal flora of the biter's mouth and that of the bite recipient's skin can be implicated. The bacteriology of the cat and dog mouth is quite similar. *Pasteurella multocida*, a gram-negative aerobe, is one of the predominant pathogens, isolated in up to 50% of dog and 75% of cat bites. *S. viridans* are the most frequently cultured bacteria from human bite wounds.[3,43] Table 70–10 provides a comprehensive list of cat, dog, and human bite-wound pathogens.

TABLE 70–10. Etiology and Presentation of Infected Bite Wounds[43,44]

Bacterial Pathogens

Dog and cat: *Pasteurella multocida,* staphylococci, streptococci *Moraxella* spp., *Eikenella corrodens, Capnocytophaga canimorsus, Actinomyces, Fusobacterium, Prevotella,* and *Porphyromonas* spp.

Human: *Viridans* streptococci, *Staphylococcus aureus, Eikenella corrodens, Hemophilus influenzae,* and β-lactamase-producing anaerobic bacteria.

Signs and Symptoms

The onset of infectious symptomatology is typically 12–24 hours after the bite.

Pain at the wound site is common.

Erythema, edema, and purulent or malodorous drainage at the wound site are manifestations of infected wounds. The patient may be febrile.

Limited range of motion may be present, especially if the hand is bitten.

Laboratory Tests

Leukocytosis may be present.

The clinician should obtain anaerobic and aerobic wound cultures only if the wound appears clinically infected.

Imaging Studies

X-rays should be obtained if the bite is on the hand, could have damaged bone or joints, or if an embedded object or tooth fragment is suspected.

Clinical Presentation and Diagnosis

The clinical presentation of infected bite wounds is presented in Table 70–10.

Complications

Complications of infected bite wounds include lymphangitis, abscess, septic arthritis, tenosynovitis, and osteomyelitis. Bites to the hand are particularly complication-prone.[43,44]

Treatment

Desired Outcomes

The goals of therapy for an infected bite wound are rapid and successful eradication of infection and prevention of related complications.

Nonpharmacologic Treatment

Thorough irrigation with normal saline is the first step in the care of an infected bite wound. The wound should be elevated and immobilized. Surgical closure may be advocated, especially for facial wounds. Wounds that are infected, at higher risk for infection, or older than 24 hours should be left open because premature closure can lead to disastrous infectious complications.[43]

Pharmacologic Treatment

Most bite wounds require antibiotic therapy only when clinical infection is present. However, prophylactic therapy is recommended for wounds at higher risk for infection. These include human bites, deep punctures, bites to the hand, and bites requiring surgical repair.[43]

❾ *The most effective agent for the treatment (and prophylaxis) of human and animal bite-wound infections is amoxicillin-clavulanate.* Alternatives for patients with significant penicillin allergies include either a fluoroquinolone or TMP-SMX in combination with clindamycin. Doxycycline also may be prescribed. The durations of prophylaxis and treatment generally are 3 to 5 and 10 to 14 days, respectively.[3]

If the wound is associated with significant cellulitis and edema, systemic signs of infection, or possible joint or bone involvement, hospitalization and IV antibiotics (typically ampicillin-sulbactam 3 g IV every 6 hours) should be initiated. Bone and joint infections will require longer durations of therapy of up to 6 weeks.[44]

Rabies and Tetanus

Patients with animal bite wounds may require rabies prophylaxis.[43,44] If the bite is from a bat, a wild animal, a domestic animal that has or is suspected to have rabies, or an unavailable animal, the patient should receive rabies immune globulin and vaccine immediately.[45]

Crush injuries and those greater than 1 cm in depth are at risk for tetanus. A tetanus and diptheria toxoid booster (Td) should be administered to any patient who has not received one in 5 or more years. A Td and tetanus immune globulin are indicated in those patients who have not previously received at least three Td boosters or whose immunization history is unknown.[43,44]

OUTCOME EVALUATION

❿ *Patients receiving antibiotic therapy for SSTIs require monitoring for efficacy and safety. Efficacy typically is manifested by reductions in temperature, white blood cell count, erythema, edema, and pain. Initially, signs and symptoms of infection may worsen owing to toxin release from certain organisms (i.e., GAS); however, they should begin to resolve within 48 to 72 hours of treatment initiation.* If no response, or worsening infection is noted after the first 3 days of antibiotics, reevaluate the patient.[3] Lack of response may be due to a noninfectious or nonbacterial diagnosis, a pathogen not covered by or resistant to current antibiotic therapy, poor patient adherence, drug or disease interactions causing decreased antibiotic absorption or increased clearance, immunodeficiency, or the need for surgical intervention.[46] ❿ *To ensure the safety of the regimen, dose antibiotics according to renal and hepatic function as appropriate, and monitor for or minimize adverse drug reactions, allergic reactions, and drug interactions.*



❿ Patient Care and Monitoring

Choosing antibiotic therapy for SSTIs:

1. To select the most effective *empirical* antibiotic agent(s) for SSTIs, review the following:
   - The diagnosis
   - Clinical manifestations and severity of illness (to assess the need for IV versus oral therapy)
   - Past medical history, chronic disease states (to determine suspected pathogens)
   - Patient's ability to adhere to the regimen (if outpatient treatment indicated)
2. To ensure the safety of your selected antibiotic agent(s), review the following:
   - Current medications (over the counter, prescription, and alternative) for potential drug interactions
   - History of medication allergies and adverse effects
   - Current laboratory analyses to determine renal and hepatic function
   - Chronic disease states or acute conditions that could be worsened by certain antimicrobial agents (e.g., QT prolongation or acute renal failure)
   - Other disease modifiers that may preclude use (e.g., pregnancy, child)

(*Continued*)

Monitoring antibiotic therapy for SSTIs:

1. Ensure that antimicrobial therapy is effective by monitoring for
   - Resolution of local and systemic signs and symptoms of infection
   - Resolution of laboratory evidence of infection
2. Narrow antibiotic coverage when possible with the use of culture and sensitivity data.
3. Assess patient adherence.
4. Ensure that antimicrobial therapy is safe by monitoring for and treating (as appropriate)
   - Common and severe adverse effects
   - Drug interactions

Patient education regarding antibiotic therapy for SSTIs:

1. It is imperative to take the antibiotic as prescribed and to finish the therapy.
2. If no symptomatic improvement is noted within 3 days, contact your health care provider.
3. Many antibiotics cause diarrhea. If it is severe, contact your health care provider.
4. Consider health initiatives to improve wound healing, such as smoking cessation and glycemic control.

ABBREVIATIONS

CA-MRSA:	community-acquired methicillin-resistant *S. aureus*
DM:	diabetes mellitus
GAS:	group A *Streptococcus* (*S. pyogenes*, one of the β-hemolytic streptococci)
HA-MRSA:	health care–associated methicillin-resistant *S. aureus*
HBO:	hyperbaric oxygen
IDU:	injection drug user
IV:	intravenous
LEA:	lower extremity amputation
MSSA:	methicillin-sensitive *S. aureus*
NF:	necrotizing fasciitis
SSTI:	skin and soft tissue infection
TMP-SMX:	trimethoprim-sulfamethoxazole

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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71 Infective Endocarditis

Ronda L. Akins



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Differentiate the causes and development of infective endocarditis (IE).
2. Identify the clinical presentation and laboratory evaluation for IE.
3. Assess diagnostic criteria used to evaluate a patient suspected of having IE.
4. Describe the most likely causative organisms of IE, particularly in specific patient populations.
5. Develop appropriate pharmacologic treatment recommendations for patients with IE.
6. Define appropriate patient populations requiring prophylactic treatment, and differentiate appropriate drug regimens.
7. Devise a monitoring plan for patients with IE to determine treatment efficacy and discern any adverse effects.

Key Concepts

❶ For infective endocarditis to develop, the occurrence of several factors is required. These factors involve alterations to the endocardial surface that allow for bacterial adherence and eventual infection.

❷ Persistent fever is the most common symptom present in patients with IE.

❸ Blood cultures are the essential laboratory test for IE because continuous bacteremia occurs in over 80% of patients. Without blood culture results, appropriate treatment would be difficult to establish.

❹ Echocardiograms are used for detecting the presence of a vegetation. Either a transthoracic echocardiogram (TTE) or a transesophegeal echocardiogram (TEE) may be used depending on certain patient characteristics.

❺ Choosing the appropriate antimicrobial therapy is crucial to achieve adequate organism kill.

❻ An extended treatment course of 4 to 6 weeks (in most cases) is required to achieve an adequate cure.

❼ The overall goal of therapy is to eradicate the infection and minimize/prevent any complications.

❽ In an effort to prevent the development of IE, prophylactic treatment generally is recommended for patients with high risk factors.

❾ Monitoring the patient's clinical course is necessary to assess the effectiveness of therapy, detect the potential development of bacterial resistance, and determine outcome.

Infective endocarditis (IE) is a serious infection affecting the lining and valves of the heart. While this disease is mostly associated with infection of the heart valves, the septal defects may become involved as well. Infections also occur in patients with prosthetic or mechanical devices, such as mechanical heart valves or who are intravenous drug users (IVDUs). Bacteria is the primary cause of IE; however, fungi and atypical organisms also can be responsible pathogens.

Typically IE is classified into acute or subacute. This difference has been based on the progression and severity of the disease. Acute disease is more aggressive, characterized by high fevers, elevated white blood cell (WBC) counts, and systemic toxicity, with death occurring within a few days to weeks. This type of IE often is caused by more virulent organisms, particularly *Staphylococcus aureus*. Subacute disease typically is caused by less virulent organisms, such as *viridans* streptococci, producing a slower and more subtle presentation. It is characterized by weakness, fatigue, low-grade fever, night sweats, weight loss, and other nonspecific symptoms, with death occurring in several months.

Successful management of patients with IE is based on proper diagnosis, treatment with adequate therapy, and

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monitoring for complications, adverse events, or development of resistance. The treatment and management of IE are best determined through identification of the causative organism. IE has varied clinical presentations; therefore, patients with this infection may be found in any medical subspecialty (i.e., medicine, surgery, critical care, etc.).

EPIDEMIOLOGY AND ETIOLOGY

Despite IE being a fairly uncommon infection, in the United States, there are about 10,000 to 20,000 new cases annually, and IE accounts for approximately 1 case per 1000 hospital admissions.[1] Although the exact number of cases is often difficult to determine owing to the diagnostic criteria and reporting methods for this disease, it continues to rise. IE is now considered the fourth leading cause of serious infectious disease syndromes following urosepsis, pneumonia, and intraabdominal sepsis.[2] Men are affected more commonly than women at a ratio of 1.7:1. Although IE occurs at any age, more than 50% of cases occur in patients older than 50 years.[1] IE in children continues to be uncommon unless they have underlying structural defects often involving surgical repair or catheter-related bacteremia.[1] With the increased use of mechanical valves, **prosthetic-valve endocarditis** (PVE) now accounts for approximately 7% to 25%.[3] Patients who are IVDUs are also at an increased risk for IE, with an estimated number of cases of 150 to 2000 per 100,000 persons per year, most being younger adults.[3] Additionally, other patients at high risk for IE include patients with any congenital or structural cardiac defects, including valvular disease; long-term hemodialysis; diabetes mellitus; poor oral hygiene; previous endocarditis; hypertrophic cardiomyopathy; and mitral valve prolapse with regurgitation.[4–6]

Although almost any type of organism is capable of causing IE, the majority of cases are caused by gram-positive organisms (Table 71–1). These consist primarily of streptococci, staphylococci, and enterococci. Consideration of gram-negative, fungal, and other atypical organisms must be taken into account, particularly in certain patient populations.

TABLE 71–1. Etiologic Agents in Infective Endocarditis

Agent	Percent of Cases
Streptococci	60–80
Viridans group streptococci	30–40
Other streptococci	15–25
Enterococci	5–18
Staphylococci	20–35
Coagulase-positive	10–27
Coagulase-negative	1–3
Gram-negative aerobic bacilli	1.5–13
Fungi	2–4
Miscellaneous bacteria	Less than 5
Mixed infections	1–2
Culture-negative	Less than 5–24

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Patient Encounter, Part 1

A 56-year-old man with a history of diabetes and coronary artery disease presents to the emergency room with complaints of weakness, fever, and chills. On interviewing the patient, you determine that he went to the dentist about 3 weeks ago and since that time has lost about 5 lb. The patient reports that the symptoms began about 1 to 2 weeks ago. He denies any use of alcohol or illicit drugs but admits to smoking about $^1/_2$ pack of cigarettes per day.

- What information would make you suspect IE?
- Does he have any risk factors for IE?
- What additional information would you like to know before deciding on an empirical treatment for this patient?

PATHOGENESIS AND PATHOPHYSIOLOGY

❶ *For infective endocarditis to develop, the occurrence of several factors is required. Typically, there must be an alteration of the endothelial surfaces of the heart valves to allow for organism attachment and colonization.* These alterations may be produced by an inflammatory process such as rheumatic heart disease or by injury from turbulent blood flow. Platelets and fibrin now deposit on the damaged valves, forming a **nonbacterial thrombotic endocarditis** (NBTE). At this point, bacteria through hematogenous spread (i.e., bacteremia) adhere to and colonize the nidus, forming a **vegetation**. Further deposits of platelets and fibrin cover the bacteria, providing a protective coating that allows for the development of a suitable environment for continued organism and vegetation progression, often producing an organism density of 10^9 to 10^{10} **colony-forming units** (CFU) per gram. This sequence of events is summarized in Fig. 71–1.

Acquisition of PVE differs in early stages, where direct inoculation may occur during surgery instead of through hematogenous seeding. The prosthetic valve also has a greater propensity for organism colonization than native valves. However, in late PVE, the process of colonization and vegetation formation is similar to native valve IE, as described earlier.[7]

Classically, vegetations typically are located on the line along valve closure on the atrial surface of the atrioventricular valves (tricuspid and mitral) or on the ventricular surface of the semilunar valves (pulmonary and aortic) (Fig. 71–2). The vegetations can vary significantly in size from only millimeters to several centimeters and may be single or multiple masses. Often, destruction of underlying tissue occurs and may cause

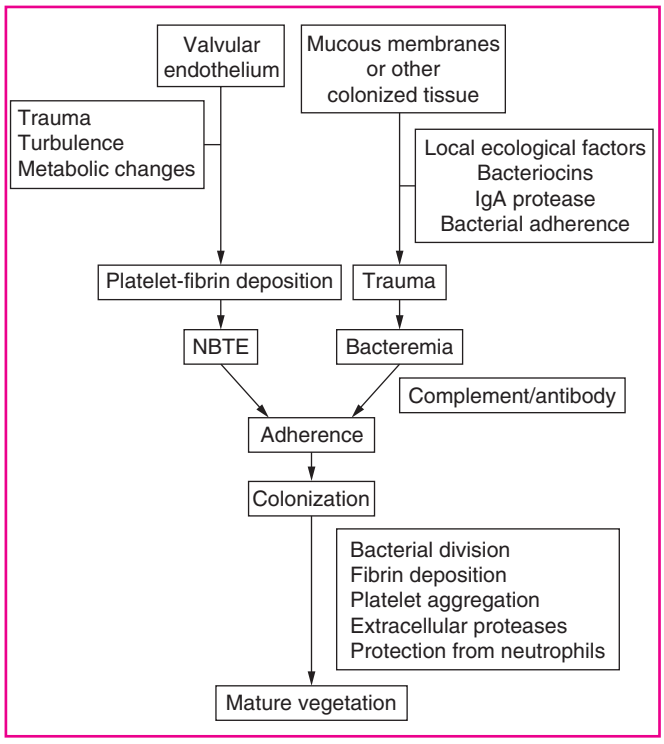


FIGURE 71–1. Pathogenesis of infective endocarditis. (From Scheld W. In: Atlas of Infectious Diseases: External Manifestations of Systemic Infections. Philadelphia: Current Medicine, Inc. Copyright © 1997. Used with permission.)

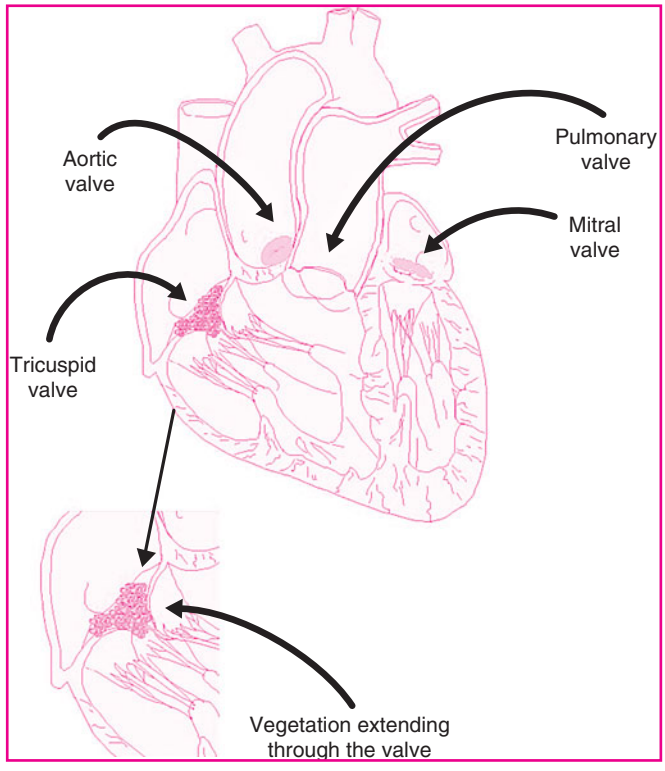


FIGURE 71–2. Diagram of the heart indicating common sites of infection.

perforation of the valve leaflet or rupture of the chordae tendinae, interventricular septum, or papillary muscle. Valve ring abscesses may occur, resulting in fistulas penetrating into the myocardium or pericardial sac, particularly with staphylococcal endocarditis.

Embolic events are also common. Embolization occurs as portions of the friable vegetation break lose and enter the bloodstream. These infected pieces are called *septic emboli.* Pulmonary abscesses are formed commonly as a result of septic emboli from right-sided IE (tricuspid and mitral valves). However, left-sided IE (pulmonary and aortic valves) is more likely to have an embolus travel to any organ system, especially the kidneys, spleen, and brain. Along with emboli, immune complex deposition may occur in organ systems, causing extracardiac manifestations of the disease. This commonly occurs in the kidneys, producing abscesses, infarction, or glomerulonephritis. Immune complexes or emboli also may produce skin manifestations of the disease, as seen with petechiae, Osler nodes, and Janeway lesions, or within the eye (e.g., Roth spots).

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation for IE is quite variable and often nonspecific. ❷ *A fever is the most frequent and persistent symptom in patients but may be blunted with previous antibiotic use, congestive hear failure, chronic liver or renal failure, or infection caused by a less virulent organism (i.e., subacute disease).*[3] Other signs and symptoms that also may occur are listed in the Clinical Presentation box with some discussed further in detail below.

Heart murmurs are heard frequently on auscultation (over 85% of cases), but a new murmur or change in murmurs is only found in 5% to 10 % or 3% to 5 %, respectively.[1] Additionally, over 90% of patients who have a new murmur will develop congestive heart failure, which is a major cause of morbidity and mortality. Splenomegaly and mycotic aneurysms also are noted in many cases of IE.

This disease is also characterized by the following peripheral manifestations that are found in up to one-half of patients with IE, although recently the prevalence has been decreasing[8]:

- *Petechiae* are very small (usually less than 3 mm) pinpoint flat red spots beneath the skin surface caused by microhemorrhaging. They occur in 20% to 40% of chronic IE, often found on the buccal mucosa, conjunctivae (Fig. 71–3*A*) and extremities[1] (Fig. 71–3*B*).
- *Splinter hemorrhages* appear as small dark streaks beneath the finger- or toenails and occur most commonly proximally with IE, typically occurring as a result of local vasculitis or microemboli (Fig. 71–3*C*).
- *Clubbing* of the finger tips typically occurs in long-standing illness and is present in approximately 10% to 20% of patients.[1]

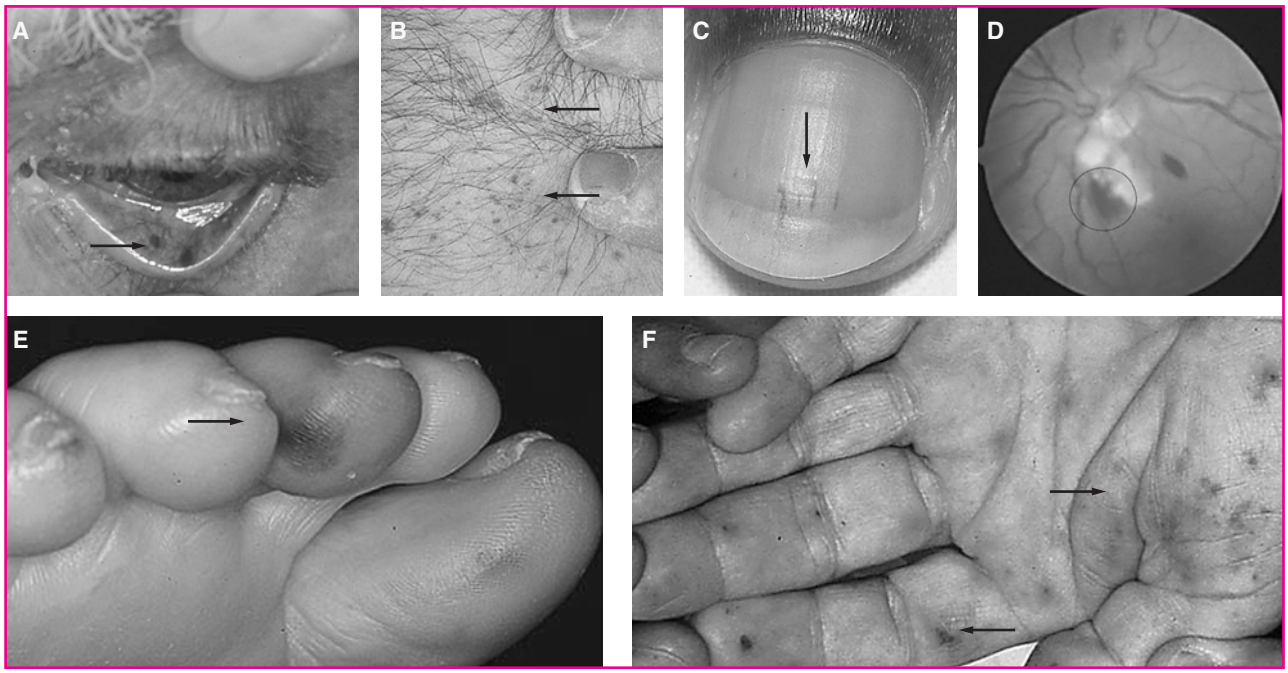


FIGURE 71–3. *A*. Conjunctival petechiae. (Copyright © 2005 The Regents of the University California. All Rights Reserved. Used by permission.) *B*. Petechial rash on neck due to *S. aureus*. (From Scheld W. In: Atlas of Infectious Diseases: External Manifestations of Systemic Infections. Philadelphia: Current Medicine, Inc. Copyright © 1997. Used with permission.) *C*. Splinter hemorrhage. (From Masoudi F, Chambers H. In: Atlas of Infectious Diseases: Cardiovascular Infections. Philadelphia. Current Medicine, Inc. Copyright © 1998. Used with permission.) *D*. Roth spots. (From Barg N, Graham B, Gregg C, et al. In: Atlas of Infectious Diseases: External Manifestations of Systemic Infections. Philadelphia. Current Medicine, Inc. Copyright © 1997. Used with permission.) *E*. Osler's nodes of the foot. (From Scheld W. In: Atlas of Infectious Diseases: External Manifestations of Systemic Infections. Philadelphia. Current Medicine, Inc. Copyright © 1997. Used with permission.) *F*. Janeway lesions. (From Opal S, Zinner S. In: Atlas of Infectious Diseases: External Manifestations of Systemic Infections. Philadelphia. Current Medicine, Inc. Copyright © 1997. Used with permission.)

- *Osler nodes* are small (usually 2–15 mm), painful, tender subcutaneous nodules located on the pads of the fingers and toes (Fig. 71–3*E*) caused primarily by either septic emboli or vasculitis. These nodes are rare in acute disease but are also nonspecific for IE despite occurring in 10% to 25% of all patients.[1]
- *Janeway lesions* are small, painless hemorrhagic macular plaques on the palms of the hands or soles of the feet due to septic emboli and more commonly associated with acute *S. aureus* IE (Fig. 71–3*F*).
- *Roth spots* are rarely occurring (in less than 5% of IE cases), oval-shaped retinal hemorrhages with a pale center near the optic disc (Fig. 71–3*D*).

Laboratory Studies

❸ *Blood cultures are the essential laboratory test for the diagnosis and treatment of IE. Typically, patients with IE have a low-grade consistent bacteremia, with approximately 80% of cases having less than 100 CFU/mL in the bloodstream.*[1] *Blood culture results are critical for determining the most appropriate therapy.* Three blood culture sets should be drawn within the initial 24 hours to determine the etiologic agent. Approximately 90% of the first two cultures will yield a positive result. If a positive blood culture is not obtained from a patient with suspected IE, the microbiology laboratory should be notified and cultures requested to be monitored for growth of fastidious organisms for up to 1 month.

❹ *Another important tool aiding in the diagnosis of IE is the echocardiogram. This imaging tool is used to visualize vegetations. Two methods of the echocardiogram are used: the transthoracic (TTE) and the transesophegeal (TEE).* The TTE has been used since the 1970s; however, it is less sensitive (58% to 63%) than the TEE (90% to 100%).[8] Despite the TEE being more sensitive, use of the TTE for patients with suspected native-valve IE usually is sufficient.[9,10] The TEE may be used as a secondary test for patients whose TTE was negative and in whom a high clinical suspicion of IE exists. Additionally, a TEE is often preferred in patients who have complicated disease, including left-sided IE, prosthetic valves, or perivalvular extension of the vegetation.[2,10] Echocardiograms also may be employed to assess the need for surgical intervention or to determine the possible source of emboli.[9,11]

Additional nonspecific tests for IE may be performed. These include hematologic parameters to determine whether the



❷ ❸ ❹ Clinical Presentation of IE

General
Patients typically present with nonspecific and variable sign or symptoms.

Symptoms
Complaints from patients may include

- Fever
- Chills
- Night sweats
- Weakness
- Dyspnea
- Weight loss
- Myalgia or arthralgias

Signs
- Fever is the most common sign of IE.
- New or changing heart murmur
- Embolic phenomena (emboli affect the heart, lungs, abdomen, or extremities)
- Skin manifestations (e.g., petechiae, splinter hemorrhages, Osler nodes, Janeway lesions)
- Splenomegaly
- Clubbing of extremities

Laboratory Tests
- Blood cultures are the most important laboratory assessment for persistent bacteremia, which occurs commonly in IE. A minimum of three blood culture sets should be collected during the initial 24 hours.
- Hematologic tests for anemia (normochromic, normocytic)
- WBC count may be elevated in acute disease but could be normal in subacute IE.
- Nonspecific findings such as thrombocytopenia, elevated erythrocyte sedimentation rate or C-reactive protein, and abnormal urinalysis (i.e., proteinuria or microscopic hematuria)

Other Diagnostic Tests
An echocardiogram (TTE or TEE) should be performed on any patient with suspected IE to detect the presence of vegetations.

patient is anemic, which occurs in a majority of patients. The white blood cells (WBCs) may be elevated, particularly in acute disease. However, in a subacute infection, the WBCs may be normal. An erythrocyte sedimentation rate (ESR) also may be obtained to determine the presence of inflammation, although this test is highly nonspecific and almost always elevated in IE.

DIAGNOSTIC CRITERIA

A definitive diagnosis of IE would consist of a biopsy or culture directly from pathologic specimens from the endocardium. However, this would be a highly invasive test. Therefore, diagnosis of IE relies on clinical presentation as well as laboratory and echocardiogram results. To guide this clinical diagnosis, criteria have been established to assess major and minor criteria for IE[12,13] (Table 71–2*A*). Depending on the number of major or minor criteria a patient demonstrates, he or she will be classified as either having definite or possible endocarditis or a rejected diagnosis of IE (Table 71–2*B*).

CAUSATIVE ORGANISMS

Gram-positive bacteria are the most common organisms that produce IE. Streptococci and staphylococci species account for the majority of cases at more than 80%.[14] *Viridans* group streptococci are the primary pathogens in IE. However, more recently, staphylococci have been increasing in prevalence as a causative organism. Other gram-positive, gram-negative, atypical, and fungal organisms are less common but still must be considered in certain patient populations.

Streptococci

Streptococci causing IE are most commonly a group of species called *viridans* group streptococci. The most common of this group are *S. salivarius, S. mutans, S. mitus,* and *S. sanguis*. This group of bacteria, considered normal flora in the human mouth, is α-hemolytic, and typically, most clinical microbiology laboratories do not differentiate the exact species. These organisms may cause bacteremia after dental procedures, which can lead to the development of IE in at-risk patients. *Viridans* group streptococci are also the predominant pathogen of IE associated with mitral valve prolapse and native valves and in children.[15,16] Another streptococci species that is commonly associated with IE is *S. bovis*, classified as group D streptococci, found in the gastrointestinal tract. However, owing to the similarities of these streptococci, including microbiologic susceptibility, treatment is similar regardless of the species.

Infective endocarditis caused by these streptococci typically has a subacute clinical course. The current cure rate is often over 90% unless complications occur, which is the case in more than 30% of patients.[17] The majority of *viridans* streptococci remain very susceptible to penicillin, with most strains having a **minimum inhibitory concentration** (MIC) of less than 0.125 mcg/mL.[15,18] Organisms with decreased susceptibilities are increasing. Therefore, antibiotic susceptibilities need to be assessed in order to determine the most appropriate treatment regimen.

Staphylococci

Staphylococcal endocarditis is increasing in prevalence, causing a minimum of 20% to 30% of all cases of IE, with the majority (80%–90%) being due to *S. aureus* (also known as

TABLE 71–2. Modified Duke Criteria for IE

2A. Definitions of Modified Duke Criteria

Major criteria
- Blood culture positive for IE
  - Typical microorganisms consistent with IE from two separate blood cultures:
    - *Viridans* streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*, or community-acquired enterococci in the absence of a primary focus, or
  - Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:
    - At least two positive cultures of blood samples drawn greater than 12 hours apart, or
    - All of three or a majority of four separate cultures of blood (with first and last sample drawn at least 1 hour apart)
  - Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer greater than 1:800
- Evidence of endocardial involvement
- Echocardiogram positive for IE [TEE recommended in patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE (paravalvular abscess) TTE as first test in other patients], defined as follows:
  - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant, or on implanted material in the absence of an alternative anatomic explanation, or
  - Abscess, or
  - New partial dehiscence of prosthetic valve
  - New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

Minor criteria
- Predisposition, predisposing heart condition or injection drug use
- Fever, temperature greater than 38°C
- Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions
- Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor
- Microbiological evidence: positive blood culture but does not meet a major criterion as noted above[a] or serological evidence of active infection with organism consistent with IE

2B. Modified Duke Criteria for the Diagnosis of Infective Endocarditis

Definite IE
- Pathologic criteria
  - (1) Microorganisms demonstrated by culture or histologic examination of a vegetation that has embolized, or an intracardiac abscess specimen, or
  - (2) Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis
- Clinical criteria[b]
  - (1) Two major criteria, or
  - (2) One major criterion and three minor criteria, or
  - (3) Five minor criteria

Possible IE
- (1) One major criterion and one minor criterion, or
- (2) Three minor criteria

Rejected
- (1) Firm alternate diagnosis explaining evidence of infective endocarditis, or
- (2) Resolution of infective endocarditis syndrome with antibiotic therapy for less than or equal to 4 days, or
- (3) No pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for less than or equal to 4 days, or
- (4) Does not meet criteria for possible infective endocarditis, as above

[a]Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.
[b]See above for definitions of major and minor criteria.
TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.
From Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocardits. Clin Infect Dis. 2000; 30:633–638, with permission. University of Chicago Press. © 2000 by the Infectious Diseases Society of America. All right reserved.

coagulase-positive staphylococci).[17,19] This increase in staphylococci has been attributed primarily to expanded use of venous catheters, more frequent valve replacement, and increased IVDU.[20] Coagulase-negative staphylococci (CNS) also cause IE; however, these organisms typically infect prosthetic valves or indwelling catheters.[21]

S. aureus historically was considered community-acquired[17]; however, more recently, almost half the cases are nosocomial in origin.[22] A key issue to consider is that any patient who is bacteremic with *S. aureus* is at an increased risk of developing IE. *S. aureus* also may infect "normal" heart valves (no prior detected valvular disease) in a third of cases.[17,20] Therefore, it is imperative to assess these patients adequately for the presence of vegetations. Any heart valve may be affected; however, when the mitral or aortic valve is involved, it often results in extensive systemic infection with a mortality rate of approximately

20% to 65%.[14,17] When treating *S. aureus* IE, one must consider whether the isolate displays methicillin resistance, the location of the infection (right or left side), presence of prosthetic valves, and history of IVDU. Despite significant resistance to penicillinase-resistant penicillins (e.g., methicillin and nafcillin), most isolates remain susceptible to vancomycin. However, there is an increasing incidence of *S. aureus* with reduced susceptibility to vancomycin, as well as a limited number of vancomycin intermediately resistant or fully resistant isolates.[23–25] Fortunately, at this point they are not widespread enough to affect empirical antibiotic selection. Susceptibility reports should be assessed to ensure antibiotic activity.

The predominant coagulase-negative organism causing IE has been *S. epidermidis*. However, in the past few years, an increase in isolation of another coagulase-negative species (*S. lugdunensis*) has been noted.[26–28] Typically, coagulase-negative IE has a subacute course with numerous complications. Treatment (with or without surgical intervention) usually is successful. On the other hand, *S. lugdunensis* produces a more virulent infection and, despite similar antibiotic susceptibilities, has a much higher mortality rate.[26,28,29]

Enterococci

Enterococci are normal flora of the human gastrointestinal tract and sometimes found in the anterior urethra. Historically, enterococci were considered part of the streptococci genus but now are separated despite similarities, such as group D classification and causing subacute disease. Frequently affected patients are older males who have undergone genitourinary manipulations or younger females who have had obstetric procedures. Although enterococci are a less common cause of IE, there are two predominant species: *E. faecium* and *E. faecalis*. *E. faecalis* is the most common and the more susceptible of the strains. However, enterococci overall are more intrinsically resistant, with enterococcal IE representing one of the most problematic gram-positive infections to treat and cure. Frequently, enterococci display resistance to multiple antibiotics, including penicillins, vancomycin, aminoglycosides, and some of the newer agents (e.g., linezolid or quninupristin/dalfopristin).[30]

Gram-Negative Organisms

Gram-negative IE is much less common (approximately 2%–4%) but typically is much more difficult to treat than gram-positive infections. Fastidious organisms, such as the HACEK group, tend to be seen most commonly, causing 3% of all IE.[31] This group consists of *Haemophilus* spp. (primarily *H. paraphrophilus*, *H. parainfluenzae,* and *H. aphrophilus*), *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens,* and *Kingella kingae*. The clinical presentation of IE by these organisms is subacute, with approximately 50% of patients developing complications. These complications primarily are due to the presence of large, friable vegetations and numerous emboli and the development of acute congestive heart failure that often requires valve replacement.[31,32] It is important to allow cultures sufficient incubation time (often 2–3 weeks) in order to isolate these organisms. Often these organisms may not be isolated on culture and thus present as **culture-negative** IE.

Other gram-negative organisms, such as *Pseudomonas* spp., have been noted to cause IE, especially in IVDUs and patients with prosthetic valves. Additionally, IE caused by *Salmonella* spp., *Escherichia coli*, *Citrobacter* spp., *Klebsiella* spp., *Enterobacter* spp., *Serratia marcescens*, *Proteus* spp. and *Providencia* spp. also has been reported.[1]

Gram-negative IE typically has a poor prognosis with high mortality rates (as high as 83%).[1,] Treatment usually consists of high-dose combination therapy, with valve replacement often a necessity in many patients.

Culture-Negative

Negative blood cultures are reported in approximately 5% of confirmed IE cases, often delaying diagnosis and treatment.[3,33,34] Sterile cultures may be the result of previous antibiotic use, subacute right-sided disease, slow growth of fastidious organisms, nonbacterial endocarditis (e.g., fungal or intracellular parasitic infections), noninfective endocarditis, or improper collection of blood cultures. If nonbacterial or fastidious organisms are suspected, additional testing is essential. The choice of treatment regimen depends on patient history and risk factors.

Other Organisms

Numerous bacteria, including gram-positive bacilli, unusual gram-negative bacteria, atypical bacteria, and anaerobes, as well as spirochetes, have been reported in IE.[31] However, infections caused by these organisms are rare. Some of the more common organisms include *Legionella*, *Coxiella burnetii* (Q fever), and *Brucella*. These rare organisms occur primarily in at-risk patients such as those who have a prosthetic valve or are IVDUs. A comprehensive discussion of these organisms is not feasible for this chapter; for further information, other references sources should be examined. Treatment of these organisms is very difficult, and cure rates are low. Therefore, consulting an infectious diseases specialist is warranted.

Fungi

Fungal endocarditis is quite uncommon but has significant mortality, typically affecting patients who have had cardiovascular surgery, received a prolonged course of broad-spectrum antibiotics, have long-term catheter placement, are immunocompromised, or are IVDUs.[8,35] Survival rates have remained

poor, at approximately 15%, but improvements (approximately 30%) have been reported owing to advances in diagnosis and treatment.[35] The poor prognosis has been attributed to large vegetations, propensity for organism invasion into the myocardium, extensive septic emboli, poor antifungal penetration into the vegetation, and low toxic-to-therapeutic ratio and lack of cidal activity of certain antifungals.[35,36] The two most commonly associated organisms are *Candida* spp. and *Aspergillus* spp. Lack of clinical studies makes treatment decisions difficult. Typically, combination and/or high-dose therapy in conjunction with surgery is required.

TREATMENT

Therapeutic Considerations

Treatment of IE often is complicated and difficult. Numerous factors involving the vegetation influence the effectiveness of the antimicrobial agents. The vegetation consists of a fibrin matrix (as discussed earlier) that provides an environment where organisms are relatively free to replicate unimpeded, allowing the microbial density to reach very high concentrations (10^9–10^{10} CFU/g). Once the organism density has reached this level, the organisms are virtually in a static growth phase. These factors hinder host defenses, as well as the ability of antimicrobials to produce sufficient kill. This is seen often with β-lactams and glycopeptides because their effectiveness can be significantly affected by the bacterial inoculum.

❺ *Selection of an appropriate antimicrobial agent must combine characteristics such as the ability to penetrate into the vegetation, the ability to achieve adequate drug concentrations, and the ability to be minimally affected by high bacterial inoculum in order to achieve adequate kill rates.* ❻ *To accomplish this, antimicrobials typically have to be given parenterally at high doses with an extended treatment course of 4 to 6 weeks (in most cases).* Other desirable drug characteristics include bactericidal and synergistic activity.

Empirical Therapy

❼ *The overall goal of therapy is to eradicate the infection and minimize/prevent any complications.* Patients with suspected IE should be evaluated for risk factors that may provide some indication as to the most likely organism causing the infection. If no risk factors can be determined, empirical therapy primarily should cover gram-positive organisms. Generally, if streptococci are suspected, empirical treatment should consist of penicillin plus gentamicin. However, if staphylococci or enterococci are suspected; empirical treatment should consist of vancomycin plus gentamicin. It is important to monitor the patient's response to therapy closely until cultures and susceptibilities are determined to ensure adequate treatment.



Patient Encounter, Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH

- Type II diabetes mellitus since age 48. He admits that his diet prevents his diabetes from being well controlled.
- Coronary artery disease
- Cardiac pacemaker since 1998

FH

Father had a history of diabetes and died at age 72 with end-stage renal disease; mother died at age 75 from complications of a broken hip.

SH

Smokes about $^1/_2$ pack of cigarettes per day. Denies any use of alcohol of illicit drugs.

Meds

- Metformin 850 mg orally three times daily
- Sotalol 80 mg orally twice daily

Allergies: No known drug allergies

ROS

Recent weight loss of 5 lb, decreased appetite, significant fatigue × 2 weeks

PE

- **Vital Signs:** 168/89 mm Hg, P 88 beats/minute, RR 19 breaths/minute, T 38.5°C
- **Cardiovascular:** Slight tachycardia, positive murmur
- **Abdomen:** Obese, soft, nontender, nondistended; (+) bowel sounds

Labs

Within normal limits, except WBC = 16.4×10^3 cells/mm^3

- Given this additional information, what is your assessment of the patient's condition?
- Identify your empirical treatment recommendations for this patient.
- What other information would be beneficial to obtain?

Specific Therapy

The American Heart Association recently published new guidelines for the management of IE, including specific treatment recommendations.[5] A summary of these treatments for the most common organisms (streptococci, staphylococci, and enterococci) is provided in Tables 71–3 through 71–6. However, for more detailed information (including dosing, length of treatment, etc.) for these organisms or less common organisms, refer to the complete guidelines.[5] These guidelines include primary and alternative regimens, as indicated in the treatment tables under strength of recommendation.

Streptococci

Most isolates are highly susceptible to penicillin; therefore, penicillin G remains the regimen of choice. However, ceftriaxone may be used as an alternative agent if the patient is allergic or resistance is suspected to penicillin. Typically, the length of treatment is 4 weeks and remains the most common regimen. However, a shorter course (i.e., 2 weeks) may be employed for a patient with uncomplicated IE due to highly penicillin-susceptible strains with no extracardiac infection or whose creatinine clearance is greater than 20 mL/minute. If the shorter length of therapy is chosen, gentamicin should be added to the previous regimens for the entire course (i.e., 2 weeks). Recommended therapies for highly penicillin-susceptible *viridans* streptococci are summarized in Table 71–3.

As penicillin MICs increase (greater than 0.12 mcg/mL but less than or equal to 0.5 mcg/mL) for *viridans* group streptococci,

TABLE 71–3. Therapy of Native-Valve Endocarditis Caused by Highly Penicillin-Susceptible *Viridans* Group Streptococci and *Streptococcus bovis*

Regimen	Dosage[a] and Route	Duration (wks)	Strength of Recommendation[g]	Comments
Aqueous crystalline penicillin G sodium ***or*** ceftriaxone sodium	12–18 million units/24 hours (h) intravenous (IV) either continuously or in 4 or 6 equally divided doses 2 g/24 hours IV/intramuscular (IM) in 1 dose *Pediatric dose*[b]: penicillin 200,000 units/kg per 24 hours IV in 4–6 equally divided doses; ceftriaxone 100 mg/kg per 24 hours IV/IM in 1 dose	4 4	IA IA	Preferred in most patients 65 years of age or older or patients with impairment of eighth cranial nerve function or renal function
Aqueous crystalline penicillin G sodium ***or*** ceftriaxone sodium ***plus*** gentamicin sulfate[c]	12–18 million units/24 hours IV either continuously or in 6 equally divided doses 2 g/24 hours IV/IM in 1 dose 3 mg/kg per 24 hours IV/IM in 1 dose *Pediatric dose:* penicillin 200,000 units/kg per 24 hours IV in 4–6 equally divided doses; ceftriaxone 100 mg/kg per 24 hours IV/IM in 1 dose; gentamicin 3 mg/kg per 24 hours IV/IM in 1 dose or 3 equally divided doses[e]	2	IB	2-week regimen not intended for patients with cardiac or extracardiac abscess or for those with creatinine clearance of less than 20 mL/minute, impaired eighth cranial nerve function, or *Abiotrophia*, *Granulicatella*, or *Gemella* spp. infection; gentamicin dosage should be adjusted to achieve peak serum concentration of 3–4 mcg/mL and trough serum concentration of less than 1 mcg/mL when 3 divided doses are used; nomogram used for single daily dosing[d]
Vancomycin hydrochloride[f]	30 mg/kg per 24 hours IV in 2 equally divided doses not to exceed 2 g/24 hours unless concentrations in serum are inappropriately low *Pediatric dose:* 40 mg/kg per 24 hours IV in 2–3 equally divided doses	4	IB	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dosage should be adjusted to obtain peak (1 hour after infusion completed) serum concentration of 30–35 mcg/mL and a trough concentration range of 10–15 mcg/mL

Minimum inhibitory concentration less than or equal to 0.12 mcg/mL.
[a]Dosage recommended are for patients with normal renal function.
[b]Pediatric dose should not exceed that of a normal adult.
[c]Other potentially nephrotoxic drugs (e.g., nonsteroidal anti-inflammatory drugs) should be used with caution in patients receiving gentamicin therapy.
[d]See Nicolau DP, Freeman CD, Belliveau PB, et al. Experience with a once-daily aminoglycoside program administered to 2184 adult patients. Antimicrob Agents Chemother 1995; 39:650–655.
[e]Data for once-daily dosing of aminoglycosides for children exist, but no data for treatment of IE exist.
[f]Vancomycin dosages should be infused during course of at least 1 hour to reduce risk of histamine-release "red man" syndrome.
[g]IA, condition with evidence and/or general agreement that a procedure or treatment is useful and effective, based on data from multiple randomized clinical trials; IB, condition with evidence and/or general agreement that a procedure or treatment is useful and effective-based on data from a single randomized trial or nonrandomized studies.
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Patient Encounter, Part 3: Additional Laboratory and Diagnostic Tests

Blood cultures
All cultures are positive for *viridans* group streptococci.

Labs
Within normal limits.

Echo
3-mm vegetation on the tricuspid valve.

- Given this additional information, are there any changes in your assessment of the patient?
- How would you tailor your treatment based on these new data?
- What would be your treatment goals, including length of treatment?
- What other information would be beneficial to have?

treatment doses are increased, and 4 weeks of treatment is suggested. In addition, combination therapy with gentamicin is recommended during the first 2 weeks. In patients who are allergic or intolerant to either of the β-lactams, vancomycin is an alternative treatment option. Additionally, in patients with resistant strains of *viridans* group streptococci (MIC greater than 0.5 mcg/mL), treatment should employ antimicrobial agents for enterococcal IE (precise agents determined by the susceptibility report).

Patients with PVE caused by penicillin-susceptible strains of *viridans* streptococci require treatment for 6 weeks with penicillin G or ceftriaxone with or without gentamicin during the initial 2 weeks of therapy. However, if the organism demonstrates less susceptibility to penicillin (MIC greater than 0.12 mcg/mL), a combination therapy with penicillin G or ceftriaxone plus gentamicin should be given for the entire 6 weeks. Vancomycin remains the primary alternative if the patient is allergic to β-lactams (e.g., penicillins, cephalosporins, etc.).

Staphylococci

It is important to determine (1) whether the isolate is methicillin-susceptible or methicillin-resistant and (2) whether the patient has a prosthetic valve. For patients with no prosthetic material, methicillin-susceptible staphylococci treatment should consist of a penicillinase-resistant penicillin (e.g., nafcillin or oxacillin) with or without gentamicin, and for methicillin-resistant strains, therapy should consist of vancomycin (see Table 71–4). Combination therapy with aminoglycosides, when used in these patients, typically is given only during the first 3 to 5 days of therapy. In the absence of prosthetic material, some treatment guidelines do not recommend combination therapy against MRSA. However, many clinicians may combine either gentamicin or rifampin with vancomycin if the patient is unresponsive to monotherapy.

Increasing resistance of staphylococci necessitates the expanded use of alternative therapies. A recent clinical study suggests that daptomycin may be a viable alternative to standard therapy (i.e., penicillinase-resistant penicillin for MSSA or vancomycin for MRSA) in staphylococcal IE.[37] The Food and Drug Administration (FDA), based on this study, has approved an indication of daptomycin for the treatment of right-sided IE or bacteremia caused by *S. aureus*. Recommended dosing for these indications are 6 mg/kg per day (unless renal adjustments are necessary).[37] Another retrospective study reported daptomycin safe and well tolerated, with 77% of patients achieving clinical resolution.[38] Additionally, other antibiotics, such as linezolid and quinupristin/dalfopristin, have been used in patients who were unresponsive to standard therapy, although they have had variable response rates.[39–41] These therapies often are reserved for patients who have been unresponsive to traditional therapy (e.g., β-lactams or vancomycin) or for organisms that remain susceptible to these agents when resistant to traditional therapy.

For staphylococcal PVE, treatment length increases significantly, typically requiring a minimum of 6 weeks (see Table 71–5). For MSSA, a penicillinase-resistant penicillin is still employed, as well as vancomycin for MRSA. However, with either regimen, the addition of both gentamicin for first 2 weeks and rifampin for the entire length of treatment is recommended.

Enterococci

For enterococci, it is imperative to determine species and antibiotic susceptibilities. If the organism is susceptible to penicillin and vancomycin, treatment may consist of high-dose penicillin G, ampicillin, or vancomycin plus gentamicin (see Table 71–6). Treatment length is usually 4 to 6 weeks, with the aminoglycoside used over the entire course. As resistance develops to penicillin, ampicillin and vancomycin remain treatment options. Once the isolate becomes resistant to ampicillin, vancomycin is considered the treatment of choice.

If the isolate is determined to be vancomycin-resistant, it is most important to know the exact species because some of the treatment options, such as quinupristin/dalfopristin, are not active against *E. faecalis*. Currently, the treatment options for vancomycin-resistant enterococci (VRE) are not well established by clinical studies or patient experience. The treatment recommendations for vancomycin-resistant *E. faecium* include linezolid or quinupristin/dalfopristin for a minimum of 8 weeks. However, newer agents, such as daptomycin, may provide another option for treatment for either enterococci species (*E. faecium* and *E. faecalis*). Additionally, guidelines suggest the use of imipenem-cilistatin plus ampicillin or ceftriaxone plus ampicillin for the treatment of *E. faecalis* with a minimum of 8 weeks of therapy. Consultation with an infectious diseases specialist is recommended.

TABLE 71–4. Therapy for Endocarditis Caused by Staphylococci in the Absence of Prosthetic Materials

Regimen	Dosage[a] and Route	Duration (wks)	Strength of Recommendation[f]	Comments
Oxacillin-Susceptible Strains				
Nafcillin or oxacillin[b]	12 g/24 hours IV in 4–6 equally divided doses	6	IA	For complicated right-sided IE and for left-sided IE, 6-week treatment; for uncomplicated right-sided IE, 2-week treatment
with optional addition of gentamicin sulfate[c]	3 mg/kg per 24 hours IV/IM in 2 or 3 equally divided doses *Pediatric dose*[d]*:* nafcillin or oxacillin 200 mg/kg per 24 hours IV in 4–6 equally divided doses; gentamicin 3 mg/kg per 24 hours IV/IM in 3 equally divided doses	3–5 days		Clinical benefit of aminoglycosides has not been established
For penicillin-allergic (nonanaphylactoid type) patients: cefazolin	6 g/24 hours IV in 3 equally divided doses	6	IB	Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin; cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β-lactams; vancomycin should be used in these cases[d]
with optional addition of gentamicin sulfate	3 mg/kg per 24 hours IV/IM in 2 or 3 equally divided doses *Pediatric dose:* cefazolin 100 mg/kg per 24 hours IV in 3 equally divided doses; gentamicin 3 mg/kg per 24 hours IV/IM in 3 equally divided doses	3–5 days		Clinical benefit of aminoglycosides has not been established
Oxacillin-Resistant Strains				
Vancomycin hydrochloride[e]	30 mg/kg per 24 hours IV in 2 equally divided doses *Pediatric dose:* 40 mg/kg per 24 hours IV in 2–3 equally divided doses	6	IB	Adjust vancomycin dosage to achieve 1 hour (peak) serum concentration of 30–45 mcg/mL and trough concentration of 10–15 mcg/mL (see text for vancomycin alternatives)

[a]Dosages recommended are for patients with normal renal function.
[b]Penicillin G 24 million units/24 hours IV in 4 to 6 equally divided doses may be used in place of nafcillin or oxacillin if strain is penicillin-susceptible (minimum inhibitory concentration less than or equal to 0.1 mcg/mL) and does not produce β-lactamase.
[c]Gentamicin should be administered in close temporal proximity to vancomycin, nafcillin, or oxacillin dosing.
[d]Pediatric dose should not exceed that of a normal adult.
[e]For specific dosing adjustment and issues concerning vancomycin, see Table 71–3 footnotes.
[f]IA, condition with evidence and/or general agreement that a procedure or treatment is useful and effective, based on data from multiple randomized clinical trails; IB, condition with evidence and/or general agreement that a procedure or treatment is useful and effective, based on data from a single randomized trial or nonrandomized studies.
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Gram-Negative Organisms

Identification of the exact isolate is crucial in gram-negative IE because treatment decisions depend on which organism is isolated. Therapy usually is targeted to the most susceptible antibiotics. Combination therapy (usually the addition of an aminoglycoside) is used commonly. For example, *Pseudomonas* spp. are treated with an antipseudomonal (e.g., piperacillin, cefepime, imipenem, etc.) plus high-dose aminoglycoside (typically tobramycin 8 mg/kg per day). However, exact dosing of antibiotics depends on the organism isolated. Length of treatment usually is a minimum of 6 weeks.

HACEK Group

The HACEK group is difficult to isolate, often taking weeks for identification. If one of these organisms is suspected (e.g., subacute disease, embolism, large vegetations, etc.), it is important to initiate appropriate empirical treatment. The preferred regimen is ceftriaxone (or another third- or fourth-generation cephalosporin), followed by ampicillin-sulbactam. However, for patients who are intolerant of these treatments, ciprofloxacin may be used. The length of treatment typically is 4 weeks for these organisms.

TABLE 71–5. Therapy for Prosthetic Valve Endocarditis Caused by Staphylococci

Regimen	Dosage[a] and Route	Duration (wks)	Strength of Recommendation[d]	Comments
Oxacillin-Susceptible Strains				
Nafcillin or oxacillin	12 g/24 hours IV in 4–6 equally divided doses	6 weeks or longer	IB	Penicillin G 24 million units/24 hours IV in 4 to 6 equally divided doses may be used in place of nafcillin or oxacillin if strain is penicillin-susceptible (MIC less than or equal to 0.1 mcg/mL) and does not produce β-lactamase; vancomycin should be used in patients with immediate-type hypersensitivity reactions to β-lactam antibiotics (see Table 71–3 for dosing guidelines); cefazolin may be substituted for nafcillin or oxacillin in patients with non-immediate-type hypersensitivity reactions to penicillins
plus rifampin	900 mg per 24 hours IV/orally (PO) in 3 equally divided doses	6 weeks or longer		
plus gentamicin sulfate[b]	3 mg/kg per 24 hours IV/IM in 2 or 3 equally divided doses *Pediatric dose*[c] *:* nafcillin or oxacillin 200 mg/kg per 24 hours IV in 4–6 equally divided doses; rifampin 20 mg/kg per 24 hours IV/PO doses; in 3 equally divided doses; gentamicin 3 mg/kg per 24 hours in 3 equally divided doses	2		
Oxacillin-Resistant Strains				
Vancomycin hydrochloride	30 mg/kg per 24 hours IV in 2 equally divided doses	6 weeks or longer	IB	Adjust vancomycin to achieve 1 hour (peak) serum concentration of 30–45 mcg/mL and trough concentration of 10–15 mcg/mL
plus rifampin	900 mg/24 hours IV/IPO in 3 equally divided doses	6 weeks or longer		
plus gentamicin sulfate	3 mg/kg per 24 hours IV/IM in 2 or 3 equally divided doses *Pediatric dose:* vancomycin 40 mg/kg per 24 hours IV in 2 or 3 equally divided doses; rifampin 20 mg/kg per 24 hours IV/PO in 3 equally divided doses (up to adult dose); gentamicin 3 mg/kg per 24 hours IV/IM in 3 equally divided doses	2		

[a]Dosages recommended are for patients with normal renal function.
[b]Gentamicin should be administered in close proximity to vancomycin, nafcillin, or oxacillin dosing.
[c]Pediatric dose should not exceed that of a normal adult.
[d]IB, condition with evidence and/or general agreement that a procedure or treatment is useful and effective, based on data from a single randomized trial or nonrandomized studies.
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Culture-Negative

Treatment for culture-negative IE presents a significant dilemma. Therapeutic regimens are guided by specific isolated organisms. When cultures fail to identify a specific organism, decisions regarding treatment should cover the most common causative organisms. If the patient is unresponsive to this initial treatment, then additional coverage for less common organisms is warranted. An infectious diseases specialist should be consulted for managing a patient with this type of infection.

Fungi

Treatment of fungal IE is exceptionally difficult. There is a significant lack of studies to identify and recommend the most appropriate therapy. Currently, amphotericin B is the most common treatment. However, valve replacement surgery is often considered an adjunct therapy. Intravenous antifungal therapy requires high doses for a minimum of 8 weeks of treatment. Oral azoles (e.g., fluconazole) are used as long-term suppressive therapy to prevent relapse. The exact role of some

TABLE 71–6. Therapy for Native-Valve or Prosthetic-Valve Enterococcal Endocarditis Caused by Strains Susceptible to Penicillin, Gentamicin, and Vancomycin

Regimen	Dosage[a] and Route	Duration (wks)	Strength of Recommendation[e]	Comments
Ampicillin sodium ***or***	12 g/24 hours IV in 6 divided doses	4–6	IA	Native valve: 4-week therapy recommended for patients with symptoms of illness less than or equal to 3 months; 6-week therapy recommended for patients with symptoms greater than 3 months
Aqueous crystalline penicillin G sodium	18–30 million units/24 hours IV either continuously or in 6 equally divided doses	4–6	IA	Prosthetic valve or other prosthetic cardiac material: minimum of 6 weeks of therapy recommended
plus gentamicin sulfate[b]	3 mg/kg per 24 hours IV/IM in 3 equally divided doses *Pediatric dose[c]:* ampicillin 300 mg/kg per 24 hours IV in 4–6 equally divided doses; penicillin 300,000 units/kg per 24 hours IV in 4–6 equally divided doses; gentamicin 3 mg/kg per 24 hours IV/IM in 3 equally divided doses	4–6		
Vancomycin hydrochloride[d]	30 mg/kg per 24 hours IV in 2 equally divided doses	6	IB	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ampicillin
plus gentamicin sulfate	3 mg/kg per 24 hours IV/IM in 3 equally divided doses *Pediatric dose:* vancomycin 40 mg/kg per 24 hours IV in 2 or 3 equally divided doses; gentamicin 3 mg/kg per 24 hours IV/IM in 3 equally divided doses	6		6 weeks of vancomycin therapy recommended because of decreased activity against enterococci

[a]Dosages recommended are for patients with normal renal function.
[b]Dosage of gentamicin should be adjusted to achieve peak serum concentration of 3–4 mcg/mL and a trough concentration of less than 1 mcg/mL. Patients with a creatinine clearance of less than 50 mL/minute should be treated in consultation with an infectious diseases specialist.
[c]Pediatric dose should not exceed that of a normal adult.
[d]See Table 71–3 for appropriate dosage of vancomycin.
[e]IA, condition with evidence and/or general agreement that a procedure or treatment is useful and effective, based on data from multiple randomized clinical trials; IB, condition with evidence and/or general agreement that a procedure or treatment is useful and effective, based on data from a single randomized trial or nonrandomized studies.
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of the newer antifungals (e.g., voriconazole and caspofungin) is unknown, but they should provide a viable option.[42,43]

Surgery

Surgical intervention has become an integral therapy in combination with pharmacologic management of IE. Valve replacement is the predominant intervention, and it is used in a minimum of 25% for all cases of IE.[1] Surgery may be indicated if the patient has unresolved infection, ineffective antimicrobial therapy (often associated with fungal IE), more than one episode of serious emboli, refractory congestive heart failure, significant valvular dysfunction, a mycotic aneurysm requiring resection, local complications (perivalvular or myocardial abscesses), or a prosthetic valve infection associated with a pathogen that demonstrates higher antimicrobial resistance (e.g., staphylococci, gram-negative organisms, and fungi).[36,44,45] Often a patient's hemodynamic status (i.e., blood pressure, heart rate, pulmonary artery pressure, etc.) is used to determine when surgical intervention is warranted.[46] Despite appropriate medical management and cure, a significant number of people who develop native-valve



Patient Encounter, Part 4: Additional Laboratory

Susceptibility Report

Drug	Penicillin	Ceftriaxone	Vancomycin
MIC (mcg/mL)	0.25	0.125	Less than 1

- Given this additional information, are there any changes in your assessment of the patient?
- Do you need to adjust your treatment regimen based on these data?
- Would your treatment goals, particularly length of treatment, change?



Patient Encounter, Part 5: Create a Care Plan

Based on this patient's information, create a care plan for the management of his IE. Be sure to include (1) a statement regarding treatment requirements and/or possible problems, (2) goals of therapy, (3) a patient-specific plan, including preventive plans, and (4) a follow- up plan to assess whether the goals have been met and to determine whether the patient experienced any adverse effects.

endocarditis require valve replacement surgery. Involvement of the aorta is considered an indication for surgery in over 70% of patients with PVE.[46]

Prophylaxis

℞ *Certain conditions have been associated more commonly with IE due to preexisting cardiac disease in the presence of a transient bacteremia. In an effort to prevent the development of IE, prophylactic treatment generally is recommended for these at-risk patients.* Although there are no well-controlled clinical studies of these recommendations, it is thought that if antibiotics are given just prior to a procedure, the number of bacteria may be decreased in the bloodstream and prevent the bacteria from adhering to the valves.

Cardiac conditions in which prophylaxis is recommended include presence of prosthetic valves, prior infective endocarditis, congenital cardiac abnormalities, rheumatic heart disease or any other valvular dysfunction, hypertrophic cardiomyopathy, and mitral valve prolapse with valvular regurgitation or thickening/redundancy of the valve leaflets.[6] While many patients have other cardiac dysfunction, only patients with these conditions are considered to be at a high risk of developing IE. No prophylaxis is advised in other patients.

Transient bacteria may be set loose by many types of dental and surgical procedures. All dental procedures, including routine cleaning, may cause gingival bleeding, which can introduce bacteria into the bloodstream. *Viridans* group streptococci are the primary bacteria targeted for prophylaxis in this circumstance. On the other hand, prophylaxis for gastrointestinal or genitourinary surgeries primarily targets enterococci.

The American Heart Association guidelines include suggested antibiotic regimens for each type of procedure.[6] Recommended regimens for dental, oral, respiratory tract, and esophageal procedures are listed in Table 71–7. These guidelines recommend a single oral or intramuscular/intravenous dose initiated shortly before the procedure. The regimen for dental/oral procedures consists primarily of a penicillin as first choice, with clindamycin for penicillin-allergic patients. For gastrointestinal or genitourinary procedures,

TABLE 71–7. Prophylactic Regimens for Dental, Oral, Respiratory Tract, or Esophageal Procedures

Situation	Agent	Regimen[a]
Standard general prophylaxis	Amoxicillin	Adults: 2 g; children: 50 mg/kg orally 1 hour before procedure
Unable to take oral medications	Ampicillin	Adults: 2 g intramuscularly (IM) or intravenously (IV) Children: 50 mg/kg IM or IV within 30 minutes before procedure
Allergic to penicillin	Clindamycin or	Adults: 600 mg; children: 20 mg/kg orally 1 hour before procedure
	cephalexin[b] or	Adults: 2 g; children: 50 mg/kg orally 1 hour before procedure
	cefadroxil[b] or	
	azithromycin or clarithromycin	Adults: 500 mg; children: 15 mg/kg orally 1 hour before procedure
Allergic to penicillin and unable take oral medications	Clindamycin or	Adults: 600 mg; children: 20 mg/kg IV within 30 minutes before procedure
	cefazolin[b]	Adults: 1g; children: 25 mg/kg IM or IV within 30 minutes before procedure

[a]Total children's dose should not exceed adult dose.
[b] Cephalosporins should not be used in individuals with immediate-type hypersensitivity reaction (urticaria, angioedema, or anaphylaxis) to penicillins.
From Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. JAMA 1997; 277:1794–1801, with permission. Copyright © 1997, American Medical Association. All rights reserved.

penicillin (e.g., amoxicillin or ampicillin) remains the primary agent, with the addition of gentamicin in high-risk patients or vancomycin for penicillin-allergic patients with gentamicin added for high-risk patients. A second prophylactic dose is not recommended. However, if an infection develops at the procedure site, additional antibiotics (i.e., a therapeutic course) may be required.

OUTCOME EVALUATION

Monitoring for successful therapy is critical in this serious infection to prevent complications, prevent resistance development, and decrease mortality. Routine assessment of clinical signs and symptoms, as well as laboratory tests (i.e., repeat blood cultures), microbiologic testing and serum drug concentrations, must be performed.

Resolution of signs and symptoms typically occurs within a few days to a week in most cases. Monitor the patient daily for febrile episodes, as well as other vital signs, with expected normal values within 2 to 3 days of initiating antimicrobial therapy.[3] Persistent signs or symptoms could be indicative of inadequate treatment or development of resistance.

Blood cultures are the primary laboratory evaluation to assess response to therapy. Typically, with appropriate treatment, they should become negative within 3 to 7 days. Use subsequent blood cultures if the patient appears not to be responding to therapy or on completing treatment to confirm eradication of infection. Evaluate all susceptibility reports to assess antimicrobial therapy.

Additionally, the patient needs to be counseled on the necessity of prophylactic antibiotics prior to any dental or surgical procedure in order to prevent recurrent infections. This is critical in patients with risk factors that predispose them to developing IE, such as prosthetic heart valves, other valvular defects, or previous IE.

Develop a follow-up plan to determine whether the patient has achieved a cure, which includes a clinical evaluation of signs/symptoms, repeat blood cultures, and possibly a repeat echocardiogram. The patient also should be assessed for any adverse events. This should be performed usually within a few weeks after the completion of therapy.

CONCLUSION

When presented with a patient with infective endocarditis, it is imperative to have an accurate diagnosis and treat appropriately. Mortality can be significant depending on the organism and the patient's comorbidities. However, outcomes can be improved through diligent care and monitoring.



⑨ Patient Care and Monitoring

1. Assess the patient's symptoms and/or laboratory results to determine if the empirical therapy is effective. Is the patient's fever resolving? Is the patient's WBC decreasing?
2. Review available microbiologic cultures and sensitivity to assess whether the initial antimicrobial regimen needs to be tailored?
3. Review any additional diagnostic tests to determine if treatment may be needed to prevent/minimize complications (e.g., emboli, congestive heart failure).
4. Evaluate therapeutic serum drug concentrations as appropriate (e.g., vancomycin and gentamicin).
5. Monitor serum creatinine in order to make appropriate renal adjustments of the antimicrobials as necessary.
6. Assess any repeat blood cultures and vital signs to determine continued treatment effectiveness.
7. Evaluate the patient for occurrence of any adverse drug reactions and possible drug allergies and/or drug interactions.
8. Develop a plan if the patient is going to continue therapy at home. Once defervescence has occurred, the patient may complete therapy outside the hospital by receiving the antimicrobials from an outpatient infusion center or through a home health agency.
9. Develop a follow-up plan to assess the resolution of infection once the patient has completed therapy. Assessment of any adverse events also should be conducted at this time.
10. Educate the patient on the importance of taking prophylactic antibiotics prior to having any dental or surgical procedure in an effort to prevent the future development of another infection. Stress the potential complications as well as the morbidity and mortality that are associated with IE and that taking precautions can minimize or prevent them.

ABBREVIATIONS

CFU:	colony-forming units
IE:	infective endocarditis
IVDUs:	intravenous drug users
MIC:	minimum inhibitory concentration
MSSA:	methicillin-sensitive *S. aureus*
MRSA:	methicillin-resistant *S. aureus*
NBTE:	nonbacterial thrombotic endocarditis
PVE:	prosthetic valve endocarditis
TEE:	transesophageal echocardiogram
TTE:	transthoracic echocardiogram

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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72 TUBERCULOSIS

Charles A. Peloquin and Rocsanna Namdar



LEARNING OBJECTIVES

UPON COMPLETION OF THE CHAPTER, THE READER WILL BE ABLE TO:

1. Compare the risk for active tuberculosis disease among patients based on their age, immune status, place of birth, and time since exposure to an active case.
2. Design, evaluate, and assess an appropriate therapeutic plan for an immunocompetent, immunocompromised, pregnant, and pediatric patient.
3. Assess the effectiveness of therapy in tuberculosis patients.
4. Cite the names of the tuberculosis drugs most likely to cause hepatotoxicity.
5. Select patients for whom therapeutic drug monitoring may be valuable.
6. Design, evaluate, and assess appropriate regimens for the treatment of latent tuberculosis infection (LTBI) in all patient populations.
7. Identify the necessary laboratory monitoring parameters for patients on antituberculosis medications.
8. Design a therapeutic plan for a patient with tuberculosis meningitis or tuberculosis osteomyelitis.

KEY CONCEPTS

❶ Tuberculosis (TB) is the most prevalent communicable infectious disease on earth and remains out of control in many developing nations. These nations require medical and financial assistance from developed nations in order to control the spread of tuberculosis globally.

❷ In the United States, tuberculosis disproportionately affects ethnic minorities as compared with whites, reflecting greater ongoing transmission in ethnic minority communities. Additional tuberculosis surveillance and preventive treatment are required within these communities.

❸ Coinfection with human immunodeficiency virus (HIV) and tuberculosis accelerates the progression of both diseases, thus requiring rapid diagnosis and treatment of both diseases.

❹ Mycobacteria are slow-growing organisms; in the laboratory, they require special stains, special growth media, and long periods of incubation to isolate and identify.

❺ Tuberculosis can produce atypical signs and symptoms in infants, the elderly, and immunocompromised hosts, and it can progress rapidly in these patients.

❻ Latent tuberculosis infection (LTBI) can lead to reactivation disease years after the primary infection occurred.

❼ The patient suspected of having active tuberculosis disease must be isolated until the diagnosis is confirmed and he or she is no longer contagious. Often, isolation takes place in specialized "negative pressure" hospital rooms to prevent the spread of tuberculosis.

❽ Isoniazid and rifampin are the two most important tuberculosis drugs; organisms resistant to both these drugs [multidrug-resistant tuberculosis (MDR-TB)] are much more difficult to treat.

❾ Never add a single drug to a failing regimen!

❿ Directly observed treatment (DOT) should be used whenever possible to reduce treatment failures and the selection of drug-resistant isolates.

Worldwide, tuberculosis (TB) kills about 2 million people each year, more than any other infectious organism. TB is caused by *Mycobacterium tuberculosis*, it presents either as latent TB infection (LTBI) or as progressive active disease.[1] The latter typically causes progressive destruction of the lungs, leading

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to death in most patients who do not receive treatment. Currently, one-third of the world's population is infected, and drug resistance is increasing in many areas.[1]

EPIDEMIOLOGY

❶ *Roughly one of every three people on earth is infected by M. tuberculosis.*[1–3] *The distribution is very uneven, with the highest incidences found in southern Asia and sub-Saharan Africa. In the United States, about 13 million people have LTBI, evidenced by a positive skin test [purified protein derivative (PPD)] but no signs or symptoms of disease.* Such patients have roughly a 1 in 10 chance of active disease during their lives, with the greatest risk in the first 2 years after infection. Active disease occurs in over 14,000 Americans each year, resulting in about 1500 deaths.[4] *[For detailed data analysis, visit the Centers for Disease Control and Prevention (CDC) Web site at* www.*cdc.gov/nchstp/tb.]*

Risk Factors for Infection

Location and Place of Birth

California, Florida, Illinois, New York, and Texas accounted for over 50% of all TB cases in 2002, reflecting the high immigration rates into these states.[4] TB is most prevalent in large urban areas, exacerbated by crowding in poor immigrant neighborhoods, where more than half of all United States cases now are found.[3,4] Mexico, the Philippines, Vietnam, India, China, Haiti, and South Korea account for the largest numbers of these immigrants.[4] Those in close contact with patients with active pulmonary TB are most likely to become infected.[2,3] These include family members, coworkers, or coresidents in places such as prisons, shelters, and nursing homes.

Race, Ethnicity, Age, and Gender

❷ *In the United States, the incidence of TB is more concentrated in non-white individuals. In 2002, non-Hispanic blacks accounted for 30% of all TB cases, followed by Hispanics at 27%.*[5] *Asians and Pacific Islanders accounted for 22%, whereas non-Hispanic whites accounted for only 20% of the new TB cases.*[5] TB is most common among people 25 to 44 years of age (35% of all cases), followed by those 45 to 64 years of age (28%) and 65+ years of age (21%).

Coinfection with Human Immunodeficiency Virus (HIV)

HIV is the most important risk factor for active TB because the immune deficit prevents patients from containing the initial infection.[2,3,5,6] ❸ *Roughly 10% of United States TB patients are coinfected with HIV, and roughly 20% of TB patients ages 25 to 44 years are coinfected with HIV.*[4,5] Consistent with HIV in general, HIV-associated TB is most common among 25- to 44-year-olds. Substance abuse and other risk factors are shared among some TB and HIV-infected individuals, promoting the spread of both diseases.[2,7,8]



Patient Encounter, Part 1

HPI

AF is a 56-year-old man who presents to the medical clinic complaining of a 1-month history of a persistent cough that has become productive over the past 2 weeks. He also complains of malaise, fever, night sweats, and a 6-kg weight loss over the past 2 months.

PMH

- *Non-insulin-dependent diabetes mellitus (NIDDM)—well controlled*
- *Hypertension (HTN) × 5 years—well controlled*

FH

- *Mother and father died in an MVA 10 years ago.*
- *One brother, age 54, is HIV+ and lives with the patient.*
- *One sister, age 50, is alive and has had breast cancer.*

SH

Single, one daughter. He works as an undercover agent and just returned from an operation in Cambodia. He denies smoking or intravenous drug use. He had a 20-year history of alcohol abuse but has been sober for 10 years.

Meds

- *Lisinopril 20 mg daily*
- *Amlodipine 5 mg daily*
- *Metformin 500 mg twice daily*

Patient reports that he tries to be compliant with his therapies and takes them regularly except when he is unable to get his refills; over the past 2 months, he has gone 3 to 4 days without medication.

Allergies: NKDA

- What information is suggestive of tuberculosis?
- What factors place this patient at increased risk for acquiring tuberculosis?

Risk Factors for Disease

Once infected with *M. tuberculosis*, a person's lifetime risk of active TB is about 10%, with about half this risk evident during the first 2 years after infection.[2,3,6] Young children, the elderly, and immunocompromised patients have greater risks. HIV-infected patients with *M. tuberculosis* infection are roughly 100 times more likely to develop active TB than normal hosts owing to the lack of normal cellular immunity.[3,9]

ETIOLOGY

❹ *Microscopic examination ("smear") detects about 8 to 10 × 10^6 organisms/L of specimen using the older AFB (acid-fast bacillus) stain, with the newer auramine-rhodamine fluorescent*

technique being perhaps one-third more sensitive. A smear-negative patient still can grow M. tuberculosis *on culture, which is more sensitive than either staining technique. Unfortunately, culture is much slower than staining due to the doubling time of the bacilli of about 20 hours.* Further, microscopic examination cannot determine which of over 90 mycobacterial species is present. The usual practice is to assume the worst (TB) until confirmed by genetic probe or positive culture.

Culture and Susceptibility Testing

Susceptibility testing is essential for directing proper treatment. The most common agar method, known as the *proportion method,* takes many weeks to produce results. The Bactec and newer MIGIT systems use liquid media and detect live mycobacteria in about 2 weeks.[1,10,11] Rapid-identification tests include nucleic acid probes and DNA fingerprinting using restriction fragment length polymorphism (RFLP) analysis, and polymerase chain reaction (PCR).[1,6,10,12–14] These tests differentiate among mycobacterial species but currently cannot provide susceptibility data. Investigational tests looking for specific mutations associated with drug resistance may facilitate rapid drug therapy decisions in the future.

Transmission

M. tuberculosis is transmitted from person to person by coughing or sneezing.[2,6,15] This produces small particles known as *droplet nuclei* that float in the air for long periods of time. Each droplet contains one to three organisms. It is estimated that 30% of individuals with prolonged contact with an infectious TB patient become infected.

PATHOPHYSIOLOGY

Primary Infection

Primary infection usually results from inhaling droplet nuclei that contain *M. tuberculosis*.[2,6,17] The progression to clinical disease depends on three factors: (1) the number of *M. tuberculosis* organisms inhaled (infecting dose), (2) the virulence of these organisms, and (3) the host's cell-mediated immune response.[2,4,6,12,15,16] If pulmonary macrophages inhibit or kill the bacilli, the infection is aborted.[15] If not, *M. tuberculosis* eventually spreads throughout the body through the bloodstream.[2,6,15] *M. tuberculosis* most commonly infects the posterior apical region of the lungs, where conditions are most favorable for its survival.

T lymphocytes become activated over the course of 3 to 4 weeks, producing interferon-γ (IFN-γ) and other cytokines. These stimulate microbicidal macrophages to surround the tuberculous foci and form granulomas to prevent further extension.[15] At this point, the infection is largely under control, and bacillary replication falls off dramatically. Any remaining mycobacteria are believed to reside primarily within granulomas or within macrophages that have avoided detection and lysis. Over 1 to 3 months, tissue hypersensitivity occurs, resulting in a positive tuberculin skin test.[2,6,17] ❺ ***Progressive primary disease*** *occurs in roughly 5% of patients, especially children, the elderly, and immunocompromised patients.*[18,19] *This presents as a progressive pneumonia and frequently spreads, leading to meningitis and other severe forms of TB, even before their skin tests become positive.*[18]

Reactivation Disease

❻ *About 10% of infected patients develop reactivation TB, with half occurring in the first 2 years after infection.*[2,6,12] Upper lobe pulmonary disease is the most common (85% of cases).[2] **Caseating granulomas** result from the vigorous immune response, and liquefaction leads to local spread. Eventually, a pulmonary cavity results, and this provides a portal to the outside that allows for person-to-person spread. Bacterial counts in the cavities can be as high 10^{11} per liter of cavitary fluid (10^{8} per milliliter).[2,15] Prior to the chemotherapy era, pulmonary TB usually was associated with hypoxia, respiratory acidosis, and eventually death.

Extrapulmonary and Miliary Tuberculosis

Caseating granulomas, regardless of location, can undergo liquefaction, spread tubercle bacilli and cause symptoms.[2,6] Because of muted or altered symptoms, the diagnosis of TB is difficult and often delayed in immunocompromised hosts.[2,3,6] HIV-infected patients may present with only extrapulmonary TB, which is very uncommon in HIV-negative persons. A widely disseminated form of the disease called *miliary TB* can occur, particularly in children and immunocompromised hosts, and it can be rapidly fatal.[17] Immediate treatment is required.

Influence of HIV Infection on Pathogenesis

HIV infection is the most important risk factor for active TB.[2,6,17] As CD4+ lymphocytes multiply in response to the mycobacterial infection, HIV multiplies within these cells and selectively destroys them, gradually eliminating the TB-fighting lymphocytes.[17] HIV-infected patients infected with TB are at a substantially higher risk of early mortality compared with HIV-negative TB patients.[20,21] Because of the large pill burden, overlapping toxicities, and paradoxical worsening of the TB when TB and HIV treatments are initiated simultaneously, most clinicians elect to begin TB treatment first.[12,22] A reasonable time to begin HIV treatment is after 2 months of TB treatment, although individual circumstances often dictate the exact timing.

CLINICAL PRESENTATION

Fever, night sweats, weight loss, fatigue, and a productive cough are the classic symptoms of TB.[1,2,6,16] Onset may be gradual, and the diagnosis is easily missed if the symptoms are muted, such as in the elderly.[2,6,16] Progressive pulmonary disease leads to cavitation visible on x-ray. Physical examination

is non-specific but may be consistent with pneumonia. Dullness to chest percussion, rales, and increased vocal **fremitus** may be observed on examination. Laboratory data often are uninformative, but a modest increase in the white blood cell (WBC) count with a lymphocyte predominance can be seen.

Atypical presentations are common in patients coinfected with HIV.[1,2,6,16,23] HIV-positive patients often have negative skin tests and fail to produce **cavitary lesions,** and fever may be absent. Symptoms for these patients range from classic pulmonary to muted and non-specific. Extrapulmonary TB typically presents as a slowly progressive decline in organ function, and lymphadenopathy is relatively common.[2,6,16,17] Abnormal behavior, headaches, or convulsions suggest tuberculous meningitis, although other acute central nervous system (CNS) infections must be exlcuded.[6,16]

The Elderly

❺ *Many clinical findings are muted in the elderly or absent altogether, so there can be considerable diagnostic uncertainty. Absent may be positive skin tests, fevers, night sweats, sputum production, or hemoptysis, making TB hard to distinguish from other bacterial or viral infections or chronic lung diseases.*[2,16,24,25] In contrast, mental status changes are twice as common in the elderly, and CNS disease must be considered when TB is entertained. Mortality is six times higher in the elderly in part owing to delays in diagnosis.[2,16,24] Ethnic distributions of disease are different in the elderly and include more white patients because these patients often were infected decades ago, when TB was more prevalent in the United States.

Children

❺ *Because very young children have immature cellular immunity, TB can be particularly dangerous in this population. TB in children may present as a typical bacterial pneumonia, called progressive primary TB, and often involves the lower and middle lobes.*[16–19] Dissemination to the lymph nodes, gastrointestinal (GI) and genitourinary tracts, bone marrow, and meninges is fairly common. For these reasons, **bacille Calmette-Guérin (BCG)** vaccinations are administered in countries where TB remains very common. BCG appears to stimulate the children's immune systems just enough to ward off the most serious forms of the disease. However, BCG does not block infection, and these same children often experience reactivation TB as young adults. Because cavitary lung lesions are uncommon, children do not spread TB readily. From the public health perspective, pediatric TB is the clearest indication of recent spread of TB.

DIAGNOSIS

Skin Testing

TB skin testing with the 5-TU strength of brand **purified protein derivative (PPD),** also known as the *Mantoux test*, is the preferred method for skin testing.[2,16,20] The product is injected into the skin (not subcutaneously) with a fine (27-gauge) needle and produces a small, raised, blanched wheal to be read by an experienced professional in 48 to 72 hours. Criteria for interpretation are listed in Table 72–1.[1,2,6,16,20] The Centers for Disease Control and Prevention (CDC) does not recommend the routine use of

TABLE 72–1. Criteria for Tuberculin Positivity, by Risk Group

Reaction greater than or equal to 5 mm of Induration	Reaction greater than or equal to 10 mm of Induration	Reaction greater than or equal to 15 mm of Induration
Human immunodeficiency virus (HIV)–positive persons	Recent immigrants (i.e., within the last 5 years) from high-prevalence countries	Persons with no risk factors for TB
Recent contacts of tuberculosis (TB) case patients	Injection drug users	
Fibrotic changes on chest radiograph consistent with prior TB	Residents and employees[b] of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with acquired immunodeficiency syndrome (AIDS), and homeless shelters	
Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of greater than or equal to 15 mg/day of prednisone for 1 month or more)[a]	Mycobacteriology laboratory personnel Persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head or neck and lung), weight loss of greater than or equal to 10% of ideal body weight, gastrectomy, and jejunoileal bypass	
	Children younger than 4 years of age or infants, children, and adolescents exposed to adults at high risk	

[a]Risk of TB in patients treated with corticosteroids increases with higher dose and longer duration.
[b]For persons who are otherwise at low risk and are tested at the start of employment, a reaction of greater than or equal to 15 mm of induration is considered positive.
With permission from ref. 23. From CDC.



Patient Encounter, Part 2

PE

- **Gen:** *Thin, emaciated man.*
- **VS:** *Blood pressure 126/78, pulse 90 beats per minute, respiratory rate 18, temperature 39.3°C (102.7°F), O_2 sat 82% on room air, wt 51 kg*
- **HEENT:** *PERRLA; EOMI*
- **Neck:** *Supple; no lymphadenopathy, bruits, or JVD; no thyromegaly*
- **Chest:** *Diffuse rhonchi, decreased breath sounds on left.*
- **CV:** *RRR; no murmurs, rubs, gallops*
- **Abd:** *(+) BS; non-tender, non-distended.*
- **Neuro:** *A&O × 3*

Laboratory Values (U.S. Units)

Lab	Normal	Lab	Normal
Na 139 mEq/L	135–145 mEq/L	Hgb 13.5 g/dL	13.5–17.5 g/dL
K 3.9 mEq/L	3.5–5 mEq/L	Hct 40%	40%–54%
Cl 98 mEq/L	95–105 mEq/L	RBC 4.6	4.6–6.0 × 10^6 mm^3
CO_2 38 mEq/L	22–30 mEq/L	WBC 4.5	4.0–10 × 10^3 mm^3
BUN 20 mg/dL	5–25 mg/dL	PMN 62%	50%–65%
SCr 1.3 mg/dL	0.8–1.3 mg/dL	Lymph 34%	25%–35%
Gluc 123 mg/dL	Less than 140 mg/dL	Mono 6%	2%–6%
AST 36 IU/L	5–40 IU/L	Other: Consent for HIV obtained.	
ALT 28 IU/L	5–35 IU/L		
Tbili 1 mg/dL	0.1–1.2 mg/dL		
PT 10 second	10–12 second		

Laboratory Values (SI Units)

Lab	Normal	Lab	Normal
Na 139 mmol/L	135–145 mmol/L	Hgb 0.84 mmol/L	0.84–1.08 mmol/L
K 3.9 mmol/L	3.5–5 mmol/L	Hct 0.4 vol fraction	0.4–0.54 vol fraction
Cl 98 mmol/L	95–105 mmol/L	RBC 4.6 × 10^{12}/L	4.6–6.0 × 10^{12}/L
CO_2 38 mmol/L	22–30 mmol/L	WBC 4.5 × 10^9/L	4.0–10 × 10^9/L
BUN 7.1 mmol/L	1.8–8.9 mmol/L	PMN 62%	50%–65%
SCr 115 µmol/L	70.1–114.9 µmol/L	Lymph 34%	25%–35%
Gluc 6.8 mmol/L	Less than 7.8 mmol/L	Mono 6%	2%–6%
AST 0.60 µKat/L	0.08–0.67 µKat/L	Other: Consent for HIV obtained.	
ALT 0.47 µKat/L	0.08–0.58 µKat/L		
Tbili 17 µmol/L	1.7–20.5 µmol/L		
PT 10 second	10–12 second		

CXR

Profound bilateral upper lobe infiltrates with cavitation on left; small left pneumothorax

Clinical Course

The patient was admitted and placed on respiratory isolation. Three separate sputum Gram stain specimens were reported to contain 3+ AFB. A PPD tuberculin skin test was placed. Sputum samples were sent for AFB, fungi, and bacterial cultures and sensitivities. After 48 hours, the PPD skin test was read as a 12-mm area of induration.

Assessment

1. Active pulmonary tuberculosis
2. Pneumothorax
3. Hypertension
4. Non-insulin-dependent diabetes mellitus

- Which signs, symptoms, and other findings are consistent with active TB infection?

anergy panels.[20,26] The "booster effect" occurs in patients who do not respond to an initial skin test but show a positive reaction if retested about a week later.[16,26]

Additional Tests

Morning sputum collections have the highest yield of organisms.[2,10,16] Daily sputum collections over three consecutive days improve the yield of positive results. Sputum induction with aerosolized hypertonic saline may produce a diagnostic sample in patients unable to produce sputum. Bronchoscopy or aspiration of gastric fluid via a nasogastric tube may be attempted in selected patients, the latter being used more often in children.[16] For patients with suspected extrapulmonary TB, samples of draining fluid, biopsies of the infected site, or both may be attempted. Blood cultures are positive occasionally, especially in acquired immune deficiency syndrome (AIDS) patients who have low CD4 counts.[16,23,27]

TREATMENT

General Approaches to Treatment

Monotherapy can be used only for infected patients who do not have active TB [**latent TB infection** (LTBI), as shown by a positive skin test in the absence of signs or symptoms of disease]. Once active disease is present, a minimum of two drugs and typically *three or four drugs* must be used simultaneously from the outset of treatment.[2,6,12,28] For most patients, the shortest duration of treatment is 6 months, and 2 to 3 years of treatment may be necessary for advanced cases of multidrug-resistant TB (MDR-TB).[2,6,12,28] **Directly observed therapy** (DOT) by a health care worker is a cost-effective way to ensure completion of treatment.[2,6,12,28–30]

Nonpharmacologic Therapy

❼ *Steps should be taken to (1) prevent the spread of TB (respiratory isolation), (2) find where TB has already spread (contact investigation), and (3) return the patient to a state of normal weight and well-being.* The older term for TB is *consumption* because wasting was a primary symptom of disease progression in the prechemotherapy era and remains descriptive today. Items 1 and 2 are performed by public health departments. Clinicians involved in the treatment of TB should verify that the local health department has been notified of all new cases of TB. Surgery may be needed to remove destroyed lung tissue, space-occupying infected lesions (tuberculomas), and certain extrapulmonary lesions.[2,12,28]

Pharmacologic Therapy

Treating Latent Infection (LTBI)

Isoniazid is used for treating LTBI.[2,6,12,28] Typically, isoniazid 300 mg daily (5–10 mg/kg of body weight) is given alone for 9 months. Lower doses usually are less effective.[2,31] The treatment of LTBI reduces a person's lifetime risk of active TB from about 10% to about 1%[20] (Table 72–2). Rifampin 600 mg

TABLE 72–2. Recommended Drug Regimens for Treatment of Latent Tuberculosis Infection (LTBI) in Adults[32]

Drug	Interval and Duration	Comments	Rating[a] HIV−	Evidence HIV+
Isoniazid	Daily for 9 months[c,d]	In human immunodeficiency virus (HIV)–infected patients, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or non-nucleoside reverse transcriptase inhibitors (NNRTIs).	A (II)	A (II)
	Twice weekly for 9 months[c,d]	Directly observed therapy (DOT) must be used with twice-weekly dosing.	B (II)	B (II)
Isoniazid	Daily for 6 months[d]	Not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs, or children.	B (I)	C (I)
	Twice weekly for 6 months[d]	DOT must be used with twice-weekly dosing.	B (II)	C (I)
Rifampin	Daily for 4 months	For persons who are contacts of patients with isoniazid-resistant rifampin susceptible TB. In HIV-infected patients, protease inhibitors or NNRTIs generally should not be administered concurrently with rifampin; rifabutin can be used as an alternative for patients treated with indinavir, nelfinavir, amprenivir, ritonavir, or efavirenz, and possibly with nevirapine or soft-gel saquinavir[e]	B (II)	B (III)

[a]*Strength of recommendation:* A = preferred; B = acceptable alternative; C = offer when A and B cannot be given.
[b]*Quality of evidence:* I = randomized clinical trial data; II = data from clinical trials that are not randomized or were conducted in other populations; III = expert opinion.
[c]Recommended regimen for children younger than 18 years of age.
[d]Recommended regimens for pregnant women. Some experts would use rifampin and pyrazinamide for 2 months as an alternative regimen in HIV-infected pregnant women, although pyrazinamide should be avoided during the first trimester.
[e]Rifabutin should not be used with hard-gel saquinavir or delavirdine. When used with other protease inhibitorsor NNRTIs, dose adjustment of rifabutin may be required.
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daily for 4 months can be used when isoniazid resistance is suspected or when the patient cannot tolerate isoniazid.[2,19,32,33] Rifabutin 300 mg daily might be substituted for rifampin in patients at high risk of drug interactions. The combination of pyrazinamide and rifampin is no longer recommended because of unacceptable rates of hepatotoxicity.[34] When resistance to isoniazid and rifampin is suspected in the isolate causing infection, there is no regimen proven to be effective.[2,28]

Treating Active Disease

In the United States, all patients diagnosed with TB can receive treatment free of charge through the local health department, and this is encouraged because local health departments generally have the greatest expertise. Treating active TB disease requires combination chemotherapy. Generally, *four drugs* are given at the onset of treatment. ❽ *Isoniazid and rifampin should be used together for most cases because they are the best drugs for preventing drug resistance.*[2,6,28,35,36] Drug susceptibility testing should be done on the initial isolate for all patients with active TB and should be used to guide the selection of drugs over the course of treatment.[2,6,12,28] Susceptibility testing may be repeated in cases where the patient remains culture-positive 8 weeks or more into therapy.

❽ *The standard TB treatment regimen is isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampin for 4 months, for a total of 6 months of treatment.*[2,12,28] *A total of 9 months of isoniazid and rifampin treatment is recommended for patients at greater risk of failure and relapse, including those with cavitation on initial chest radiograph or positive cultures at the completion of the initial 2-month phase of treatment, as well as for patients treated initially without pyrazinamide. Treatment should be continued for at least 6 months from the time that patients convert to smear- and culture-negative.*[2,6,12,28] Some authors recommend therapeutic drug monitoring for such patients because one of the proven reasons for treatment failure is malabsorption of orally administered drugs.[2,28,36,37] Table 72–3 shows the recommended treatment regimens for tuberculosis. When isoniazid and rifampin cannot be used, treatment durations become 2 years or more, regardless of immune status.[2,12,28,36] When intermittent therapy is used, DOT is essential. Doses missed during an intermittent TB regimen decrease the efficacy of the regimen and increase the relapse rate. Further, outcomes appear to be worse for immunocompromised patients when intermittent treatment, especially twice-weekly treatment, is used. Therefore, HIV-positive TB patients should receive TB drugs at least three times weekly. When the patients' **sputum smears** convert to negative, the risk of them infecting others is greatly reduced, but it is not zero.[2,15,28] Such patients can be removed from respiratory isolation, but they must be careful not to cough on others and should meet only in well-ventilated places.

Adjustments to the regimen should be made once the susceptibility data are available.[2,12,28] Drug resistance should be expected in patients who have been treated previously for TB. Two or more drugs with in vitro activity against the patient's isolate that were not used before should be added to the regimen as needed.[2,12,28] TB specialists should be consulted regarding cases of drug-resistant TB or in any setting where there is uncertainty regarding appropriate treatment.[2,12,28] ❾ *It is critical to avoid monotherapy, and it is critical to avoid adding a single drug to a failing regimen.*[2,12,28]

Special Populations

Patients with CNS tuberculosis usually are treated for longer periods (9–12 months instead of 6 months) because the consequences of undertreatment are severe.[2,12,28] TB of the bone typically is treated for 9 months, occasionally with surgical débridement.[2,12,28] Drug selection is the same as for pulmonary disease. Extrapulmonary TB of the soft tissues can be treated with conventional regimens.[2,12,28] TB in children may be treated with regimens similar to those used in adults, although some physicians extend treatment to 9 months.[2,12,16,18,28,32,38] Pediatric doses of isoniazid and rifampin on a milligram per kilogram basis are higher than those used in adults[28] (Table 72–4).

Pregnant women receive the usual treatment of isoniazid, rifampin, and ethambutol for 9 months.[2,28,32,36,38] Pyrazinamide has not been studied in large numbers of pregnant women, but anecdotal data suggest that it may be safe.[28] B vitamins should be provided. Streptomycin, other aminoglycosides, capreomycin, and ethionamide generally are avoided because they have been associated with toxic effects on the fetus.[28,39] *Para*-Aminosalicylic acid and cycloserine are used sparingly.[39] Quinolones generally are avoided in pregnancy because of concern about adverse effects on cartilage development.[28,39] Although most antituberculosis drugs are excreted in breast milk, the amount of drug received by the infant through nursing is insufficient to cause toxicity. Quinolones should be avoided in nursing mothers, if possible, for the same reason as above.

Human Immunodeficiency Virus

Patients with AIDS and other immunocompromised hosts may be managed with chemotherapeutic regimens similar to those used in immunocompetent individuals, although treatment is



Patient Encounter, Part 3: Creating a Care Plan

Based on the information provided, what are the goals of therapy for this patient? Select and recommend a therapeutic plan for treatment of this patient's TB infection. What drugs, dose, schedule, and duration of therapy are best for this patient? How should any contacts infected by this patient be evaluated and treated? Select and recommend a therapeutic plan. What drugs, dose, and schedule of therapy are best for his close contacts?

TABLE 72–3. Drug Regimens for Culture-Positive Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms[32]

		Initial Phase			Continuation Phase	
Regimen	**Drugs**	**Interval and Doses[c] (*Minimal Duration*)**	**Regimen**	**Drugs**	**Interval and Doses[c,d] (*Minimal Duration*)**	**Range of Total Doses (*Minimal Duration*)**
1	INH RIF PZA EMB	Seven days per week for 56 doses (8 weeks) *or* 5 days/week for 40 doses (8 weeks)[e]	1a	INH/RIF	Seven days per week for 126 doses (18 weeks) *or* 5 days/week for 90 doses (18 weeks)[e]	182–130 (26 weeks)
			1b	INH/RIF	Twice weekly for 36 doses (18 weeks)	92–76 (26 weeks)[f]
			1c[g]	INH/RPT	Once weekly for 18 doses (18 weeks)	74–58 (26 weeks)
2	INH RIF PZA EMB	Seven days per week for 14 doses (2 weeks)[e], *then* twice weekly for 12 doses (6 weeks) *or* 5 days/week for 10 doses (2 weeks), *then* twice weekly for 12 doses (6 weeks)	2a	INH/RIF	Twice weekly for 36 doses (18 weeks)	62–58 (26 weeks)[f]
			2b[g]	INH/RPT	Once weekly for 18 doses (18 weeks)	44–40 (26 weeks)
3	INH RIF PZA EMB	Three times weekly for 24 doses (8 weeks)	3a	INH/RIF	Three times weekly for 54 doses (18 weeks)	78 (26 weeks)
4	INH RIF EMB	Seven days per week for 56 doses (8 weeks) *or* 5 days/week for 40 doses (8 weeks)[e]	4a	INH/RIF	Seven days per week for 217 doses (31 weeks) *or* 5 days/week for 155 doses (31weeks)[e]	273–195 (39 weeks)
			4b	INH/RIF	Twice weekly for 62 doses (31 weeks)	118–102 (39 weeks)

[a]*Definitions of evidence ratings*: A = preferred; B = acceptable alternative; C = offer when A and B cannot be given; E = should never be given.
[b]*Definitions of evidence ratings*: I = randomized clinical trial; II = data from clinical trials that were not randomized or were conducted in other populations; III = expert opinion.
[c]When DOT is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.
[d]Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month [31-week; either 217 doses (daily) or 62 doses (twice weekly)] continuation phase.
[e]Five-day-a-week administration is always given by DOT. Rating for 5 day/week regimens is A(III).
[f]Not recommended for HIV-infected patients with CD4+ cell counts less than 100 cells/mL.
[g]Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on the initial chest radiograph. For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.
EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; RPT, rifapentine.
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often extended to 9 months[2,12,28] (Table 72–3). The precise duration to recommend remains a matter of debate. Highly intermittent regimens (twice or once weekly) are not recommended for HIV-positive TB patients.[28] Prognosis has been particularly poor for HIV-infected patients infected with MDR-TB. Some patients with AIDS malabsorb their oral medications, and drug interactions are common.[2,28,36,37] It is advisable that such patients are managed by TB-HIV experts because the challenges are many.

Renal Failure

Because they are hepatically cleared, isoniazid and rifampin do not require dose modification in renal failure.[31,36,39] Pyrazinamide and ethambutol typically are reduced to three times weekly to avoid accumulation of the parent drug (ethambutol) or metabolites (pyrazinamide).[28,31] Renally cleared TB drugs include the aminoglycosides (e.g., amikacin, kanamycin, and streptomycin), capreomycin, ethambutol, cycloserine, and levofloxacin.[28,31,33,39] Dosing intervals need to be extended for

TABLE 72–4. Antituberculosis Drugs for Adults and Children[a32]

Drug	Daily Doses[b]	Adverse Effects	Monitoring
Isoniazid	Adults: 5 mg/kg (300 mg) Children: 10–15 mg/kg (300 mg)	Asymptomatic elevation of aminotransferases, clinical hepatitis, fatal hepatitis, peripheral neurotoxicity, CNS system effects, lupus-like syndrome, hypersensitivity, monoamine poisoning, diarrhea	LFT monthly in patients who have preexisting liver disease or who develop abnormal liver function that does not require discontinuation of drug Dosage adjustments may be necessary in patients receiving anticonvulsants or warfarin
Rifampin	Adults[c]: 10 mg/kg (600 mg) Children: 10–20 mg/kg (600 mg)	Cutaneous reactions, gastrointestinal reactions (nausea, anorexia, abdominal pain), flulike syndrome, hepatotoxicity, severe immunologic reactions, orange discoloration of bodily fluids (sputum, urine, sweat, tears), drug interactions owing to induction of hepatic microsomal enzymes	Rifampin causes many drug interactions. For a complete list of drug interactions and effects refer to CDC Web site: www.cdc.gov/nchstp/tb/tb
Rifabutin	Adults[c]: 5 mg/kg (300 mg) Children: Appropriate dosing unknown	Hematologic toxicity, uveitis, gastrointestinal symptoms, polyarthralgias, hepatotoxicity, pseudojaundice (skin discoloration with normal bilirubin), rash, flulike syndrome, orange discoloration of bodily fluids (sputum, urine, sweat, tears)	Drug interactions are less problematic than rifampin
Rifapentine	Adults: 10 mg/kg (continuation phase) (600 mg) Dosed weekly. Children: The drug is not approved for use in children	Similar to those associated with RIF	Drug interactions are being investigated and are likely similar to RIF
Pyrazinamide	Adults: Based on IBW: 40–55 kg: 1000 mg; 56–75 kg: 1500 mg; 76–90 kg: 2000 mg Children: 15–30 mg/kg	Hepatotoxicity, gastrointestinal symptoms (nausea, vomiting), non-gouty polyarthralgia, asymptomatic hyperuricemia, acute gouty arthritis, transient morbilliform rash, dermatitis	Serum uric acid can serve as a surrogate marker for compliance LFTs in patients with underlying liver disease
Ethambutol[d]	Adults: Based on IBW: 40–55 kg: 800 mg; 56–75 kg: 1200 mg; 76–90 kg: 1600 mg Children[c]: 15–20 mg/kg daily	Retrobulbar neuritis, peripheral neuritis, cutaneous reactions	Baseline visual acuity testing and testing of color discrimination Monthly testing of visual acuity and color discrimination in patients taking greater than 15–20 mg/kg, renal insufficiency, or receiving the drug for greater than 2 months
Cycloserine	Adults[e]: 10–15 mg/kg per day, usually 500–750 mg/day in two doses Children: 10–15 mg/kg per day	Central nervous system effects	Monthly assessments of neuropsychiatric status Serum concentration may be necessary until appropriate dose is established
Ethionamide	Adults[f]: 15–20 mg/kg per day, usually 500–750 mg/day in a single daily dose or two divided doses Children: 15–20 mg/kg per day	Gastrointestinal effects, hepatotoxicity, neurotoxicity, endocrine effects	Baseline LFTs Monthly LFTs if underlying liver disease is present TSH at baseline and monthly intervals

(*Continued*)

TABLE 72–4. Antituberculosis Drugs for Adults and Children[a32] (*Continued*)

Drug	Daily Doses[b]	Adverse Effects	Monitoring
Streptomycin	Adults: See footnote[g] Children: 20–40 mg/kg per day	Ototoxicity, neurotoxicity, nephrotoxicity	Baseline audiogram, vestibular testing, Romber testing and SCr Monthly assessments of renal function and auditory or vestibular symptoms
Amikacin/ kanamycin	Adults: See footnote[g] Children: 15–30 mg/kg per day intravenous or intramuscular as a single daily dose	Ototoxicity, nephrotoxicity	Baseline audiogram, vestibular testing, Romber testing and SCr Monthly assessments of renal function and auditory or vestibular symptoms
Capreomycin	Adults: See footnote[g] Children: 15–30 mg/kg per day as a single daily dose	Nephrotoxicity, ototoxicity	Baseline audiogram, vestibular testing, Romberg testing and SCr Monthly assessments of renal function and auditory or vestibular symptoms Baseline and monthly serum K^+ and Mg^{2+}
p-Aminosalicylic acid (PAS)	Adults: 8–12 g/day in two or three doses Children: 200–300 mg/kg per day in two to four divided doses	Hepatotoxicity, gastrointestinal distress, malabsorption syndrome, hypothyroidism, coagulopathy	Baseline LFTs and TSH TSH every 3 mos
Levofloxacin	Adults: 500–1000 mg daily Children: See footnote[h]	Gastrointestinal disturbance, neurologic effects, cutaneous reactions	No specific monitoring recommended
Moxifloxacin	Adults: 400 mg daily Children: See footnote[i]		
Gatifloxacin	Adults: 400 mg daily Children: See footnote[j]		

[a]For purposes of this document, adult dosing begins at age 15 years.
[b]Dose per weight is based on ideal body weight. Children weighing more than 40 kg should be dosed as adults.
[c]Dose may need to be adjusted when there is concomitant use of protease inhibitors or nonnucleoside reverse transcriptase inhibitors.
[d]The drug likely can be used safely in older children but should be used with caution in children younger than 5 years of age, in whom visual acuity cannot be monitored. In younger children, EMB at the dose of 15 mg/kg per day can be used if there is suspected or proven resistance to INH or RIF.
[e]It should be noted that although this is the dose recommended generally, most clinicians with experience using cycloserine indicate that it is unusual for patients to be able to tolerate this amount. Serum concentration measurements are often useful in determining the optimal dose for a given patient.
[f]The single daily dose can be given at bedtime or with the main meal.
[g]Dose: 15 mg/kg per day (1 g) and 10 mg/kg in persons older than 50 years of age (750 mg). Usual dose: 750–1000 mg administered intramuscularly or intravenously, given as a single dose 5–7 days/week, and reduced to two or three times per week after the first 2–4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen.
[h]The long-term (more than several weeks) use of levofloxacin in children and adolescents has not be approved because of concerns about effects on bone and cartilage growth. However, most experts agree that the drug should be considered for children with tuberculosis caused by organisms resistant to both INH and RIF. The optimal dose is not known.
[i]The long-term (more than several weeks) use of moxifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.
[j]The long-term (more than several weeks) use of gatifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.
LFT, liver function test; SCr, serum creatinine; TSH, thyroid-stimulating hormone.
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these drugs. Serum concentration monitoring must be performed for cycloserine to avoid dose-related toxicities in renal failure patients.[33,36,37]

Hepatic Failure

Elevations of serum transaminase concentrations generally are not correlated with the residual capacity of the liver to metabolize drugs, so these markers cannot be used directly as guides for residual metabolic capacity. Hepatically cleared TB drugs include isoniazid, rifampin, pyrazinamide, ethionamide, and *p*-aminosalicylic acid.[39] Ciprofloxacin is about 50% cleared by the liver. Further, isoniazid, rifampin, pyrazinamide, and to a lesser degree ethionamide, *p*-aminosalicylic acid, and rarely ethambutol may cause hepatotoxicity.[28,36,39] These patients require close monitoring, and serum concentration monitoring may be the most accurate way to dose them.

The TB Drugs

The interested reader is referred to several other publications for more detailed information regarding these drugs.[2,11,28,34–37,39–42] A summary of daily doses, adverse effects, and monitoring

parameters of first- and second-line antituberculosis drugs is provided in Table 72–4.[28] Isoniazid and rifampin are considered the two key drugs for the treatment of active TB, followed by pyrazinamide, which has a special role in the first 2 months of treatment. Other drugs are used to suppress the emergence of drug resistance in conjunction with the first-line drugs or for preexisting drug-resistant TB. In general, the most important toxicity with first-line drugs is hepatotoxicity, whereas various organs may be affected by each of the second-line drugs. Recent research is placing emphasis on the potential role of quinolones such as levofloxacin and moxifloxacin in the treatment of TB. It is possible that future regimens may consider these agents part of the first-line drugs.

EVALUATION OF OUTCOMES

Effectiveness of TB therapy is determined by AFB smears and cultures. Sputum samples should be sent for AFB staining and microscopic examination (smears) every 1 to 2 weeks until two consecutive smears are negative. This provides early evidence of a response to treatment.[28] Once on maintenance therapy, **sputum cultures** can be performed monthly until two consecutive cultures are negative, which generally occurs over 2 to 3 months. If sputum cultures continue to be positive after 2 months, drug susceptibility testing should be repeated, and serum concentrations of the drugs should be checked.

⑩ *The most serious problem with TB therapy is patient nonadherence to the prescribed regimens.*[43,44] *Unfortunately, there is no reliable way to identify such patients a priori. The most effective way to achieve this end is with DOT.*[2,11,28] The use of DOT in non-compliant patients may be of benefit.[45] DOT also provides increased opportunities to observe the patient for any apparent toxicities, thus improving overall care.

Serum chemistries, including blood urea nitrogen (BUN), creatinine, aspartate transaminase (AST), and alanine transaminase (ALT), and a complete blood count with platelets should be performed at baseline and periodically thereafter depending on the presence of other factors that may increase the likelihood of toxicity (e.g., advanced age, alcohol abuse, and pregnancy).[2,28] Hepatotoxicity should be suspected in patients whose transaminases exceed five times the upper limit of normal or whose total bilirubin exceeds 51 µmol/L and in patients with symptoms such as nausea, vomiting, and jaundice. At this point, the offending agent(s) should be discontinued. Sequential reintroduction of the drugs with frequent testing of liver enzymes is often successful in identifying the offending agent; other agents may be continued[28] (Table 72–4).

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) or applied pharmacokinetics is the use of serum drug concentrations to optimize therapy.[28,36,37] Non-AIDS patients with drug-susceptible TB generally do well. TDM may be used if patients are failing appropriate DOT (no clinical improvement after 2 to 4 weeks or smear-positive after 4 to 6 weeks). On the other hand, patients with AIDS, diabetes, and various GI disorders often fail to absorb these drugs properly and are candidates for TDM. Also, patients with hepatic or renal disease should be monitored, given their potential for overdoses. In the treatment of MDR-TB, TDM may be particularly useful.[39,41] Finally, TDM of the TB and HIV drugs is perhaps the most logical way to untangle the complex drug interactions that take place. For a complete list of drug interactions visit the CDC Web site at www.cdc.gov/nchstp/tb/tb_hiv_drugs/toc.htm[46] In particular, interactions between the rifamycins (e.g., rifampin, rifapentine, and rifabutin) and the HIV protease inhibitors and nonnucleoside reverse transcriptase inhibitors are common and require dose and frequency modifications in many cases. Since these are constantly being updated, the preceding link is an excellent way to keep current.



Patient Encounter, Part 4: Creating a Care Plan

Based on the information provided, which clinical and laboratory parameters should be monitored in this patient to determine efficacy and avoid toxicity? Is this patient a candidate for therapeutic drug monitoring? Why or why not?



Patient Care and Monitoring

1. Rapidly identifiy a new TB case.
2. Assess the patient's risk factors and signs and symptoms to determine if the patient might be infected with TB.
3. Isolate the patient with active disease to prevent the spread of the disease.
4. Collect appropriate samples for smears and cultures.
5. Obtain a throrough medication history.
6. Select and recommend appropriate antituberculosis treatment. Consider HIV status, pregnancy, type of TB infection, renal function, liver function etc.
7. Ensure adherence to the treatment regimen by the patient.
8. Obtain AFB stains to evaluate the effectiveness of treatment.
9. Consider TDM if no clinical improvement.
10. Secondary goals are identification of the index case that infected the patient, identification of all persons infected by both the index case and the new case of TB, and the completion of appropriate treatments for those individuals.

ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
ALT	Alanine transaminase
AST	Aspartate transaminase
CNS	Central nervous system
(HIV)	Human immunodeficiency virus
(HTN)	Hypertension
NIDDM	Non-insulin dependent diabetes mellitus
PCR	Polymerase chain reaction
RFLP	Restriction fragment length polymorphism
TB	Tuberculosis
WBC	White blood cell

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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73 Gastrointestinal Infections

Elizabeth D. Hermsen and Ziba Jalali



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Describe the epidemiology and clinical presentation of the various gastrointestinal infections.
2. Develop an individualized treatment plan given a patient with each of the gastrointestinal infections.
3. Understand the impact of resistance on the treatment of the various gastrointestinal infections.
4. Recognize the effect of immunosuppression on gastrointestinal infections.
5. Educate patients on appropriate prevention measures.
6. Describe the role of antimicrobial prophylaxis and/or vaccination for gastrointestinal infections.

Key Concepts

❶ Rehydration is the foundation of therapy for gastrointestinal infections.
❷ Blood in stool indicates the possibility of inflammatory mucosal disease of the colon. Enterohemorrhagic *Escherichia coli* (EHEC) is an important cause of bloody diarrhea in the United States.
❸ Travelers' diarrhea is most commonly caused by bacteria such as *Shigella, Salmonella, Campylobacter*, and *Escherichia coli*, although viruses are being recognized increasingly as a significant cause of travelers' diarrhea as well.
❹ Education of travelers about high-risk food items is the key to the prevention of travelers' diarrhea.
❺ Nosocomial *Clostridium difficile*–associated diarrhea (CDAD) is almost always associated with antimicrobial use; therefore, we should avoid unnecessary and inappropriate antibiotic therapy. Almost all antibiotics except aminoglycosides have been associated with CDAD.
❻ Viruses are the most common cause of diarrheal illness in the world. A live, oral vaccine is licensed and recommended for use in infants for the prevention of rotavirus infection.

One of the primary concerns related to gastrointestinal (GI) infection, regardless of the cause, is dehydration, which is the second leading cause of worldwide morbidity and mortality.[5] Worldwide, dehydration is especially problematic for children younger than age 5. However, the highest rate of death in the United States occurs among the elderly.[5] ❶ *Rehydration is the foundation of therapy for GI infections, and oral rehydration therapy (ORT) is usually preferred* (Table 73–1).

BACTERIAL INFECTIONS

Shigellosis

Epidemiology

Shigella causes bacillary **dysentery,** which refers to a diarrheal stool containing pus and blood. Worldwide, there are an estimated 165 million cases of shigellosis annually with 1 million associated deaths.[6] Shigellosis is a disease that mostly affects children 6 months to 10 years of age. In the United States, shigellosis is a serious problem in day-care centers and areas with crowded living conditions such as urban centers. Most cases of shigellosis are a result of person-to-person transmission. *Shigella* transmission from contaminated food and water, although less common, is associated with large outbreaks.

Pathogenesis

Shigella are nonmotile, gram-negative, non-lactose-fermenting rods and are members of the family Enterobacteriaceae. There

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TABLE 73–1. Clinical Assessment of Degree of Dehydration in Children Based on Percentage of Body Weight Loss

Variable	Mild, 3–5%	Moderate, 6–9%	Severe, 10% or More
Blood pressure	Normal	Normal	Normal to reduced
Quality of pulses	Normal	Normal to slightly decreased	Moderately decreased
Heart rate	Normal	Increased	Increased (bradycardia in severe cases)
Skin turgor	Normal	Decreased	Decreased
Fontanelle	Normal	Sunken	Sunken
Mucous membranes	Slightly dry	Dry	Dry
Eyes	Normal	Sunken orbits/ decreased tears	Deeply sunken orbits/ decreased tears
Extremities	Warm, normal capillary refill	Delayed capillary refill	Cool, mottled
Mental status	Normal	Normal to listless	Normal to lethargic to comatose
Urine output	Slightly decreased	Less than 1 mL/kg per hour	Less than 1 mL/kg per hour
Thirst	Slightly increased	Moderately increased	Very thirsty
Fluid replacement	ORT 50 mL/kg over 2–4 hours	ORT 100 mL/kg over 2–4 hours	Lactated Ringers 40 mL/kg in 15–30 minutes, then 20–40 mL/kg if skin turgor, alertness, and pulse have not returned to normal *or* Lactated Ringers or normal saline 20 mL/kg, repeat if necessary, and then replace water and electrolyte deficits over 1–2 days, followed by ORT 100 mL/kg over 4 hours

From Martin S, Jung R. Gastrointestinal infections and enterotoxigenic poisonings. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005:2037.

are four species of *Shigella*: *S. dysenteriae* (serogroup A), *S. flexneri* (serogroup B), *S. boydii* (serogroup C), and *S. sonnei* (serogroup D). Infection with *Shigella* occurs after ingestion of as few as 10 to 100 organisms.[7] This low dose of organisms probably explains the person-to-person spread and the high secondary attack rate when an index case is introduced into a family.

Shigella strains invade intestinal epithelial cells with subsequent multiplication, inflammation, and destruction.[8] The organism infects the superficial layer of the gut, rarely penetrates beyond the mucosa, and seldom invades the bloodstream. However, bacteremia can occur in malnourished children and **immunocompromised** patients.



Clinical Presentation and Diagnosis

- Biphasic illness
  - Early—high fever, watery **diarrhea** without blood
  - Later—after approximately 48 hours, colitis develops with urgency, **tenesmus**, and dysentery.
    - Low-grade fever
    - More frequent small-volume stools ("fractional stools")
    - Abdominal cramping
- Major complications of shigellosis include
  - Proctitis or rectal prolapse (infants and young children)
  - Toxic megacolon (primarily in the setting of *S. dysenteriae* 1 infection)
  - Intestinal obstruction
  - Colonic perforation
  - Bacteremia (more common in children)
  - Metabolic disturbances
  - **Leukemoid reaction**
  - Neurologic disease
  - Reactive arthritis or Reiter's syndrome
  - **Hemolytic-uremic syndrome (HUS)**
- Microscopic examination of stool is extremely useful and reveals multiple polymorphonuclear leukocytes and red blood cells. Diagnosis is usually confirmed by stool culture.

Treatment and Monitoring

Although infection with *Shigella* generally is self-limited and responds to supportive care, antibiotic therapy is indicated because it shortens the duration of illness and shedding and consequently reduces the risk of transmission. Antibiotic resistance is a worldwide concern and growing problem for enteric bacterial pathogens. Currently, the treatment of choice is a fluoroquinolone when the antibiotic susceptibility of the organism is unknown[9] (Table 73–2). Cephalosporins or azithromycin can be used in the management of pediatric shigellosis.

TABLE 73–2. Antibacterial Therapy for Adults with Shigellosis

Agent	Dosage
Levofloxacin	500 mg daily × 3 days
Ciprofloxacin	500 mg twice daily × 3 days
Norfloxacin	400 mg twice daily × 3 days
Azithromycin	500 mg daily × 3 days
Rifaximin	200 mg three times daily × 3 days

DuPont H. Shigella species (bacillary dysentery). IN: Mandell GL, Bennett JE, and Dolin R, (eds.) Principles and Practice of Infectious Diseases, 6th ed. New York: Churchill Livingstone; 2004:2655.

Rifaximin is likely to be effective in the treatment of milder forms of shigellosis and has been shown to be effective at preventing infection owing to *S. flexneri*.[10] Antimotility agents are not recommended because they can worsen dysentery and may be related to the development of toxic megacolon. No vaccines are licensed currently for the prevention of shigellosis.

Salmonellosis

Epidemiology

Salmonella typhi and *Salmonella paratyphi*, which cause typhoid fever, have high host specificity for humans. In the United States, typhoid fever has become less prevalent and is associated primarily with international travel, especially to developing countries. Nontyphoidal *Salmonella* are important causes of reportable foodborne infection. There are an estimated 1.4 million cases of nontyphoid *Salmonella* illness annually in the United States.[11] The highest incidence is in those younger than 1 year of age and older than 65 years of age or in those with HIV/AIDS. Outbreaks of intestinal salmonellosis have been reported owing to unpasteurized orange juice, tomatoes, cantaloupe, alfalfa sprouts, and cilantro. Exotic pets, especially reptiles (e.g., snakes, turtles, and iguanas), are an increasing source of human salmonellosis, accounting for an estimated 3% to 5% of all cases.

Risk factors for salmonellosis include extremes of age, alteration of the endogenous bowel flora of the intestine (e.g., as a result of antimicrobial therapy or surgery), diabetes, malignancy, rheumatologic disorders, human immunodeficiency virus (HIV) infection, and therapeutic immunosuppression of all types.

Pathogenesis

Salmonella are motile, non-lactose-fermenting, gram-negative bacilli. In salmonellosis, the organisms penetrate the epithelial lining to the lamina propia with production of diffuse inflammation. The distal ileum and colon are sites of infection.

Treatment and Monitoring

Gastroenteritis

Salmonella gastroenteritis is usually self-limited, and antibiotics have no proven value. Patients respond well to ORT. Symptoms typically diminish in 3 to 7 days without sequelae. Antibiotic use may result in a higher rate of chronic carriage and relapse. Antimicrobial use should be limited to preemptive therapy among patients at higher risk for extraintestinal spread or invasive disease (Table 73–3). Antimotility agents should not be used.

Enteric Fever

The current drug of choice for typhoid fever is a fluoroquinolone, such as ciprofloxacin. The recommended dose of ciprofloxacin for uncomplicated typhoid is 500 mg orally twice daily for 5 to 7 days. Drug resistance is a recognized problem in the Indian subcontinent, Southeast Asia, Mexico, the Arabian Gulf, and Africa. All *S. typhi* isolates should be screened for nalidixic acid and fluoroquinolone resistance. If nalidixic acid resistance is present, the patient should be given higher doses of ciprofloxacin or ofloxacin (10 mg/kg twice



Clinical Presentation and Diagnosis

Gastroenteritis

- Onset 8 to 48 hours after ingestion of contaminated food.
- Fever, diarrhea, and cramping
- Stools are loose, of moderate volume, and without blood.
- Headache, myalgias, and other systemic symptoms can occur.
- Diagnosis relies on isolation of the organism from stool or ingested food.
- Certain underlying conditions (e.g., AIDS, inflammatory bowel disease, and prior gastric surgery) predispose the patient to more severe disease.

Enteric Fever

- Febrile illness 5 to 21 days after ingestion of contaminated food or water
- Chills, diaphoresis, headache, anorexia, cough, weakness, sore throat, dizziness, and muscle pains are frequently present before the onset of fever.
- Diarrhea is an early symptom and occurs only in 50% of cases. Intestinal hemorrhage or perforation, leukopenia, anemia, and subclinical disseminated intravascular coagulopathy may be seen.
- Culture of stool, blood, or bone marrow for *Salmonella* species is helpful.

Vascular Infection and Bacteremia

S. choleraesuis and *S. dublin* are the most common causative organisms. The risk of bacteremia is greater for infants, the elderly, and the immunocompromised.

Localized Infections

Localized infections occur in 5% to 10% of cases with *Salmonella* bacteremia. Sites for extraintestinal complications of salmonellosis include endocarditis, arteritis, central nervous system, lung, bone, joints, muscle/soft tissue, splenic, and genitourinary.

Chronic Carriers

The chronic carrier state, defined as positive stool or urine cultures for more than 12 months, develops in 1% to 4% of adults with typhoid fever. Persistence of the organism, in many cases, is due to billiary tract carriage, and the frequency of chronic carriage is higher in persons with biliary abnormalities.

Salmonella and HIV Infection

Salmonella is more likely to cause severe invasive infection in the HIV-infected population. Recurrent nontyphoidal *Salmonella* bacteremia is an AIDS-defining illness.

TABLE 73–3. Antimicrobial Indications for Nontyphoidal Salmonellosis

Less than or equal to 3 months, greater than or equal to 65 years of age
Fever and systemic toxicity
AIDS and other immunodeficiencies (including steroid use or organ transplantation)
Uremia or hemodialysis or renal transplant
Malignancy
Sickle cell anemia or hemoglobinopathy
Inflammatory bowel disease
Aortic aneurysm, prosthetic heart valve, vascular or orthopedic prosthesis

daily) for 10 to 14 days. A third-generation cephalosporin and azithromycin (1000 mg once on day 1 followed by 5 days of 500 mg daily) are alternative agents for *S. typhi* strains, with minimum inhibitory concentration (MIC) values for ciprofloxacin of 2 mcg/mL or greater.[12]

Patients with complicated typhoid fever (i.e., metastatic foci, ileal perforation, etc.) should receive parenteral therapy with ciprofloxacin 400 mg twice daily or ceftriaxone 2000 mg once daily. Antimicrobial therapy can be completed with an oral agent after initial control of the symptoms of typhoid fever. In persons with AIDS and a first episode of *Salmonella* bacteremia, a longer duration of antibiotic therapy (1–2 weeks of parenteral therapy followed by 4 weeks of oral fluoroquinolone) is recommended to prevent relapse of bacteremia.

Three typhoid vaccines are available currently for use in the United States: (1) an oral live-attenuated vaccine (Vivotif Berna-TM vaccine, Swiss Serum and Vaccine Institute), (2) a parenteral heat-phenol-inactivated vaccine (Typhoid Vaccine, Wyeth-Ayerst), and (3) a parenteral capsular polysaccharide vaccine (Typhim Vi, Pasteur Merieux). Immunization is recommended only for travelers going to endemic areas such as Latin America, Asia, and Africa; household contacts of a chronic carrier; and laboratory personnel who frequently work with *S. typhi*.[13]

Chronic Carriers

In patients with normal gallbladder function, effective agents for eradication of chronic carriage include amoxicillin (3 g divided three times a day in adults for 3 months), trimethoprim-sulfamethoxazole (one double-strength tablet twice a day for 3 months), and ciprofloxacin (750 mg twice daily for 4 weeks). In patients with anatomic abnormalities, such as biliary or kidney stones, surgery combined with antibiotic therapy is indicated.

Campylobacteriosis

Epidemiology

Campylobacter jejuni is the most commonly identified bacterial cause of diarrhea worldwide. The organism accounts for 2.1 to 2.4 million cases of illness in the United States each year. Risk factors for *Campylobacter* infection include consumption of chicken, sausage, red meat, and contaminated water; foreign travel; receipt of an antimicrobial agent; household exposure to chickens; and contact with pets (especially birds and cats). Between 25% and 50% of *C. jejuni* infections in the United States appear to be related to chicken exposure or consumption.

The age and sex distributions of *Campylobacter* infections are unique among bacterial enteric pathogens. In developed countries, there are two age peaks: younger than 1 year of age and 15 to 44 years of age. There is a mild male predominance among infected persons. The reason for this distinct age and sex distribution remains unknown. The epidemiology of *Campylobacter* infections is quite different in developing countries; *Campylobacter* diarrhea is primarily a pediatric disease in developing countries.

Pathogenesis

Campylobacter spp. are gram-negative bacilli that have a curved or spiral shape. *Campylobacter* are sensitive to stomach acidity; as a result, diseases or medications that buffer gastric acidity may increase the risk of infection. Data suggest that the infectious dose for *C. jejuni* is similar to that for *Salmonella* spp. After an incubation period, infection is established in the jejunum, ileum, colon, and rectum.



Clinical Presentation and Diagnosis

- Incubation period of 1 to 7 days
- Abdominal cramps, fever, and diarrhea
- Dysentery is seen in approximately 50% of cases.
- Diarrhea is either loose and watery or grossly bloody.
- Some patients present mainly with abdominal cramps and pain and minimal diarrhea.
- Fecal leukocytes and red blood cells (RBCs) are detected in the stools of 75% of infected individuals. Diagnosis of *Campylobacter* is established by stool culture.
- Extraintestinal *C. jejuni* infection, including septic arthritis, cholecystitis, pancreatitis, meningitis, endocarditis, osteomyelitis, and neonatal sepsis, can present in three different ways:
  - Transient bacteremia with acute *Campylobacter* enteritis in a normal host with benign course
  - Sustained bacteremia or deep focus of infection in a previously normal host that responds to antimicrobial therapy
  - Sustained bacteremia or deep infection in a compromised host
- The most important postinfectious complication of *C. jejuni* is Guillain-Barré syndrome (GBS). The risk of developing GBS is very small (less than one case of GBS per 1000 *C. jejuni*). GBS typically occurs 1 to 3 weeks after diarrhea.

Treatment and Monitoring

Hydration and electrolyte balance, often with ORT, are the cornerstone of treatment. The specific circumstances that antibiotics should be considered include high fevers, bloody stools, symptoms longer than 1 week, pregnancy, infection with HIV, and other immunocompromised hosts.

Until a few years ago, fluoroquinolones were the drug of choice for campylobacteriosis. However, a major problem among *Campylobacter* strains is growing resistance, occurring worldwide. Fluoroquinolone resistance in human isolates of *C. jejuni* in the United States occurs at a rate of 18%, and resistance levels in Barcelona and Thailand are over 80%. Fluoroquinolones should not be used unless susceptibility is confirmed.

Erythromycin is considered the optimal drug for treatment of *Campylobacter* infections. The rate of resistance of *Campylobacter* to erythromycin remains low. Other advantages of this drug include ease of administration, low cost, lack of major toxicity, and narrow spectrum of activity.[14] The recommended dosage for adults is 250 mg orally four times daily or 500 mg orally twice daily for 5 to 7 days. For very ill patients, treatment with gentamicin, imipenem, cefotaxime, or chloramphenicol is indicated, but susceptibility tests should be performed.

Enterohemorrhagic *Escherichia coli* (EHEC)

Epidemiology

EHEC are the pathogenic subgroup of Stx-producing *E. coli* (STEC). Acute hemorrhagic colitis has been associated mainly with the O157:H7 serotype. This serotype has been responsible for larger outbreaks of infection, has higher rates of complications, and appears to be more pathogenic than non-EHEC STEC strains. ❷ *The spectrum of disease associated with E. coli O157:H7 includes bloody diarrhea, which is seen in as many as 95% of patients, nonbloody diarrhea, hemolytic-uremic syndrome (HUS), and thrombotic thrombocytopenic purpura.*

Approximately 70,000 cases of EHEC illness occur each year in the United States. The highest incidence is in patients aged 5 to 9 years and 50 to 59 years. Outbreaks of diarrhea due to O157:H7 *E. coli* and other STECs have occurred from contaminated beef, classically hamburgers served at fast-food chains, raw milk and other dairy products, vegetables (e.g., alfalfa sprouts, coleslaw, and lettuce), and apple juice. The most important reservoir for *E. coli* O157:H7 is the gastrointestinal tract of cattle. Person-to-person transmission is also possible because of the low infectious dose. Swimming in infant pools or contaminated lakes or drinking municipal water also appears to be a risk factor. The incidence of diagnosed *E. coli* O157:H7 infections in the United States is greater among rural than urban populations, and *E coli* O157:H7 infections occur in summer and autumn.

Pathogenesis

The infectious dose of EHEC is very low, between 1 and 100 colony-forming units (CFUs).[15] The two major virulence factors for EHEC are the production two Shigalike cytotoxins (Stx I and II) and adhesion-causing attachment-effacement (A/E) lesions. These Stx cytotoxins are responsible for vascular damage and systemic effects such as HUS. Adhesion mediates initial attachment of EHEC to intestinal epithelial cells. Following attachment, these organisms produce A/E lesions on individual intestinal epithelial cells. A/E lesions infect the small or large intestine and cause diarrhea.



Clinical Presentation and Diagnosis

- Incubation period of 3 to 5 days
- Bloody stools
- Fever usually absent
- Leukocytosis
- Abdominal tenderness
- HUS in 2% to 10% of patients (especially children 1–5 years of age and the elderly in nursing homes). Develops on average 1 week after the onset of diarrhea.
- EHEC belonging to serotype 0157:H7 characteristically do not ferment sorbitol, whereas more than 70% of intestinal floral *E. coli* do. To properly screen EHEC strains in cases of diarrhea, stool should be placed on special sorbitol-MacConkey agar. Colonies of *E. coli* 0157:H7, which do not ferment the sorbitol, can be identified readily and confirmed by serotyping with specific antisera. In addition, stool should be tested directly for the presence of Stx I and II by enzyme immunoassay (EIA).

Treatment and Monitoring

The only current treatment of EHEC infection is supportive, including fluid and electrolyte replacement, often in the form of ORT. Most illnesses resolve in 5 to 7 days. Patients should be monitored for the development of HUS. Antibiotics are currently contraindicated because they can induce the expression and release of toxin. Antimotility agents should be avoided because they may delay clearance of the pathogen and toxin. This, in turn, may increase the risk of systemic complications.

Proper cooking of foods is essential. Supervision of hand washing by children in day-care centers and exclusion of symptomatic children may reduce person-to-person spread.

Cholera

Epidemiology

Cholera, the first reportable disease, is endemic in South Asia, particularly in the Ganges delta region.[2] The biotypes of *Vibrio cholerae* responsible for pandemics are serogroup O1 (El Tor) and serogroup O139.[16,17] Cholera can be transmitted by water or by food contaminated with contaminated water, particularly undercooked seafood. *V. cholerae* grows well in warm temperatures, causing marked seasonality in the incidence of cholera.[2]

People of blood type O are more susceptible to El Tor vibrios than people of other blood types.[18] Inoculum size affects the likelihood and severity of cholera infection. The infectious dose is lower in patients who are taking antacids owing to the neutralization of gastric acid.[19]

Pathogenesis

V. cholerae is a gram-negative bacillus. Vibrios pass through the stomach to colonize the upper small intestine. Vibrios have filamentous protein extensions that attach to receptors on the intestinal mucosa, and their motility assists with penetration of the mucus layer.[2] The cholera enterotoxin consists of two subunits, one of which (subunit A) is transported into the cells and causes an increase in cyclic AMP, which leads to a deluge of fluid into the small intestine.[20] This large volume of fluid results in the watery diarrhea that is characteristic of cholera. The stools are an electrolyte-rich isotonic fluid, the loss of which results in blood volume depletion followed by low blood pressure and shock.[2] Of note, the diarrheal fluid is highly infectious.

Treatment and Monitoring

The cornerstone of cholera treatment is fluid replacement. Without treatment, the case-fatality rate for severe cholera is approximately 50%. For cholera, rice-based ORT is better than glucose-based ORT because it reduces the number of stools.[21] Patients with significant disease should receive a short antibiotic course, 1 to 3 days, to shorten the duration of illness and decrease the number of stools. Doxycycline 300 mg once daily is the drug of choice. Other antibiotics shown to be effective include erythromycin, azithromycin, trimethoprim-sulfamethoxazole, and ciprofloxacin.[2] Antibiotic resistance has been documented in *V. cholerae* since 1977.[2] Antibiotic prophylaxis is not warranted.

The main prevention strategies include ensuring a safe water supply and safe food preparation, improving sanitation, and patient education. Several oral vaccines are in development, and two are available in countries outside the United States.[22–27] However, these vaccines do not provide protection against all cases of cholera because the immunity may be overcome by high inocula.[2]



Clinical Presentation and Diagnosis[2]

- Incubation period of 18 hours to 5 days
- Abrupt onset of watery diarrhea and vomiting
- Large volumes of rice-water stools
- Dehydration, may be severe. Patients suffering from severe dehydration owing to rapid fluid loss are at risk for death within several hours of disease onset.
- Severe muscle cramps in extremities owing to the electrolyte imbalance caused by the fluid loss. These cramps should resolve with treatment.
- Metabolic acidosis

Travelers' Diarrhea

Epidemiology

Travelers' diarrhea occurs commonly when visitors from developed countries travel to developing countries. Over 50 million people are at risk for travelers' diarrhea each year.[28] Travelers' diarrhea can occur following the consumption of food or water contaminated with bacteria, viruses, or parasites. ❸ *Bacteria such as Shigella, Salmonella, Campylobacter, and E. coli are responsible for 60% to 85% of the travelers' diarrhea cases.*[28] *Noroviruses are being recognized increasingly as a significant cause of travelers' diarrhea as well.*[29]

Risky foods include tap water; uncooked foods, including seafood, fruits, and vegetables; and foods that are stored inadequately, particularly buffet-style meals. Additionally, alcohol consumption of more than five drinks per day has been demonstrated to be a risk factor, especially in males.[30] Education about the types of foods to avoid during travel can be an effective method of prevention.

Pathogenesis

Refer to the specific microorganism sections of this chapter for pathogenesis information.

Treatment and Monitoring

The goal of treatment is to maintain hydration and functional status to prevent disruption of travel plans. For travelers with mild cases of diarrhea, ORT is often all that is needed. However, antibiotics are very effective at reducing the duration of illness. The use of trimethoprim-sulfamethoxazole has fallen out of favor because of the development of resistance in many regions. In general, fluoroquinolones, specifically levofloxacin (500 mg once daily) and ciprofloxacin (500 mg twice daily), are the drugs of choice for travelers' diarrhea. A 24-hour regimen can be used unless the traveler has a fever or bloody stools, in which case a 3-day regimen is necessary.[28] Alternatives to fluoroquinolones should be used in Asia, where resistance is high among *Campylobacter*. Azithromycin, as a single 1000-mg dose, represents an alternative to the fluoroquinolone class.[28] Additionally, the Food and Drug Administration (FDA) recently approved rifaximin for the treatment of travelers' diarrhea at a dose of 200 mg three times daily for 3 days. Rifaximin is not effective against *C. jejuni,* and efficacy has not been documented against *Salmonella* or *Shigella*.



Clinical Presentation and Diagnosis

- Frequent, loose stools
- Associated with nausea and vomiting
- Abdominal pain
- Fecal urgency
- Dysentery
- Signs and symptoms related to specific causative pathogen

Although antimotility agents are effective at shortening the duration of illness, they do not eradicate microorganisms and should not be used in moderate to severe cases with systemic symptoms unless in combination with an antibiotic. The combination of an antimotility agent and an antibiotic can reduce the duration of illness to a few hours.[28]

❹ *Education of travelers about high-risk food items is the key to the prevention of travelers' diarrhea.* Slogans such as "Peel it, boil it, cook it, or forget it" can help to remind travelers of the foods that may be contaminated. Prophylaxis of travelers' diarrhea with antibiotics is effective but should be restricted to individuals who have a repeated history of travelers' diarrhea; cannot afford to make travel alterations (e.g., business trip, competitors, or politicians); have a predisposing factor for travelers' diarrhea, such as achlorhydria, gastrectomy, or inflammatory bowel disease; or are immunosuppressed.[28] The use of antibiotics for prophylaxis is not widely recommended because of the selective pressure for the development of resistance, adverse effects, effect on the normal flora of the gastrointestinal tract, and cost. The fluoroquinolones are used when prophylaxis is necessary. However, rifaximin may represent an ideal option for prophylaxis of travelers' diarrhea, with virtually no systemic absorption and an excellent safety profile, although it is not approved by the FDA for this indication. Bismuth subsalicylate 525 mg one to four times daily is also effective for travelers' diarrhea prophylaxis. No effective vaccines exist for travelers' diarrhea.

Clostridium difficile–Associated Diarrhea (CDAD)

Epidemiology

C. difficile is the leading cause of nosocomial enteric infection. *C. difficile* toxins can be found in the stool of 15% to 25% of patients with antibiotic-associated diarrhea (AAD) and more than 95% of patients with pseudomembranous colitis.[31] More than 90% of health care–associated CDAD occurs after or during antimicrobial therapy. ❺ *Clindamycin, cephalosporins, and penicillins are the antibiotics most associated with CDAD, but almost all antimicrobial agents except aminoglycosides have been associated with CDAD.*[32] Recent studies have shown fluoroquinolones to be strongly associated with CDAD.[33,34] Other risk factors for CDAD include increasing age, severe underlying disease, nonsurgical GI procedures, presence of a nasogastric tube, receipt of antiulcer medications, stay on an intensive-care unit, long duration of hospital stay, long duration of antibiotic, and receiving multiple antibiotics.[35]

The incidence of community-associated *C. difficile* infection (defined as occurring in patients not hospitalized in the year prior to diagnosis) is increasing.[36] In addition to antibiotic use, community-associated *C. difficile* cases are associated with the use of gastric acid suppressive agents (e.g., proton pump inhibitors and H_2-receptor antagonists).

C. difficile is spread by the fecal-oral route, and patient-to-patient transmission has been documented.

Pathogenesis

C. difficile is a gram-positive, spore-forming anaerobe. The organism is ingested either as the vegetative form or spores, which can survive for long periods in the environment and



Clinical Presentation and Diagnosis

- Symptoms can start as early as the first day of antimicrobial therapy or several weeks after antibiotic therapy is completed.
- Asymptomatic carriage
- Diarrhea
  - Acute watery diarrhea with lower abdominal pain, low-grade fever, and mild or absent leukocytosis
  - Mild, with only three or four loose watery stools per day
  - *C. difficile* toxins are present in stool, but sigmoidoscopic examination is normal.
- Colitis
  - Profuse, watery diarrhea with 5 to 15 bowel movements per day, abdominal pain, abdominal distention, nausea, and anorexia
  - Left or right lower quadrant abdominal pain and cramps that are relieved by passage of diarrhea
  - Dehydration and low-grade fever
  - Sigmoidoscopic examination may reveal a nonspecific diffuse or patchy erythematous colitis without pseudomembranes.
- Pseudomembranous colitis: Same symptoms as colitis, but sigmoidoscopic examination reveals a characteristic membrane with adherent yellow or off-white plaques, usually in distal colon.
- Toxic megacolon: Suggested by acute dilatation of the colon to a diameter greater than 6 cm, associated systemic toxicity, and the absence of mechanical obstruction. It carries a high mortality rate.
- Fulminant colitis: Acute abdomen and systemic symptoms such as fever, tachycardia, dehydration, and hypotension. Some patients have marked leukocytosis (up to 40,000 white blood cells/mm^3). Diarrhea is usually prominent but may not occur in patients with paralytic ileus and toxic megacolon.
- Relapsing colitis
  - Risk factors include increased age, recent abdominal surgery, increased number of *C. difficile* diarrheal episodes, and leukocytosis.
  - 12% to 24% of patients develop a second episode of CDAD within 2 months of the initial diagnosis.
- In most instances, *C. difficile* toxin testing of a single stool specimen effectively establishes the diagnosis. Various ELISA kits are available to detect toxin A or toxin B or both. Those that detect both toxin A and B are preferred. Repeated testing can boost sensitivity.
- Leukocytosis, hypoalbuminemia, and fecal leukocytes are nonspecific but suggestive of *C. difficile* infection.
- In selected patients, sigmoidoscopy, colonoscopy, or abdominal computed tomographic (CT) scan can provide useful diagnostic information.

can transverse the acidic stomach. In the small intestine, spores germinate into the vegetative form. In the large intestine, CDAD can develop if the normal flora is disrupted by antibiotic therapy. Toxin production is essential for disease to occur. The main virulence factor for disease related to *C. difficile* is the production of toxins A and B. These toxins are responsible for inflammation, fluid and mucus secretion, and mucosal damage, which lead to diarrhea or colitis.

Treatment and Monitoring

Stopping the inciting antibiotic is the most important step in the initial treatment of CDAD.[37] If stopping antibiotic therapy is not effective or not practical, antimicrobial therapy directed specifically against *C. difficile* should be given for 10 days. Oral metronidazole (500 mg three times daily or 250 mg four times daily) and oral vancomycin (125 mg four times daily) have similar rates of efficacy, but metronidazole is considered the drug of choice for most cases because of cost and concerns regarding the emergence of vancomycin-resistant enterococcus (VRE).

Severe disease is defined as the presence of complications of colitis, such as sepsis, volume depletion, electrolyte imbalance, hypotension, paralytic ileus, and toxic megacolon. Patients with signs of severe disease should receive oral vancomycin as initial therapy. Surgical intervention may be indicated and lifesaving, particularly in cases complicated by toxic megacolon or colonic perforation.

In circumstances where oral therapy cannot be given, intravenous metronidazole (500 mg every 6–8 hours), vancomycin retention enemas (500 mg every 4–8 hours), or vancomycin via colonic catheter should be considered.[38] Antiperistaltic agents should not be given because the use of these agents is associated with the development of toxic megacolon.

Therapeutic response should be based on clinical signs and symptoms. A repeat toxin assay as a "test of cure" is not recommended because some patients may remain colonized with this organism following recovery. Treatment of asymptomatic colonized patients is not recommended as an infection-control measurement.

Relapse is suggested by the returning of symptoms 3 to 21 days after stopping metronidazole or vancomycin. Since antibiotic resistance is not a factor in relapse, most relapses usually respond to another course of either metronidazole or vancomycin.

Vigilant hand washing and isolation precautions are keys to controlling *C. difficile*.

PARASITIC INFECTIONS

Please refer to Chapter 75 for information regarding giardiasis.

Cryptosporidiosis

Epidemiology

Cryptosporidiosis has been recognized as a human disease since the 1970s, with increasing importance in the 1980s and 1990s because of its relationship with HIV/AIDS. *Cryptosporidium* accounts for 2.2% and 6.1% of diarrhea cases in immunocompetent people in developed and developing countries, respectively.[3] These percentages increase to 7% and 12% in children in developed and developing countries, respectively, and to 14% and 24% in immunocompromised persons in developed and developing countries, respectively.[3]

Infection is spread person to person, usually via the fecal-oral route; by animals, particularly cattle and sheep; and through the environment, especially water. People at increased risk of contracting cryptosporidiosis include household and family contacts and sexual partners of someone with the disease, health care workers, day-are workers, users of public swimming areas, and people traveling to regions of high endemicity.[3]

Pathogenesis

Cryptosporidium is an intracellular protozoan parasite that is capable of completing its entire life cycle within one host. Humans become infected on ingestion of the oocysts, and autoinfection and persistent infections are possible owing to repeated life cycles within the GI tract.[3] As few as 10 to 100 oocysts can cause infection.[3]

Treatment and Monitoring

There is no antimicrobial available that is effective at consistently eradicating *Cryptosporidium*, particularly in immunocompromised hosts. In general, immunocompetent persons



Clinical Presentation and Diagnosis[3,4]

General

- 7- to 10-day incubation period
- Profuse, watery diarrhea with mucus but not blood or leukocytes that lasts for approximately 2 weeks
- Nausea, vomiting, and abdominal cramps often accompany the diarrhea.
- Fever may be present.
- Simplest method of diagnosis is detection of oocysts by modified acid-fast staining of a stool specimen. Standard ova and parasite test does not include *Cryptosporidium*.

Immunocompetent

- May manifest as asymptomatic disease, acute diarrhea, or persistent diarrhea lasting for several weeks
- Usually self-limiting

Immunocompromised

- May manifest as asymptomatic disease; transient infection for less than 2 months; chronic diarrhea lasting at least 2 months, or fulminant infection, with at least 2 L of watery stool per day
- Asymptomatic disease more common in those with a CD4+ cell count greater than 200 cells/mm^3, and fulminant infection more common in those with a CD4+ cell count of less than 50 cells/mm^3

and those with asymptomatic infection do not require antimicrobial therapy. In patients with HIV/AIDS, the optimal therapy is restoration of immune function through the use of antiretroviral therapy (ART). In persons in whom antimicrobial therapy is deemed necessary or in HIV/AIDS patients in whom ART is ineffective, a combination of an antimicrobial and an antidiarrheal agent is recommended.[3]

Azithromycin and clarithromycin have shown some success for cryptosporidiosis, even in HIV-positive patients.[4] However, the most promising agent is nitazoxanide, which was approved recently by the FDA for the treatment of cryptosporidiosis in children. In randomized, placebo-controlled trials, nitazoxanide has demonstrated efficacy in cryptosporidiosis in immunocompetent persons, malnourished children, and HIV/AIDS patients with CD4+ cell counts above 50 cells/mm^3.[39] Limited evidence suggests that patients with CD4+ cell counts of less than 50 cells/mm^3 may benefit from higher doses, longer durations, or both.[39]

Prevention of cryptosporidiosis can prove difficult because the oocysts are resilient to many disinfectants and antiseptics, including ammonia, alcohol, and chlorine.[3] Therefore, most traditional water-treatment methods, including filtration, do not eradicate all oocysts, which is problematic in the face of the small infective dose of *Cryptosporidium*. Routine screening of drinking water should be considered for water-treatment plants, and severely immunocompromised individuals should be advised to avoid water in lakes and streams and contact with young animals.[3] For these persons, drinking water should be brought to a boil and cooled before ingestion.

VIRAL GASTROENTERITIS

❻ *Viruses are the most common cause of diarrheal illness in the world, resulting in about 450,000 and 160,000 hospitalizations for adults and children, respectively, and over 4000 deaths.*[40,41] A number of viruses may cause gastroenteritis, including rotaviruses, noroviruses, astroviruses, enteric adenoviruses, and coronoviruses (Table 73–4). This chapter will focus on rotaviruses.



Clinical Presentation and Diagnosis[1]

- Incubation period of 2 days
- 2- to 3-day **prodrome** of fever and vomiting
- Profuse diarrhea without blood or leukocytes (up to 10–20 stools per day)
- Severe dehydration
- Anorexia
- Fever may be present.
- Presentation in adults may vary from asymptomatic to nonspecific symptoms of headache, malaise, and chills to severe diarrhea, nausea, and vomiting.
- Diagnosis can be made by PCR of the stool.

Rotavirus

Epidemiology

Rotavirus causes between 600,000 and 875,000 deaths each year, with the highest rates in the very young and in developing countries.[1] Rotavirus is the leading cause of childhood **gastroenteritis** and death worldwide. Most infections occur in children between 6 months and 2 years old, typically during the winter season, but adults may be infected as well. Rotavirus causes over 2 million hospitalizations and 600,000 deaths per year in children younger than 5 years of age.[42] Person-to-person transmission occurs through the fecal-oral route.

Pathogenesis

The mechanism of diarrhea has not been clearly elucidated, but theories include a reduction in the absorptive surface along with impaired absorption owing to cellular damage, enterotoxigenic effects of a rotavirus protein, and stimulation of the enteric nervous system.[43]

Treatment and Monitoring

The cornerstone of rotavirus treatment is supportive care and rehydration with ORT or intravenous fluids if necessary. Antimotility and antisecretory agents should not be used

TABLE 73–4. Agents Responsible for Acute Viral Gastroenteritis and Diarrhea

Virus	Peak Age	Peak Time	Duration	Transmission	Symptoms
Rotavirus	6 mo–2 yr	Winter	3–8 days	Fecal-oral, water, food	Diarrhea, vomiting, fever, abdominal pain
Enteric adenovirus	less than 2 yr	Year-round	7–9 days	Fecal-oral	Diarrhea, respiratory symptoms, vomiting, fever
Astrovirus	less than 7 yr	Winter	1–4 days	Fecal-oral, water, shellfish	Vomiting, diarrhea, fever, abdominal pain
Noroviruses	greater than 5 yr	Variable	12–24 hours	fecal-oral, food, aerosol	Nausea, vomiting, diarrhea, abdominal cramps, headache, fever, chills, myalgia

Modified from Martin S, Jung R. Gastrointestinal infections and enterotoxigenic poisonings. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach.* 6th ed. New York: McGraw-Hill; 2005:2049.



Patient Care and Monitoring

1. Observe the patient for signs and symptoms of dehydration, and rehydrate as necessary (see Tables 73–1 and 73–2).
2. Monitor for increase in stool consistency and decrease in stool frequency.
3. If pharmacologic agents are used, monitor for any adverse effects.
4. Evaluate the patient for any complications or effects specific to the afflicting pathogen.

owing to their potential side effects in children and the self-limited nature of the disease. ❻ *A new live oral rotavirus vaccine was approved recently by the FDA for use in infants aged 6 weeks to 32 weeks and provides protection against rotavirus infection for at least 24 months.*[44] The CDC Advisory Committee on Immunization Practices recommends vaccination at 2, 4, and 6 months.

FOOD POISONING

Each year in the United States, approximately 76 million foodborne illnesses occur, leading to 325,000 hospitalizations and over 5000 deaths.[40] A number of bacterial and viral pathogens that have been discussed previously in this chapter (e.g., *Salmonella*, *Shigella*, *Campylobacter*, *E. coli*, and noroviruses) can cause food poisoning. Other bacteria that can cause foodborne illness include *Staphylococcus aureus*, *C. perfringens*, *C. botulinum*, and *Bacillus cereus* (Table 73–5). Food poisoning should be suspected if at least two individuals present with similar symptoms after the ingestion of a common food in the prior 72 hours.



Patient Encounter 1

A 70-year-old man presents to the emergency department because of diffuse abdominal pain and nonbloody diarrhea. One day earlier he had been discharged from the hospital, where he had received ceftriaxone and levofloxacin for 7 days for an upper respiratory infection. Soon after going home, he passed numerous liquid brown stools. A few hours later, the patient became disoriented, and an ambulance was called. His medical history is unremarkable. Laboratory values: White blood cell count 50,000 cells/mm^3, hematocrit 43%, sodium 125 mmol/L, potassium 5.6 mmol/L, CO_2 14 mmol/L, and metabolic acidosis. An abdominal radiograph series show no evidence of obstruction. The patient was admitted to the hospital.

What GI disease do you suspect based on this information? From your suspicion, what diagnostic tests and treatment would you recommend for this patient?

In the hospital, he receives fluids and metronidazole 500 mg every 8 hours intravenously. Stool was sent for *C. difficile* toxin assay, which came back positive. The patient continues to have abdominal pain but no bowel movement. On day 3 of hospitalization, his abdomen is distended with diffuse pain. His white blood cell count remains elevated. A CT scan of the abdomen showed colonic dilatation to greater than 6 cm. The patient became febrile and hypotensive, requiring multiple pharmacologic support for hypotension.

- What are this patient's risk factors for CDAD?
- What do these new findings suggest?
- How does this progression change your treatment recommendations?

TABLE 73–5. Food Poisonings

Organism	Onset (hour)	Associated Foods	Duration	Symptoms	Treatment
Staphylococcus aureus	1–6	Salad, pastries, ham, poultry	12 hour	Nausea, vomiting	Supportive
Bacillus cereus—emetic	0.5–6	Rice, noodles, pasta, pastries	24 hour	Vomiting	Supportive
Bacillus cereus—diarrheal	8–16	Meats, vegetables, soups, sauces, milk products	24 hour	Diarrhea, abdominal pain	Supportive
Clostridium perfringens (type A)	8–12	Meats, poultry	24 hour	Nausea, abdominal cramps, profuse, watery diarrhea	Supportive
Clostridium botulinum	18–24	Canned fruits, vegetables, meats, honey, salsa, relish	Weeks	Acute GI symptoms followed by symmetric, descending, flaccid paralysis; death is possible	Supportive (including mechanical ventilation); trivalent antitoxin



Patient Encounter 2

A 45-year-old Hispanic man with AIDS presents to the emergency department with fever, nausea, two episodes of vomiting, abdominal pain, and nonbloody diarrhea for 2 days. He reports that his diarrhea is improving, but he developed fever and chills a few hours before he came to the emergency room. Other history is noncontributory. His physical examination is positive for fever and diffuse abdominal pain. An abdominal ultrasound did not show any abnormal findings. Two sets of blood cultures were sent. He was admitted to the hospital.

1. What GI pathogen(s) do you suspect in this patient?
2. His blood cultures came back positive for nontyphoidal *Salmonella*.
3. What treatment do you recommend? Do any further tests need to be performed before you can decide on your treatment recommendation? Are there any special considerations owing to this patient's HIV infection?

OUTCOME EVALUATION

Patients with GI infections should be evaluated for resolution of GI symptoms, as well as any related systemic signs and symptoms. If antimicrobial therapy was used, completion of the course of therapy should be assessed. Documented clearance of the offending microorganism is not necessary.

ABBREVIATIONS

AAD: antibiotic-associated diarrhea
A/E: attaching-effacing
AMP: adenosine monophosphate
ART: antiretroviral therapy
CDC: Centers for Disease Control and Prevention
CDAD: *Clostridium difficile*–associated diarrhea
CFU: colony-forming units
EHEC: enterohemorrhagic *Escherichia coli*
ELISA: enzyme-linked immunosorbent assay
FDA: Food and Drug Administration
GI: gastrointestinal
GBS: Guillain-Barré syndrome
HIV/AIDS: human immunodeficiency virus/acquired immune deficiency syndrome
HUS: hemolytic-uremic syndrome
ORT: oral rehydration therapy
PCR: polymerase chain reaction
STEC: Shiga toxin–producing *E. coli*
Stx: Shiga toxin
VRE: vancomycin-resistant enterococcus
WHO: World Health Organization

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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74 Intraabdominal Infections

Joseph T. DiPiro and Thomas R. Howdieshell



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Define and differentiate between primary and secondary intraabdominal infections.
2. Describe the microbiology typically seen with primary and secondary intraabdominal infections.
3. Describe the clinical presentation typically seen with primary and secondary intraabdominal infections.
4. Describe the role of culture and susceptibility information for diagnosis and treatment of intraabdominal infections.
5. Recommend the most appropriate drug and nondrug measures to treat intraabdominal infections.
6. Recommend an appropriate antimicrobial regimen for treatment of a primary and a secondary intrabdominal infection.
7. Describe the patient-assessment process during the treatment of intraabdominal infections.

Key Concepts

❶ Most intraabdominal infections are "secondary" infections that are caused by a defect in the gastrointestinal tract that must be treated by surgical drainage, resection, and/or repair.

❷ Primary peritonitis generally is caused by a single organism (*Staphylococcus aureus* in patients undergoing continuous ambulatory peritoneal dialysis (CAPD) and *Escherichia coli* in patients with cirrhosis).

❸ Secondary intraabdominal infections usually are caused by a mixture of enteric gram-negative bacilli and anaerobes. This mix of organisms enhances the pathogenic potential of the bacteria.

❹ For peritonitis, early and aggressive intravenous fluid resuscitation and electrolyte replacement therapy are essential. A common cause of early death is hypovolemic shock caused by inadequate intravascular volume expansion and tissue perfusion.

❺ Cultures of secondary intraabdominal infection sites generally are not useful for directing antimicrobial therapy. Treatment generally is initiated on a "presumptive" or empirical basis.

❻ Antimicrobial regimens for secondary intraabdominal infections should include coverage for enteric gram-negative bacilli and anaerobes. Antimicrobial agents that may be used for treatment of secondary intraabdominal infections include (1) a β-lactam–β-lactamase-inhibitor combination, (2) a carbapenem, and (3) a quinolone plus metronidazole or an aminoglycoside plus clindamycin (or metronidazole).

❼ The duration of antimicrobial treatment should be for a total of 5 to 7 days for most intraabdominal infections.

Intraabdominal infections are those contained within the peritoneal cavity or retroperitoneal space. The peritoneal cavity extends from the undersurface of the diaphragm to the floor of the pelvis and contains the stomach, small bowel, large bowel, liver, gallbladder, and spleen. The duodenum, pancreas, kidneys, adrenal glands, great vessels (aorta and vena cava), and most mesenteric vascular structures reside in the retroperitoneum. Intraabdominal infections may be generalized or localized. They may be contained within visceral structures, such as the liver, gallbladder, spleen, pancreas, kidney, or female reproductive organs. Two general types of intraabdominal infection are discussed throughout this chapter: peritonitis and abscess.

Peritonitis is defined as the acute inflammatory response of the peritoneal lining to microorganisms, chemicals, irradiation, or foreign-body injury. This chapter deals only with peritonitis of infectious origin.

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Patient Encounter

A 67-year-old man presents to the emergency room in acute distress with abdominal pain, nausea, and vomiting. The patient was in a reasonably good state of health until yesterday evening when he had a sudden onset of excruciating abdominal pain. During the night, he had a few episodes of vomiting, and the pain did not diminish.

The patient is taking glyburide for non-insulin-dependent diabetes mellitus and has been treated in the past for peptic ulcer disease with ranitidine and omeprazole. He has a history of allergy to various types of pollen but reports no allergies to drugs. He reports moderate consumption of alcohol and smoking 2 packs of cigarettes per day.

- What other information would you like to have about this patient?

An **abscess** is a purulent collection of fluid separated from surrounding tissue by a wall consisting of inflammatory cells and adjacent organs. It usually contains necrotic debris, bacteria, and inflammatory cells. Peritonitis and abscess differ considerably in presentation and approach to treatment.

EPIDEMIOLOGY AND ETIOLOGY

Peritonitis may be classified as primary, secondary, or tertiary. Primary peritonitis, also called *spontaneous bacterial peritonitis,* is an infection of the peritoneal cavity without an evident source of bacteria from the abdomen.[1,2] In secondary peritonitis, a focal disease process is evident within the abdomen. Secondary peritonitis may involve perforation of the gastrointestinal (GI) tract (possibly because of ulceration, ischemia, or obstruction), postoperative peritonitis, or posttraumatic peritonitis (e.g., blunt or penetrating trauma). Tertiary peritonitis occurs in critically ill patients and is infection that persists or recurs at least 48 hours after apparently adequate management of primary or secondary peritonitis.

❶ *Primary peritonitis develops in up to 25% of patients with alcoholic cirrhosis.*[3] *Patients undergoing continuous ambulatory peritoneal dialysis (CAPD) average one episode of peritonitis every 2 years.*[4] *Secondary peritonitis may be caused by perforation of a peptic ulcer; traumatic perforation of the stomach, small or large bowel, uterus, or urinary bladder; appendicitis; pancreatitis; diverticulitis; bowel infarction; inflammatory bowel disease; cholecystitis; operative contamination of the peritoneum; or diseases of the female genital tract such as septic abortion, postoperative uterine infection, endometritis, or salpingitis. Appendicitis is one of the most common causes of intraabdominal infection. In 1998, 278,000 appendectomies were performed in the United States for suspected appendicitis.*[5]

Primary peritonitis in adults occurs most commonly in association with alcoholic cirrhosis, especially in its end stage, or with ascites caused by postnecrotic cirrhosis, chronic active hepatitis, acute viral hepatitis, congestive heart failure, malignancy, systemic lupus erythematosus, and nephrotic syndrome. It also may result from the use of a peritoneal catheter for dialysis with renal failure or central nervous system (CNS) ventriculoperitoneal shunting for hydrocephalus. Abscesses are the result of chronic inflammation and may occur without preceding generalized peritonitis. They may be located within the peritoneal cavity or in a visceral organ and may vary in size, taking a few weeks to years to form.

The causes of intraabdominal abscess overlap those of peritonitis and, in fact, may occur sequentially or simultaneously. Appendicitis is the most frequent cause of abscess.

PATHOPHYSIOLOGY

Intraabdominal infection results from bacterial entry into the peritoneal or retroperitoneal spaces or from bacterial collections within intraabdominal organs. In primary peritonitis, bacteria may enter the abdomen via the bloodstream or the lymphatic system by transmigration through the bowel wall, through an indwelling peritoneal dialysis catheter, or via the fallopian tubes in females. Hematogenous bacterial spread (through the bloodstream) occurs more frequently with tuberculosis peritonitis or peritonitis associated with cirrhotic ascites. When peritonitis results from peritoneal dialysis, skin-surface flora are introduced via the peritoneal catheter.[7] In secondary peritonitis, bacteria most often enter the peritoneum or retroperitoneum as a result of perforation of the GI or female genital tracts caused by diseases or traumatic injuries.

If bacteria that enter the abdomen are not handled by cellular and humoral defense mechanisms, bacterial dissemination occurs throughout the peritoneal cavity, resulting in peritonitis. This is more likely to occur in the presence of a foreign body, hematoma, necrotic tissue, large bacterial inoculum, continuing bacterial contamination, and contamination involving a mixture of synergistic organisms.

The fluid and protein shift into the abdomen (called *third-spacing*) may be so dramatic that circulating blood volume is decreased, which causes decreased cardiac output and hypovolemic shock. Accompanying fever, vomiting, or diarrhea may worsen the fluid imbalance. A reflex sympathetic response, manifested by sweating, tachycardia, and vasoconstriction, may be evident. With an inflamed peritoneum, bacteria and endotoxins are absorbed easily into the bloodstream (translocation), and this may result in septic shock. Other foreign substances present in the peritoneal cavity potentiate peritonitis, notably feces, dead tissues, barium, mucus, bile, and blood.

Many of the manifestations of intraabdominal infections, particularly peritonitis, result from cytokine activity. Inflammatory cytokines are produced by macrophages and neutrophils in

response to bacteria and bacterial products or to tissue injury resulting from the surgical incision.[8] These cytokines produce wide-ranging effects on the endothelium of organs, particularly the liver, lungs, kidneys, and heart. With uncontrolled activation of these mediators, sepsis may result.[9] Peritonitis may result in death because of the effects on major organ systems.

An abscess occurs if peritoneal contamination is localized but bacterial elimination is incomplete. The location of the abscess often is related to the site of primary disease. For example, abscesses resulting from appendicitis tend to appear in the right lower quadrant or the pelvis; those resulting from diverticulitis tend to appear in the left lower quadrant or pelvis. A mature abscess may have a fibrinous capsule that isolates bacteria and the liquid core from antimicrobials and immunologic defenses.

Microbiology of Intraabdominal Infection

❷ *Primary bacterial peritonitis is often caused by a single organism. In children, the pathogen is usually Streptococcus pneumoniae or a group A Streptococcus.*[4] *When peritonitis occurs in association with cirrhotic ascites, Escherichia coli is isolated most frequently. Other potential pathogens are Hemophilus pneumoniae, Klebsiella, Pseudomonas, anaerobes, and S. pneumoniae.*[10] *Occasionally, primary peritonitis may be caused by Mycobacterium tuberculosis. Peritonitis in patients undergoing peritoneal dialysis is caused most often by common skin organisms such as S. epidermidis, Staphylococcus aureus, streptococci, and diphtheroids.* Occasionally, aerobic gram-negative bacilli may cause infections, particularly in patients undergoing dialysis during hospitalization. Death from primary peritonitis caused by gram-negative bacteria occurs much more frequently than from gram-positive bacteria.[11]

❸ *Because of the diverse bacteria present in the GI tract, secondary intraabdominal infections are often polymicrobial.*[12] *The mean number of different bacterial species isolated from infected intraabdominal sites ranged from 2.9 to 3.7, including an average of 1.3 to 1.6 aerobes and 1.7 to 2.1 anaerobes.*[13,14]

Bacterial Synergism

A combination of aerobic and anaerobic organisms appears to increase the severity of infection. ❸ *Facultative bacteria (such as E. coli) may provide an environment conducive to the growth of anaerobic bacteria.*[12] *Although many bacteria isolated in mixed infections are nonpathogenic by themselves, their presence may be essential for the pathogenicity of the bacterial mixture.*[3] Facultative bacteria in mixed infections can:

- Promote an appropriate environment for anaerobic growth through oxygen consumption
- Produce nutrients necessary for anaerobes
- Produce extracellular enzymes that promote tissue invasion by anaerobes

Bacteria such as *E. coli* appear responsible for the early mortality from peritonitis, whereas anaerobic bacteria are major pathogens in abscesses, with *B. fragilis* predominating.[15] *Enterococcus* can be isolated from many intraabdominal infections in humans, but its role as a pathogen is not clear.[16]

CLINICAL PRESENTATION AND DIAGNOSIS

Intraabdominal infections have a wide spectrum of clinical features. Peritonitis usually is easily recognized, but intraabdominal abscess often may continue for long periods of time. Patients with primary and secondary peritonitis present quite differently.

TREATMENT

Desired Outcomes

The primary goals of treatment are correction of the intraabdominal disease processes or injuries that have caused infection and drainage of collections of purulent material (abscess). A secondary objective is to resolve the infection without major organ system complications (e.g., pulmonary, hepatic, cardiovascular, or renal failure) or adverse drug effects. Ideally, the patient should be discharged from the hospital with full function for self-care and routine daily activities.



Clinical Presentation of Primary Peritonitis

General
Patients may not be in acute distress, particularly with peritoneal dialysis.

Symptoms
Patient may complain of nausea, vomiting (sometimes with diarrhea), and abdominal tenderness.

Signs
- Temperature may be only mildly elevated or not elevated in patients undergoing peritoneal dialysis.
- Bowel sounds are hypoactive
- Cirrhotic patients may have worsening encephalopathy.
- There may be cloudy dialysate fluid with peritoneal dialysis.

Laboratory Tests
- The white blood cell (WBC) count may be only mildly elevated.
- Ascitic fluid usually contains greater than 300 leukocytes/mm^3, and bacteria may be evident on Gram stain of a centrifuged specimen.

Other Diagnostic Tests
Culture of peritoneal dialysate or ascitic fluid should be positive.



Clinical Presentation of Secondary Peritonitis

General
Patients may be in acute distress.

Symptoms
- Patients may complain of nausea, vomiting, and generalized abdominal pain.
- Patients may demonstrate abdominal guarding and a "boardlike abdomen."

Signs
- Tachypnea and tachycardia are present.
- Temperature is normal initially, then may increase to 100 to 102°F (37.7–38.8°C) within the first few hours, and may continue to rise for the next several hours.
- Hypotension and shock may develop if intravascular volume is not restored.
- Decreased urine output may develop owing to dehydration.
- Bowel sounds are faint initially and eventually cease.

Laboratory Tests
- The WBC count is high (15,000–20,000 WBCs/mm^3), with neutrophils predominating and an elevated percentage of immature neutrophils (bands).
- The hematocrit and blood urea nitrogen increase because of dehydration.
- Hyperventilation and vomiting result in early alkalosis, which changes to acidosis and lactic acidemia.

Other Diagnostic Tests
Abdominal radiographs may be useful because free air in the abdomen (indicating intestinal perforation) or distension of the small or large bowel is often evident.



Patient Encounter, Part 2: Physical Examination and Diagnostic Tests

PE
The patient is found responsive but in acute distress. He is lying on the examination table with knees drawn up to his chest. There is involuntary abdominal guarding with a rigid abdomen. There are no audible bowel sounds. He is alert and oriented × 3. Neurologic function is intact. Mucous membranes are dry. Stool is heme-negative.

VS: Temp 38.3°C, BP 105/70 mm Hg, P 132, wt 82 kg, (180 lbs) Ht 170 cm, RR 24/minute.

Labs
Hct 46% (0.46 volume fraction), Hgb 15.4 g/dL, WBC count 15,200/mm^3 (45% neutrophils, 20% bands)

Serum: Glucose 213 mg/dL (11.8 mmol/L), serum creatinine 1.9 mg/dL (168 µmol/L), BUN 42 g/dL, Na 138 mEq/L (138 mmol/L), K 3.7 mEq/L (3.7 mmol/L), Cl 101 mEq/L (101 mmol/L), CO_2 21 mEq/L (21 mmol/L), calcium 9.8 mg/dL (2.45 mmol/L), magnesium 2.0 mEq/L (0.822 mmol/L), total bilirubin 0.4 mg/dL (6.84 µmol/L), albumin 4.2 g/dL (42 g/L), lactic acid 3.2 mEq/L

KUB: An upright abdominal x-ray shows dilated loops of small bowel and free air under the diaphragm.

DPL (Diagnostic Peritoneal Lavage: Examination of Fluid in Peritoneal Cavity): No blood is found, but WBCs are evident.

- What is your assessment of the patient's condition?
- Develop a care plan for this patient for the first 7 days of his hospitalization. This plan should include the goals of therapy, specific drug recommendations, and monitoring parameters to evaluate outcome.

General Approach to Treatment

The treatment of intraabdominal infection most often requires the coordinated use of three major modalities: (1) prompt drainage, (2) support of vital functions, and (3) appropriate antimicrobial therapy to treat infection not eradicated by surgery. Antimicrobials are an important adjunct to drainage procedures in the treatment of secondary intraabdominal infections; however, the use of antimicrobial agents without surgical intervention usually is inadequate. For most cases of primary peritonitis, drainage procedures may not be required, and antimicrobial agents become the mainstay of therapy.

In the early phase of serious intraabdominal infections, attention should be given to preserving major organ system function. ❹ *With generalized peritonitis, large volumes of intravenous (IV) fluids are required to maintain intravascular volume, to improve cardiovascular function, and to ensure adequate tissue perfusion and oxygenation. Adequate urine output should be maintained to ensure appropriate fluid resuscitation and to preserve renal function. A common cause of early death is hypovolemic shock caused by inadequate intravascular volume expansion and tissue perfusion.*

An additional important component of therapy is nutrition. Intraabdominal infections often involve the GI tract directly or disrupt its function (paralytic ileus). The return of GI motility may take days, weeks, and occasionally, months. In the interim, enteral or parenteral nutrition as indicated facilitates improved immune function and wound healing to ensure recovery.

Nonpharmacologic Therapy

Drainage Procedures
Primary peritonitis is treated with antimicrobials and rarely requires drainage. Secondary peritonitis requires surgical removal of the inflamed or gangrenous tissue to prevent further bacterial contamination. If the surgical procedure is suboptimal, attempts are made to provide drainage of the infected or gangrenous structures.

The drainage of purulent material is the critical component of management of an intraabdominal abscess. This may be performed surgically or with percutaneous image-guided techniques.[17,18] Without adequate drainage of the abscess, antimicrobial therapy and fluid resuscitation can be expected to fail. The most valuable microbiologic information may be obtained at the time of percutaneous or operative abscess drainage.

Fluid Therapy

In patients with peritonitis, hypovolemia is often accompanied by acidosis, so large volumes of a solution such as lactated Ringers may be required initially to restore intravascular volume. Maintenance fluids should be instituted (after intravascular volume is restored) with 0.9% sodium chloride and potassium chloride (20 mEq/L) or 5% dextrose and 0.45% sodium chloride with potassium chloride (20 mEq/L). The administration rate should be based on estimated daily fluid loss through urine and nasogastric suction, including 0.5 to 1.0 L for insensible fluid loss. Potassium would not be included routinely if the patient is hyperkalemic or has renal insufficiency. Aggressive fluid therapy often must be continued in the postoperative period because fluid will continue to sequester in the peritoneal cavity, bowel wall, and lumen.

Pharmacologic Therapy

Antimicrobial Therapy

The goals of antimicrobial therapy are

- To control bacteremia and prevent the establishment of metastatic foci of infection
- To reduce suppurative complications after bacterial contamination
- To prevent local spread of existing infection

After suppuration has occurred (e.g., an abscess has formed), a cure by antibiotic therapy alone is difficult to achieve; antimicrobials may serve to improve the results with surgery.

❺ *An empirical antimicrobial regimen should be started as soon as the presence of intraabdominal infection is suspected and before identification of the infecting organisms is complete. Therapy must be initiated based on the likely pathogens, which vary depending on the site of intraabdominal infection and the underlying disease process. Cultures of secondary intraabdominal infection sites generally are not useful for directing antimicrobial therapy.* Table 74–1 lists the likely pathogens against which antimicrobial agents should be directed.

Antimicrobial Experience

Many studies have been conducted evaluating or comparing the effectiveness of antimicrobials for treatment of intraabdominal infections. Substantial differences in patient outcomes from treatment with a variety of agents generally have not been demonstrated.

Important findings from the last 20 years of clinical trials regarding selection of antimicrobials for intraabdominal infections are

- Antimicrobial regimens for secondary intraabdominal infections should cover a broad spectrum of aerobic and anaerobic bacteria from the GI tract.
- Single-agent regimens (such as antianaerobic cephalosporins, extended-spectrum penicillins with β-lactamase inhibitors, or carbapenems) are as effective as combinations of aminoglycosides or fluoroquinolones with antianaerobic agents. This is also true for antimicrobial treatment of acute bacterial contamination from penetrating abdominal trauma.[19,20]
- Clindamycin and metronidazole appear to be equivalent in efficacy when combined with agents effective against aerobic gram-negative bacilli (e.g., gentamicin or aztreonam).
- For most patients, antimicrobial treatment can be completed orally with amoxicillin-clavulanate or the combination of ciprofloxacin and metronidazole.
- Five to seven days of antimicrobial treatment are sufficient for most intraabdominal infections of mild to moderate severity.

TABLE 74–1. Likely Intraabdominal Pathogens

Type of Infection	Aerobes	Anaerobes
Primary Bacterial Peritonitis		
Children (spontaneous)	Pneumococci, group A *Streptococcus*	—
Cirrhosis	*E. coli, Klebsiella,* pneumococci (many others)	—
Peritoneal dialysis	*Staphylococcus, Streptococcus*	—
Secondary Bacterial Peritonitis		
Gastroduodenal	*Streptococcus, E. coli*	—
Biliary tract	*E. coli, Klebsiella,* enterococci	*Clostridium* or *Bacteroides* (infrequent)
Small or large bowel	*E. coli, Klebsiella* spp., *Proteus* spp.	*Bacteroides fragilis* and other *Bacteroides*; *Clostridium.*
Appendicitis	*E. coli, Pseudomonas*	*Bacteroides* spp.
Abscesses	*E. coli, Klebsiella,* enterococci	*B. fragilis* and other *Bacteroides, Clostridium,* anaerobic cocci
Liver	*E. coli, Klebsiella,* enterococci staphylococci, amoeba	*Bacteroides* (infrequent)
Spleen	*Staphylococcus, Streptococcus*	

From DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005:Table 112–5.

Intraabdominal infection presents in many different ways and with a wide spectrum of severity. The antibiotic regimen employed and duration of treatment depend on the specific clinical circumstances (i.e., the nature of the underlying disease process and the condition of the patient).

Recommendations

❻ *For most intraabdominal infections, the antimicrobial regimen should be effective against both aerobic and anaerobic bacteria.*[21] Although it is impossible to provide antimicrobial activity against every possible pathogen, agents with activity against enteric gram-negative bacilli, such as *E. coli* and *Klebsiella,* and anaerobes, such as *B. fragilis* and *Clostridia* spp., should be administered.

Table 74–2 presents the recommended agents for treatment of community-acquired and complicated intraabdominal infections from the Infectious Diseases Society of America and the Surgical Infection Society.[21–23] *These recommendations were formulated using an evidence-based approach.* Most community-acquired infections are "mild to moderate," whereas health care–associated infections tend to be more severe and difficult to treat. Table 74–3 presents guidelines for treatment and alternative regimens for specific situations. These are general guidelines; there are many factors that cannot be incorporated into such a table.

When used for intraabdominal infection, aminoglycosides should be combined with agents that are effective against the majority of *B. fragilis.* Clindamycin or metronidazole is the agent of first choice, but others, such as antianaerobic cephalosporins (e.g., cefoxitin, cefotetan, or ceftizoxime), piperacillin, mezlocillin, and combinations of extended-spectrum penicillins with β-lactamase inhibitors, would be suitable alternatives. Patients receiving multiple broad-spectrum antimicrobial agents who are immunocompromised should receive an oral antifungal agent (nystatin) for prevention of fungal overgrowth in the mouth and GI tract. The benefits of systemic antifungal prophylaxis (with fluconazole) have not been established for intraabdominal infection and should not be used routinely.

TABLE 74–2. Recommended Agents for the Treatment of Community-Acquired Complicated Intraabdominal Infections

Agents Recommended for Mild to Moderate Infections	Agents Recommended for High-Severity Infections
β-Lactam/β-Lactamase Inhibitor Combinations	
Ampicillin-sulbactam Ticarcillin-clavulanate	Piperacillin-tazobactam
Carbapenems	
Ertapenem	Imipenem/cilistatin Meropenem
Combination Regimens	
Cefazolin or cefuroxime plus metronidazole	Third- or fourth-generation cephalosporins (cefotaxime, ceftriaxone, ceftizoxime, ceftazidime, cefepime) plus metronidazole
Ciprofloxacin, levofloxacin moxifloxacin, or gatifloxacin, in combination with metronidazole	Ciprofloxacin, in Combinaion with metronidazole
	Aztreonam plus metronidazole

From DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: Table 112–6.[21–23]

In immunocompromised patients or patients with valvular heart disease or a prosthetic heart valve, there is justification to provide specific antimicrobial activity against enterococci. Ampicillin or other penicillins that are active against enterococci (e.g., penicillin, piperacillin, and mezlocillin) should be used in patients at high risk, patients with persistent or recurrent intraabdominal infection, or patients who are immunosuppressed, such as after organ transplantation. Ampicillin remains the drug of choice for this indication because it is most active in vitro against enterococci and is relatively inexpensive. Vancomycin is active against most enterococci; however, resistance is increasing, and this agent should be reserved for established infections when first-line therapies cannot be used.

Intraperitoneal (IP) administration of antibiotics is preferred over IV therapy in the treatment of peritonitis that occurs in patients undergoing continuous ambulatory peritoneal dialysis (CAPD). The International Society of Peritoneal Dialysis (ISPD) recently revised its guidelines for the diagnosis and pharmacotherapy of peritoneal dialysis (PD)–associated infections.[24] The guidelines provide dosing recommendations for intermittent and continuous therapy based on the modality of dialysis [CAPD or automated peritoneal dialysis (APD)] and the extent of the patient's residual renal function.

Antimicrobial agents effective against both gram-positive and gram-negative organisms should be used for initial IP empirical therapy for peritonitis in PD patients. The most important factors to take into consideration for initial antimicrobial selection are the dialysis center's and the patient's history of infecting organisms and their sensitivities. The use of cefazolin [loading dose (LD) 500 mg/L, maintenance dose (MD) 125 mg/L] plus ceftazidime (LD 500 mg/L, MD 125 mg/L) or cefepime (LD 500 mg/L, MD 125 mg/L) or an aminoglycoside (gentamicin-tobramycin LD 8 mg/L, MD 4 mg/L) is suitable for initial empirical therapy; if patients are allergic to cephalosporin antibiotics, vancomycin (LD 1000 mg/L, MD 25 mg/L) or an aminoglycoside should be substituted. Another option is monotherapy with imipenem-cilastin (LD 500 mg/L, MD 200 mg/L) or cefepime. Antimicrobial doses should be increased empirically by 25% in patients with residual renal function (more than 100 mL/day urine output).[24] Antimicrobial therapy should be continued for at least 1 week after the dialysate fluid is clear and for a total of at least 14 days. The reader is referred to these guidelines for additional information.[27]

After acute bacterial contamination, such as with abdominal trauma where GI contents spill into the peritoneum, combination antimicrobial regimens are not required. If the patient is seen soon after injury (within 2 hours) and surgical measures are instituted promptly, antianaerobic cephalosporins

TABLE 74–3. Guidelines for Initial Antimicrobial Agents for Intraabdominal Infections

	Primary Agents	Alternatives
Primary Bacterial Peritonitis		
Cirrhosis	Cefotaxime	1. Add clindamycin or metronidazole if anaerobes are suspected 2. Other third-generation cephalosporins, extended-spectrum penicillins, aztreonam, and imipenem as alternatives 3. Aminoglycoside with antipseudomonal penicillin
Peritoneal dialysis	Regimen based on organism isolated 1. Staphylococcus: penicillinase-resistant penicillin or first-generation cephalosporin 2. *Streptococcus:* penicillin G 3. Aerobic gram-negative bacilli: cefotaxime, ceftazidime, or aminoglycoside plus an antipseudomonal penicillin 4. *Pseudomonas aeruginosa:* aminoglycoside plus antipseudomonal penicillin or ceftazidime	1. Alternative for resistant staphylococci is vancomycin 2. Alternative for Streptococcus is a first-generation cephalosporin 3. Alternatives for gram-negative bacilli are other third-generation cephalosporins, aztreonam, and extended-spectrum penicillins with *β-lactamase inhibitors*
Secondary Bacterial Peritonitis		
Perforated peptic ulcer	First-generation cephalosporins	1. Antianaerobic cephalosporins[a] 2. Possibly add aminoglycoside if patient condition is poor 3. Aminoglycoside with clindamycin or metronidazole; add ampicillin if patient is immunocompromised or if biliary tract origin of infection
Other	Imipenem/cilistatin, meropenem, ertapenem, or extended-spectrum penicillins with β-lactamase inhibitor	1. Ciprofloxacin with metronidazole 2. Aztreonam with clindamycin or metronidazole 3. Antianaerobic cephalosporins.[a]
Abscess		
General	Imipenem/cilastatin, meropenem, ertapenem, or extended-spectrum penicillins with β-lactamase inhibitor	1. Aztreonam with clindamycin or metronidazole 2. Ciprofloxacin with metronidazole 3. Aminoglycoside with clindamycin or metronidazole;
Liver	As above but add a first-generation cephalosporin	Use metronidazole if amoebic liver abscess is suspected
Spleen	Aminoglycoside plus penicillinase-resistant penicillin	Alternatives for penicillinase-resistant penicillin are first-generation cephalosporins or vancomycin
Appendicitis		
Normal or inflamed	Antianaerobic cephalosporins[a] (discontinued immediately postoperation)	1. Ampicillin-sulbactam
Gangrenous or perforated	Imipenem/cilastatin, meropenem, ertapenem, antianaerobic cephalosporins or extended-spectrum penicillins with β-lactamase inhibitor	1. Aztreonam with clindamycin or metronidazole 2. Ciprofloxacin with metronidazole 3. Aminoglycoside with clindamycin or metronidazole
Acute Cholecystitis	First-generation cephalosporin	Aminoglycoside plus ampicillin if severe infection
Cholangitis	Aminoglycoside with ampicillin with or without clindamycin or metronidazole	Use vancomycin instead of ampicillin if patient is allergic to penicillin
Acute Contamination from Abdominal Trauma	Antianaerobic cephalosporins[a] or ampicillin-sulbactam	1. A carbapenem 2. Ciprofloxacin plus metronidazole
Pelvic Inflammatory Disease	Cefotetan or cefoxitin with doxycycline	1. Clindamycin with gentamicin 2. Ampicillin-sulbactam with doxycycline 3. Ciprofloxacin with doxycycline and metronidazole

[a]Cefoxitin, cefotetan, and ceftizoxime.
From DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005:Table 112–7.

(such as cefoxitin or cefotetan) or extended-spectrum penicillins are effective in preventing most infectious complications. Antimicrobials should be administered as soon as possible after injury.

For appendicitis, the antimicrobial regimen used should depend on the appearance of the appendix at the time of operation, which may be normal, inflamed, gangrenous, or perforated. Because the condition of the appendix is unknown preoperatively, it is advisable to begin antimicrobial agents before the appendectomy is performed. Reasonable regimens would be antianaerobic cephalosporins or, if the patient is seriously ill, a carbapenem or β-lactam–β-lactamase-inhibitor combination.

If, at operation, the appendix were normal or inflamed, postoperative antimicrobials would not be required. If the appendix is gangrenous or perforated, a treatment course of 5 to 7 days with the agents listed in Table 74–2 is appropriate.

❼ *Acute intraabdominal contamination, such as after a traumatic injury, may be treated with a very short course (24 hours) of antimicrobials.*[25] *For established infections (i.e., peritonitis or intraabdominal abscess), an antimicrobial course limited to 5 to 7 days is justified.* Under certain conditions, therapy for longer than 7 days would be justified, e.g., if the patient remains febrile or is in poor general condition, when relatively resistant bacteria are isolated, or when a focus of infection in the abdomen still may be present. For some abscesses, such as pyogenic liver abscess, antimicrobials may be required for a month or longer.

OUTCOME EVALUATION

Whether diagnosed with primary or secondary peritonitis, monitor the patient for relief of symptoms. Once antimicrobials are initiated and the other important therapies described earlier are used, most patients should show improvement within 2 to 3 days. Successful antimicrobial therapy with resolution of infection will result in decreased pain, manifested as resolution of abdominal guarding and decreased use of pain medications over time. The patient should not appear in distress, with the exception of recognized discomfort and pain from incisions, drains, and a nasogastric tube.

Monitor vital signs and WBC count with differential; each should normalize as the infection resolves. At 24 to 48 hours, aerobic bacterial culture results should be available. If a suspected pathogen is not sensitive to the antimicrobial agents being given, the regimen should be changed if the patient has not shown sufficient improvement. If the isolated pathogen is extremely sensitive to one antimicrobial and the patient is progressing well, concurrent antimicrobial therapy often may be discontinued.

With anaerobic culturing techniques and the slow growth of these organisms, anaerobes often are not identified until 4 to 7 days after culture, and sensitivity information is difficult to obtain. For this reason, anaerobic culture information generally is not helpful for selection of the antianaerobic component of the antimicrobial regimen. A report indicating that anaerobes were not isolated should not be the sole justification for discontinuing antianaerobic drugs because anaerobic bacteria that were present in the infectious process may not have been transported properly to the microbiology laboratory, or other problems may have led to bacterial death in vitro.

Once the temperature is normal for 48 to 72 hours and the patient is eating, consider changing the IV antibiotic to an oral regimen for the duration of antibiotic treatment. Monitor the serum creatinine level to evaluate for renal complications as well as potential drug toxicity, especially if an aminoglycoside is a component of the antibiotic regimen. Bowel sounds should return to normal. Evaluate the patient daily for development of rash or other drug-related adverse effects.

For patients with primary peritonitis, if peritoneal dialysate cultures were positive initially, repeat cultures should be negative. For patients with secondary peritonitis, monitor the amount of fluid draining if a drain was placed. The volume of drainage should lessen as the infection resolves. Repeat abdominal radiographs should return to normal.

If symptoms do not improve, the patient should be evaluated for persistent infection. There are many reasons for poor patient outcome with intraabdominal infection; improper antimicrobial selection is only one. The patient may be immunocompromised, which decreases the likelihood of successful outcome with any regimen. It is impossible for antimicrobials to compensate for a nonfunctioning immune system. There may be surgical reasons for poor patient outcome. Failure to identify all intraabdominal foci of infection or leaks from a GI anastomosis may cause continued intraabdominal infection. Even when intraabdominal infection is controlled, accompanying organ system failure, most often renal or respiratory, may lead to patient demise.

The outcome from intraabdominal infection is not determined solely by what transpires in the abdomen. Unsatisfactory outcomes in patients with intraabdominal infections may result from complications that arise in other organ systems. A complication commonly associated with mortality after intraabdominal infection is pneumonia.[26] A high APACHE (Acute Physiology And Chronic Health Evaluation) II score, a low serum albumin, and a high New York Heart Association cardiac function status were significantly and independently associated with increased mortality from intraabdominal infection.[27]

Reasons for antimicrobial failure may not always be apparent. Even when antimicrobial susceptibility tests indicate that an organism is susceptible in vitro to the antimicrobial agent, therapeutic failures may occur. Possibly there is poor penetration of the antimicrobial agent into the focus of infection, or bacterial resistance may develop after initiation of antimicrobial therapy. Also, it is possible that an antimicrobial regimen may encourage the development of infection by organisms not susceptible to the regimen being used. Superinfection in patients being treated for intraabdominal infection can be caused by *Candida;* however, enterococci or opportunistic gram-negative bacilli such as *Pseudomonas* and *Serratia* may be involved.

Treatment regimens for intraabdominal infection can be judged as successful if the patient recovers from the infection without recurrent peritonitis or intraabdominal abscess and without the need for additional antimicrobials. A regimen can be considered unsuccessful if a significant adverse drug reaction occurs, reoperation or percutaneous drainage is necessary, or patient improvement is delayed beyond 1 or 2 weeks.



Patient Care and Monitoring

1. A thorough patient medication history should be taken at the time of admission to document all recent medication use, including nonprescription medications and use of complementary or alternative medicines. Any drug allergies or intolerances also should be documented.
2. The initial antimicrobial regimen should conform to standard guidelines unless an appropriate justification for an alternative regimen is evident. With the first few doses of antimicrobial, assess the patient for hypersensitivity reactions or other acute intolerances.
3. Review the dosages of all medications to be sure that they are appropriate for age, weight, and major organ function. Verifiy that the drugs selected are not contraindicated in the patient with allergies or other intolerances.
4. Confirm that all necessary acute and chronic medications are continued postoperatively.
5. Monitor vital signs (i.e., temperature and heart rate) and laboratory assessments (i.e., WBC count) daily to assess resolution of infection and efficacy of pain medications. When possible, interview the patient to obtain additional information about pain control.
6. Evaluate fluid status to ensure that the patient is not hypovolemic. In a seriously ill patient, assess intravascular volume by monitoring blood pressure and heart rate, but do so more accurately by measuring central venous pressure or urinary output via a urinary bladder catheter. Urine output should equal or exceed 0.5 mL/kg of body weight per hour.
7. Review results of cultures obtained preoperatively or during the surgical procedure. Evaluate the appropriateness of antibiotic therapy based on susceptibility information. Although some investigators suggest that routine culturing of patients with community-acquired intraabdominal infections contributes little to their management,[28] other investigators suggest that antimicrobial therapy should be based on susceptibility of the bacteria collected from the operative site because this has been shown to correlate with clinical outcome.[29]
8. Assess serum creatinine and aminoglycoside serum concentrations if the patient is being treated with an aminoglycoside. Adjust aminoglycoside dose based on serum concentrations; target peak concentration with multiple doses per day = 6 mcg/mL (12.54 µmol/L).
9. On the fifth day of antimicrobial treatment, determine if parenteral antimicrobial agents can be switched to oral agents to complete therapy.
10. Assess nutritional needs and recommend appropriate supplementation. When the patient is tolerating an oral diet, determine if any parenteral medications can be switched to the oral route.
11. Monitor the patient for the development of potential complications of treatment such as delayed hypersensitivity reactions, antibiotic-induced diarrhea, pseudomembraneous colitis, or fungal superinfections (manifested as oral thrush).
12. Provide information to the patient concerning the medications administered in the hospital as well as any new medications prescribed for use at home. Advise the patient to contact his or her doctor or pharmacist if he or she experience any adverse effects from medications.

ABBREVIATIONS

APACHE:	Acute Physiology And Chronic Health Evaluation
APD:	automated peritoneal dialysis
CAPD:	continuous ambulatory peritoneal dialysis
CT:	computed tomography
GI:	gastrointestinal
INF:	interferon
IL:	interleukin
IP:	intraperitoneal
LD:	loading dose
MD:	maintenance dose
PD:	peritoneal dialysis
TNF:	tumor necrosis factor
WBC:	white blood cell

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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75 Parasitic Diseases

J.V. Anandan



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Identify the primary reasons why some parasitic diseases may be more prevalent in the United States population.
2. Describe the treatment algorithm for giardiasis and amebiasis.
3. List one effective therapy for nematodes and select the drugs of choice for strongyloidiasis and tapeworms.
4. List three major reasons why travelers are infected with malaria.
5. Describe the presenting signs and symptoms of malaria.
6. List some specific toxicities of mefloquine.
7. Identify the monitoring parameters for quinidine gluconate in severe malaria.
8. Define the major complications of falciparum malaria.
9. Discuss the cardiovascular complications of chronic South American trypanosomiasis.
10. Describe the steps to take to eradicate lice infestation and scabies.

Key Concepts

❶ For treatment of giardiasis (or as empirical treatment), metronidazole 250 mg three times daily for 7 days or tinidazole 2 g as a single dose is recommended.

❷ Diagnostic tests for amebiasis include stool for ova, antigen detection, or polymerase chain reaction (PCR) testing.

❸ The drug of choice for nematode infestations (hookworm, enterobiasis, and ascariasis) is mebendazole, while ivermectin is indicated for strongyloidiasis and praziquantel is indicated for tapeworms.

❹ The primary reasons why travelers are infected with malaria are failure to take chemotherapy, inappropriate chemotherapy, and delay in seeking medical care.

❺ Falciparum malaria must be considered a life-threatening medical emergency.

❻ Treatment of serious malarial infection requires admission to an acute care service, intravenous administration of quinidine gluconate, and symptomatic support.

❼ Complications of falciparum malaria include hypoglycemia, acute renal failure, pulmonary edema, seizure, and coma.

❽ The chronic presentation of American trypanosomiasis includes cardiovascular, gastrointestinal, and central nervous system manifestations.

❾ Lice infestation should be treated with 1% permethrin followed by treatment of immediate family members and sexual partners. Bedding and clothes should be sterilized by washing in the hot cycle of the washing machine.

❿ The diagnosis of scabies is made by obtaining skin scrapings and detecting the mite in a wet mount. Topical therapy is 5% permethrin.

Parasitic medicine is an ever changing field. The increased desire of large segments of the United States population to travel to Asia, Africa, and other parts of the world can expose them to parasitic infections that are endemic in those areas. The influx of refugees and new immigrant populations from Asia and other parts of the world have brought new parasitic infections to our shores. Migrant farm workers who work and live in substandard hygienic conditions, the large and growing Central and South American immigrant population, and the presence of immunosuppressed populations (e.g.,

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those with the acquired immunodeficiency syndrome [AIDS] and transplant patients) represent other significant sources of parasitic infections in the United States. Clearly, there is a need for health professionals in the United States to be familiar with the pathophysiology and treatment of parasitic diseases.

Defined below are some terms that are frequently used when discussing parasitic diseases. *Symbiosis* is defined as "living together," when two species are dependent on each other for food and protection. The term *commensalism,* from the Latin translation of "eating at the same table," implies a mutual association in which both organisms may benefit, or at least one benefits but does no harm to the other. In contrast, *parasitism*, although resembling symbiosis in one aspect (i.e., it is also an intimate relationship between two species), does not represent a mutually beneficial association. One species (the host) does not benefit from the relationship, and in fact the relationship may be detrimental to its very survival. Parasites have made morphologic, biochemical, reproductive, and defensive adaptations over time. These adaptations have increased the ability of parasites to survive host defenses and have allowed them to utilize the host's biochemical systems to synthesize necessary cellular components. Beef and pork tapeworms (cestodes) possess highly developed reproductive systems which allow them to transfer easily to new hosts. Because of the lack of digestive systems cestodes are completely host-dependent for all nutrients. Cestodes (tapeworms) (*Taenia saginata* and *T. solium*) use specialized suckers which enable them to obtain blood and vital nutrients from their host. *Entamoeba histolytica*, the causative agent for amebiasis, once it has gained access to the human colon or large intestine is able to invade and utilize its specialized proteolytic enzyme to penetrate and erode the gastrointestinal mucosa. *E. histolytica* is also able to survive in adverse conditions when it leaves the host by walling itself off and forming **cysts**; this protects the parasite from environmental conditions until it is ready to infect the next host.

Although acquired immunity to some parasitic diseases may lower the level of infection, absolute immunity as seen in bacterial and viral infections is seldom seen in parasitic diseases. Since parasitic infections produce a wide variety of antigens because of the many life cycle phases, it is more difficult to identify a constant antigenic protein against which specific antibodies are protective. However, malaria remains a likely candidate for a vaccine and there are ongoing studies to develop one.

Space constraints do not allow detailed discussions of the world of parasites, and clinicians and students are directed to some excellent resources for further details on parasites and parasitic diseases.[1,2] Discussion in this chapter will include those parasitic diseases that are more likely to be seen in the United States and will include gastrointestinal parasites (primarily giardiasis and amebiasis), protozoan infections (malaria and South American trypanosomiasis), some common helminthic diseases (specifically those caused by nematodes and cestodes), and ectoparasites (lice and scabies).

GIARDIASIS

Epidemiology and Etiology

Giardia lamblia (also known as *G. intestinalis* or *G. duodenalis*), an enteric protozoan, is the most common intestinal parasite responsible for diarrheal syndromes throughout the world. Giardia is the most frequently identified intestinal parasites in the United States, with a prevalence rate of 5% to 15% in some areas. *G. lamblia* has been identified as the first enteric pathogen seen in children in developing countries, with prevalence rates between 15% and 30%.

There are two stages in the life cycle of *G. lamblia*: the **trophozoite** and the cyst. *G. lamblia* is found in the small intestine, the gallbladder, and in biliary drainage. The distribution of giardiasis is worldwide with children being more susceptible than adults.

Pathology

Giardiasis is caused by ingestion of *G. lamblia* cysts in fecally contaminated water or food.[2] The protozoan excysts in the low gastric pH to release the trophozoite. Colonization and multiplication of the trophozoite lead to mucosal invasion, localized edema, and flattening of the villi, resulting in malabsorption states in the host. Achlorhydria, hypogammaglobulinemia, or deficiency in secretory immunoglobulin A (IgA) predispose to giardiasis. Individuals with human immunodeficiency virus (HIV) infection and AIDS may have higher carriage rates than the general population. Some patients may develop lactose intolerance after chronic giardiasis.



Patient Encounter

MK is a 15-year old high school student who had traveled to Mexico as part of a school group to practice his Spanish language skills. While in Mexico, he was careful in not drinking any local water and only consumed warm or heated food and soda. He is seen in the travel clinic with complaints of some "explosive" crampy diarrhea and has had constipation alternating with diarrhea for the last 2 weeks. MK indicates that his stools have been foul-smelling.

- Are his symptoms characteristic of giardiasis?
- How would you differentiate giardiasis from possible *Escherichia coli*–induced diarrhea?

Clinical Presentation and Diagnosis



Clinical Presentation of Giardiasis

Acute Onset
- Diarrhea, cramp-like abdominal pain, bloating, and flatulence
- Malaise, anorexia, nausea, and belching

Chronic Symptoms
- Diarrhea: Foul-smelling, copious, light-colored and fatty stools
- Weight loss, steatorrhea, and vitamin B_{12} and fat-soluble vitamin deficiencies

Diagnosis
- Diagnosis is made by examination of fresh stool or a preserved specimen during acute diarrheal phase
- Fresh stool may show trophozoites while preserved specimens yield cysts. (*Note*: stool for ova may show the presence of other parasites [e.g., *Cryptosporidium parvum*, *E. histolytica*, or *E. hartmanni*]; multiple stool samples may be needed.)
- Even though stool examination for ova and parasites has remained the major means of diagnosis, other diagnostic tests include enzyme-linked immunosorbent assay (ELISA), which is considered to be between 85% to 98% sensitive and almost 100% specific (ProSpec T, Giardia Microplate Assay, Remel, Lenexa, KS).

Pharmacologic Therapy

❶ *All symptomatic adults and children over the age of 8 years should be treated with metronidazole 250 mg three times daily for 7 days, or tinidazole 2 g as a single dose, or nitazoxanide 500 mg twice daily for 3 days.*[3] *The pediatric dose of metronidazole is 15 mg/kg per day three times daily for 7 days. Alternative drugs include furazolidone 100 mg four times daily or paromomycin 25 to 30 mg/kg per day in divided doses daily for 7 days. Paromomycin may be used in pregnancy instead of metronidazole. Pediatric patients can also be treated with suspensions of either furazolidone 8 mg/kg per day in four divided doses for 7 days, or nitazoxanide (Alina) 100 to 200 mg every 12 hours for 3 days.*

Quinacrine 100 mg three times in adults or 5 mg/kg per day in pediatric patients for 5 to 7 days, is available from a specialized pharmacy (e.g., Ponorama Compounding Pharmacy).[3]

Outcome Evaluation

Patients with symptomatic giardiasis and positive stool samples or positive ELISA tests should be treated with metronidazole for 7 days. Patients who fail initial therapy with metronidazole should receive a second course of therapy. Pregnant patients can receive paromomycin 25 to 30 mg/kg per day in divided doses for 7 days. Giardiasis can be prevented by good hygiene and by using caution in food and drink consumption.



Patient Care and Monitoring

- Metronidazole produces cure rates between 85% and 95%.
- Diarrhea will cease within a few days, although in some patients it may take 1 to 2 weeks.
- Cyst excretion will cease within days.
- Intestinal dysfunction (manifested as increased transit time) and radiologic changes primarily due to chronic infection may take months to resolve.
- Patients who fail therapy with metronidazole should receive a second course with either metronidazole or an alternative agent; nitazoxanide has been shown to be effective in resistant giardiasis.

AMEBIASIS

Epidemiology and Etiology

Amebiasis remains one of the most important parasitic diseases because of its worldwide distribution and serious gastrointestinal manifestations. The major causative agent in amebiasis is *Entamoeba histolytica*, which invades the colon and must be differentiated from *E. dispar*, which is associated with an asymptomatic carrier state and is considered nonpathogenic.[4] Invasive amebiasis is almost exclusively the result of ingesting *E. histolytica* cysts found in fecally-contaminated food or water. Approximately 50 million cases of invasive disease result each year worldwide, leading to an excess of 100,000 deaths. In the general population, the highest incidence is found in institutionalized mentally retarded patients, sexually active homosexuals, AIDS patients, the Native American population, and new immigrants from endemic areas (e.g., Mexico, South and Southeast Asia, West and South Africa, and portions of Central and South America).

Pathology

E. histolytica invades mucosal cells of colonic epithelium, producing the classic flask-shaped ulcer in the submucosa. The trophozoite toxin has a cytocidal effect on cells. If the trophozoite gets into the portal circulation, it will be carried to the liver, where it produces abscess and periportal fibrosis. Liver abscesses are more common in men than women and are rarely seen in children. Amebic ulcerations can affect the perineum and genitalia, and abscesses may occur in the lung and brain.

Erosion of liver abscesses can result in peritonitis. Liver abscesses that are located in the right lobe can spread to the lungs and pleura. Pericardial infection, although rare, may be associated with extension of the amebic abscesses from the liver.

Clinical Presentation and Diagnosis



Clinical Presentation of Amebiasis

Review of the patient's history should include: recent travel, type of foods ingested (e.g., salads or unpeeled fruit), the nature of water and fluid consumed, and description of any symptoms of friends or relatives who ate the same food.

Intestinal Disease

- Vague abdominal discomfort
- Symptoms may range from malaise to severe abdominal cramps, flatulence, and nonbloody or bloody diarrhea (heme-positive in 100% of cases) with mucus
- May have low-grade fever, but this may be absent in many patients
- Eosinophilia is usually absent, although mild leukocytosis is not unusual

Note: Fecal screening may show other intestinal parasites, including *Cryptosporidium* spp., *Balantidium coli*, *Dientamoeba fragilis*, *Isospora belli*, *G. lamblia*, or *Blastocystis hominis*.

Amebic Liver Abscess

- May present with high fever with significant leukocytosis with left shift, anemia, elevated alanine aminotransferase, and dull abdominal pain on palpation
- Physical findings: Right upper quadrant pain, hepatomegaly, and liver tenderness, with referred pain to the left or right shoulder (*Note:* Erosion of liver abscesses may present as peritonitis)

❷ Diagnosis

- *Intestinal amebiasis is diagnosed by demonstrating* E. histolytica *cysts or trophozoites (may contain ingested erythrocytes) in fresh stool or from a specimen obtained by sigmoidoscopy.*
- *Microscopy may not differentiate between the pathogenic E. histolytica and the nonpathogenic E. dispar or E. moshkovskii in stools.*
- *Sensitive techniques are available to detect E. histolytica in stool: antigen detection, antibody test (ELISA) and PCR.*
- **Endoscopy** with scrapings or biopsy and stained slides (**iron hematoxylin** or trichrome) may provide more definitive diagnosis of amebiasis.
- Diagnosis for liver abscess includes serology and liver scans (using isotopes by **ultrasound** or **computed tomography**) or **magnetic resonance imaging**; however, none of these are specific for liver abscess. In rare instances, needle aspiration of hepatic abscess may be attempted using ultrasound guidance.

Patient Encounter

WR is a 37-year-old native of India and a permanent resident in the United States who has recently returned from a trip to Calcutta, India where he was visiting a relative. He presents in the emergency department with complaints of a 3-week history of sharp, crampy, and postprandial abdominal pain. The pain is more intense over the right lower quadrant, and associated with watery nonbloody diarrhea and **tenesmus**.

- What specific findings in this patient suggest that he may have giardiasis or amebiasis?
- What other information do you need to confirm a diagnosis of amebiasis?
- What is the major complication of amebiasis?

Pharmacologic Therapy

Metronidazole (Flagyl), dehydroemetine, and chloroquine (Aralen) are tissue-acting agents, and iodoquinol (Yodoxin), diloxanide furoate (Furamide), and paromomycin (Humatin) are luminal amebicides. A systemic or tissue-acting agent may be so well absorbed that the amounts of the drug remaining in the bowel may be insufficient to have luminal or local effects. A luminally-active agent, on the other hand, may not attain effective enough levels in the tissue to be efficacious. Asymptomatic cyst passers (identified by stool examinations, and who may develop invasive disease) and patients with mild intestinal amebiasis should receive a luminal agent: paromomycin 25 to 30 mg/kg per day three times daily for 7 days, or iodoquinol 650 mg three times daily for 20 days, or diloxanide furoate 500 mg three times daily for 10 days. These regimens have cure rates of between 84% and 96%. Diloxanide furoate is available from Ponorama Compounding Pharmacy (6744 Balboa Blvd., Lake Balboa, CA 91406; [800] 247-9767).[3]

The pediatric dose of paromomycin is the same as that used in adults, whereas the pediatric dose of iodoquinol is 30 to 40 mg/kg (maximum: 2 g) per day in three doses for 20 days, and the pediatric dose of diloxanide furoate is 20 mg/kg per day in three doses for 10 days. Paromomycin is the preferred agent in pregnant patients.[3]

Patients with severe intestinal disease or liver abscess should receive metronidazole 750 mg three times daily for 10 days, followed by the luminal agents indicated above. The pediatric dose of metronidazole is 50 mg/kg per day in divided doses, which should be followed by a luminal agent. An alternative regimen of metronidazole is 2.4 g/day for 2 days in combination with the luminal agent. Tinidazole (Tindamax, recently introduced on the United States market) administered in a dose of 2 g daily for 3 days (pediatric dose: 60 mg/kg for 5 days) is an alternative to metronidazole. If there is no prompt response to metronidazole or aspiration of the abscess, an antibiotic regimen should be added. Patients who cannot tolerate oral doses of metronidazole should receive an equivalent dose intravenously.



Patient Care and Monitoring

1. Follow-up in patients with amebiasis should include repeat stools (one to three), colonoscopy (in colitis) or computed tomography (CT, in liver abscess) between days 5 and 7, at the end of the course of therapy, and a month after the end of therapy.
2. Most patients with either intestinal amebiasis or colitis will respond in 3 to 5 days with amelioration of symptoms.
3. Those with liver abscess may take up to 7 days before there will be decreases in pain and fever. In liver abscess, patients not responding by the fifth day may require aspiration of the abscesses or exploratory laparotomy.
4. Serial liver scans have demonstrated that healing of liver abscesses take from 4 to 8 months following adequate therapy.

Preventive Measures

- Travelers and tourists visiting endemic areas should avoid local tap water, ice, salads, and unpeeled fruits. Boiled water is safe.
- Water can be disinfected by the use of iodine 2% (5 drops/L) or chlorine 6% (laundry bleach: 4 drops/L) or use of a commercial water purifier, such as Portable Aqua tablets (Wisconsin Pharmaceutical).

Outcome Evaluation

Follow-up in patients with amebiasis should include repeat stool examinations, serology, colonoscopy (in colitis) or CT on day 7, at the end of therapy, and a month after the end of therapy. Serial liver scans have demonstrated healing of liver abscesses over 4 to 8 months after adequate therapy.

HELMINTHIC DISEASES

Helminthic infections include three groups of organisms: roundworms or nematodes, flukes (trematodes), and tapeworms (cestodes). Because of space constraints, only brief descriptions of some of the helminthic infections most commonly seen in North America and their treatments will be provided here. Although helminthic infections may not produce clinical manifestations, they can cause significant pathology. One factor that determines the pathogenicity of helminthic infections is their population density; a high-density population ("worm burden") results in predictable disease presentation. In the United States, these infections are reported most frequently in recent immigrants from Southeast Asia, the Caribbean, Mexico, and Central America.[5,6] Populations at risk include institutionalized patients (both young and elderly), preschool children in day care centers, residents of Native American reservations, and homosexuals. Certain conditions and drugs (anesthesia and corticosteroids) can cause atypical localization of worms. Immunocompromised hosts can be overwhelmed by some helminthic infections, such as *Strongyloides stercoralis*.

Nematodes

Hookworm Disease

Hookworm infection is caused by *Ancylostoma duodenale* or *Necator americanus*. *N. americanus* is found in the southeastern United States. Infective larvae enter the host in contaminated food or water or penetrate the skin and migrate to the small intestine. The adult worm attaches to gastrointestinal mucosa and causes injury by lytic destruction of the tissue. Over a period of time, the adult worm can cause anemia and hypoproteinemia in the host.

Treatment

❸ *The drug of choice is mebendazole (Vermox), which is also active against ascariasis, enterobiasis, trichuriasis, and hookworm.*[3] The adult and pediatric (age greater than 2 years) oral dose of mebendazole for hookworm is 100 mg twice daily for 3 days. An alternative agent that can be used in both pediatric and adult patients is albendazole (Zentel), 400 mg as a single dose. Diagnosis is by detection of eggs or larvae in stool. Stool examination for eggs and the larvae should be repeated in 2 weeks and the patient retreated if necessary.

Ascariasis

The causative agent in ascariasis is the giant roundworm *Ascaris lumbricoides,* which is found worldwide and is responsible about 4 million infections in the United States (it primarily affects residents of the Appalachian mountain range and the Gulf Coast states). Migration of the worm into the lungs usually produces pneumonitis, fever, cough, eosinophilia, and pulmonary infiltrates. *Ascaris* infection can also cause abdominal discomfort, intestinal obstruction, and appendicitis. Diagnosis is made by detection of the characteristic eggs in the stool or passed worms.

Treatment

In both adults and pediatric patients older than 2 years of age, mebendazole 100 mg twice daily for 3 days is the treatment to use. An alternative agent is pyrantel pamoate (Antiminth). The stool should be checked within 2 weeks and the patient retreated when warranted.

Enterobiasis

Enterobiasis, or pinworm infection, is caused by *Enterobius vermicularis*. It is the most widely distributed helminthic infection in the world. There are approximately 42 million cases in the United States, primarily affecting children. The most common manifestation of the infection is cutaneous irritation

in the perianal region, resulting from the migrating female or the presence of eggs. The intense pruritus may lead to dermatitis and secondary bacterial infections. Diagnosis is made by the use of a perianal swab and cellophane tape sampling, which will aid in egg identification.

Treatment

The three agents that are administered for enterobiasis include pyrantel pamoate, mebendazole, and albendazole. The dose of pyrantel pamoate is 11 mg/kg (maximum: 1 g) as a single dose that can be repeated in 2 weeks. The dose of mebendazole for both adults and children older than 2 years of age is 100 mg as a single dose. This may be repeated in 2 weeks. Following treatment, to eradicate the eggs all bedding and underclothing should be sterilized by steaming or washing in the hot cycle of the washing machine.

Strongyloidiasis

Strongyloidiasis is caused by *Strongyloides stercoralis*, which has a worldwide distribution and is predominantly prevalent in South America (Brazil and Columbia) and in Southeast Asia. Strongyloidiasis is primarily seen among institutionalized populations (those in mental hospitals and children's hospitals) and immunocompromised individuals (those with HIV infection, AIDS, and patients with hematologic malignancies). The worm is usually found in the upper intestine where the eggs are deposited and hatch to form the rhabditiform larvae. The rhabditiform larva (male and female) migrate to the bowel where they may be excreted in the feces. If excreted in the feces, the larva can evolve into either one of two forms after **copulation**: a free-living noninfectious rhabditiform larvae, or an infectious filariform larvae. The filariform larva can penetrate host skin and migrate to the lungs and produce progeny, a process called autoinfection. This can result in hyperinfection (i.e., an increased number of larva in the intestine, lungs, and other internal organs), especially in an immunocompromised host.

Patients with acute infection may develop a localized pruritic rash, but heavy infestations can produce eosinophilia (10 % to 15%), diarrhea, abdominal pain, and intestinal obstruction. Administration of corticosteroids or other immunosuppressive drugs to an infected individual can result in hyperinfections and disseminated strongyloidiasis. Diagnosis of strongyloidiasis is made by identification of the rhabditiform larva in stool, sputum, or duodenal fluid, or from small bowel biopsy specimens or via antigen testing (ELISA essay). Multiple stool and other samples may need to be checked, both for diagnosis and to ensure eradication of the larva in patients after treatment.

Treatment

❸ *The drug of choice for strongyloidiasis is oral ivermectin 200 mcg/kg per day for 2 days, while albendazole 400 mg twice daily is given for 7 days as an alternative.*[3] With hyperinfection or disseminated strongyloidiasis, immunosuppressive drugs should be discontinued and treatment should be initiated with ivermectin 200 mcg/kg per day until all symptoms are resolved. Patients should be tested periodically to ensure the elimination of the larva. Individuals from an endemic area who are candidates for organ transplantation should be screened for *S. stercoralis*.

CESTODIASIS

Cestodiasis (tapeworm infection) is caused by species of the phylum Platyhelminthes (flatworms), and include among others the pork tapeworm (*Taenia solium*) and the beef tapeworm (*T. saginata*). The tapeworm attaches itself to the mucosal wall of the upper jejunum by the scolex (mouth parts), and by two to four cup-shaped suckers and a structure called a rostellum, which may have hooks in some species. Since the parasite lacks a digestive system it obtains all nutrients directly from the host. The scolex, proglottids (segments), and eggs are specific for each species and used for identification of tapeworms. Tapeworm infections are caused by ingestion of poorly cooked meat which contains the larva or cysticerci. Cysticerci, when released from the contaminated meat by host digestive juices, mature in the host jejunum. Cystericercosis is a systemic disease caused by the larva of *T. solium* (oncosphere or hexacanth), and is usually acquired by ingestion of eggs in contaminated food or by autoinfection. The larvae can penetrate the bowel and migrate through the bloodstream to infect different organs including the central nervous system (neurocysticercosis). Diagnosis of both *T. saginata* and *T. solium* is accomplished by recovery of the gravid proglottids and the scolex in the stool.

Treatment

❸ *Tapeworm infections (*T. saginata *and* T. solium*) are treated with praziquantel 5 to 10 mg/kg as a single dose (use the same dose for adults and pediatric patients).*[3] The treatment for cysticercosis and neurocysticercosis may include surgery, anticonvulsants (neurocysticercosis can cause seizures), and anthelmintic therapy. The anthelmintic therapy of choice is albendazole 400 mg twice daily for 8 to 30 days. The pediatric dose of albendazole is 15 mg/kg (maximum: 800 mg) in two divided doses for 8 to 30 days. The doses for both adults and pediatric subjects can be repeated if necessary. Praziquantel is an alternative therapy.[3]

Outcome Evaluation

Morbidity and disease due to helminthic infections is related to the intensity of infection. The major adverse effects of helminthic infections are malnutrition, fatigue, and diminished

work capacity. Unlike other helminthic infections, strongyloidiasis can cause autoinfection, and in the presence of immunosuppression, it can cause central nervous system and disseminated infections which have high mortality.

The most serious complication of cysticercosis is neurocysticercosis that can cause strokes and seizures. Treatment of neurocysticercosis with anthelmintic treatment remains controversial.

MALARIA

Malaria is one of the most devastating parasitic diseases, affecting a population in excess of 500 million and causing between 700,000 and 2.7 million deaths a year worldwide.[7,8] It is reported that in the year 2000, approximately 27 million United States travelers visited countries where malaria is endemic. In 2002, the Centers for Disease Control and Prevention (CDC) indicated that there were 1,337 cases of malaria, of which 849 were in United States civilians, 33 in United States military personnel, and the rest in foreign civilians. There were eight fatalities, all due to *Plasmodium falciparum*. ❹ *The primary reasons for morbidity and death in malaria are failure to take recommended chemoprophylaxis, inappropriate chemoprophylaxis, delay in seeking medical care or in initiating therapy promptly, and misdiagnosis*. Evaluation of a patient should include specific travel history, details of chemoprophylaxis, and physical findings (e.g., splenomegaly).

Malaria is transmitted by the bites of the *Anopheles* mosquitoes which introduce into the bloodstream one of four species of sporozoites of the plasmodia (*Plasmodium falciparum*, *P. ovale*, *P. vivax* or *P. malariae*). Initial symptoms of malaria are nonspecific and may resemble influenza and include: chills, headache, fatigue, muscle pain, rigors, and nausea. The onset of the symptoms is between 1 to 3 weeks following exposure. Fever may appear 2 to 3 days after initial symptoms and may follow a pattern and occur every 2 or 3 days (*P. vivax, P. ovale* and *P. malariae*). Fever with *P. falciparum* can be erratic and may not follow specific patterns. It is not unusual for patients to have concomitant infections with *P. vivax* and *P. falciparum*. Falciparum malaria must always be regarded as a life-threatening medical emergency.

Epidemiology and Etiology

The distribution of the various species of malaria is not well defined but *P. vivax* is reported to be prevalent in the Indian subcontinent, Central America, North Africa, and the Middle East, whereas *P. falciparum* is predominantly in Africa (including sub-Saharan Africa), both East and West Africa, Haiti, the Dominican Republic, the Amazon region of South America, Southeast Asia, and New Guinea. Most *P. ovale* infections occur in Africa, while the distribution of *P. malariae* is worldwide.[7] Most infections in the United States are reported in American travelers, recent immigrants, or immigrants who have visited friends and family in an endemic area.[8] Placental transmission and blood transfusions are also sources of malaria.



Patient Encounter, Part 1

TW is a 27-year-old male who had returned from Bamako, Mali in West Africa after visiting his college classmate who was in the Peace Corps. While there, he accompanied his friend on a river trip to visit a number of villages. He indicates that he took steps to minimize mosquito bites and had slept under a mosquito net. He was well since returning from Africa until the previous day, when he had a temperature as high 39°C (102°F), with anorexia, headache, chills, sweats, myalgias, and abdominal pain. He took a few doses of ibuprofen but his fever came back after a few hours and he now presents in the emergency department with chills, high fever (greater than 39.8°C) (greater than 104°F) , headache, abdominal pain, nausea, stiffness of the neck, and back pain.

- Are the symptoms in this patient consistent with malaria?
- What places this patient at risk for malaria?
- What additional information do you need to develop a therapeutic plan for this patient?

Within minutes after the bite of the *Anopheles* mosquito, the sporozoites invade hepatocytes in the liver and begin an asexual phase called schizonts (exoerythrocytic stage or schizogony). The patient may be asymptomatic during this period. After a lapse of between 5 and 15 days (depending on the species), schizonts rupture to release daughter cells (merozoites) into the blood, which then invade erythrocytes. In erythrocytes the merozoites undergo a number of sequential forms: a ring form, trophozoite, schizont, and merozoite, which then invade new erythrocytes. This asexual phase is about 48 hours for *P. falciparum*, *P. vivax,* and *P. ovale,* and 72 hours for *P. malariae*. Subsequently, the merozoites develop into gametocytes and undergo a sexual phase (sporogony) in the *Anopheles* mosquito. In the mosquito, the gametocytes undergo a number of stages: zygote, ookinete, and oocyst, and finally transform into sporozoites in the salivary glands where it is again able to infect the next host. Unlike *P. falciparum* and *P. malariae,* which only remain in the liver for about 3 weeks before invading erythrocytes, *P. ovale* and *P. vivax* can remain in the liver for extended periods in a latent stage (as hypnozoites); this can result in the recurrence of the infection after weeks or months. Primaquine therapy is necessary to eradicate this stage of the infection.

Pathology

The clinical presentation of malaria can be quite variable. Normally, the appearance of a prodrome with headache, abdominal pain, fatigue, fever, and chills, which coincides

with the erythrocytic phase of malaria occurs frequently between 10 and 21 days after being exposed. This phase causes extensive hemolysis, which results in anemia and splenomegaly. The most serious complications are caused by *P. falciparum* infections. Infants and children under the age of 5 years and nonimmune pregnant women are at high risk for severe complications with falciparum infections. The complications associated with falciparum malaria are related to two unique features of *P. falciparum*: (1) its ability to produce high parasitism (up to 80%) of red cells of all ages, and (2) the propensity to be sequestered in postcapillary venules of critical organs such as brain, liver, heart, lungs, and kidneys.[7] It has been postulated that tissue hypoxia from anemia, together with *P. falciparum*–parasitized red blood cell adherence to endothelial cells in capillaries, contribute to severe ischemia and metabolic derangements. *P. malariae* is implicated in immune-mediated **glomerulonephritis** and nephrotic syndrome.

Clinical Presentation and Diagnosis



Clinical Presentation of Malaria

Initial Presentation

Include a careful travel history of patient and physical findings (e.g., splenomegaly) and details of antimalarial chemoprophylaxis, when obtainable.

Erythrocytic Phase

1. Prodrome: Headache, anorexia, malaise, fatigue, and myalgia
2. Nonspecific complaints include: abdominal pain, diarrhea, chest pain, and arthralgia
3. Paroxysm: High fever, chills, and rigor
4. Cold phase: Severe pallor, cyanosis of the lips and nail beds
5. Hot phase: Fever between 40.5°C (104.9°F) and 41°C (105.8°F) (seen more frequently with *P. falciparum*)
6. Sweating phase: Follows the hot phase by 2 to 6 hours
7. When fever resolves, it is followed by marked fatigue and drowsiness, warm dry skin, tachycardia, cough, headache, nausea, vomiting, abdominal pain, diarrhea and delirium, anemia, and splenomegaly

❺ *P. falciparum malaria is a life-threatening emergency. Complications include hypoglycemia, acute renal failure, pulmonary edema, severe anemia (high parasitism), thrombocytopenia, heart failure, cerebral congestion, seizures, coma, and adult respiratory distress syndrome.*

Diagnostic Procedures for Malaria

1. To ensure a positive diagnosis, blood smears (both thick and thin films) should be obtained every 12 to 24 hours for 3 consecutive days.
2. The presence of parasites in the blood 3 to 5 days after initiation of therapy suggests resistance to the drug regimen.



Patient Encounter, Part 2

HPI

TW presents with fever, nausea, headache, myalgias, chills, and body aches including back pain. When questioned about his travels, he indicates that he had not taken any antimalarial prophylaxis.

PMH

Healthy 27-year-old male

FH

Father died of stroke at age 87 years; mother, who is 82 years old, has rheumatoid arthritis and lives with an unmarried daughter

SH

Systems analyst, works for local school district; occasionally drinks wine with meals

Meds

Ibuprofen 200 mg

ROS

In addition to the complaints noted above, he complains of severe nausea and fatigue

PE

Gen: Patient is lucid but slightly agitated and febrile
VS: Blood pressure 105/70 mm Hg; pulse 120 bpm, respiratory rate 32/minute, temperature 40.1°C (104.1°F)
Skin: Warm and dry to touch
HEENT: Slightly icteric sclerae and dry oral mucosa
ABD: Soft with diffuse tenderness with hepatomegaly and splenomegaly
Rest of the systems were WNL

Labs

Sodium 131mEq/L (131 mmol/L)
Hemoglobin 10.2 g/dL (6.3 mmol/L)
Potassium 4.9 mEq/L (4.9 mmol/L)
Hematocrit 31% (0.31)
Chloride 96 mEq/L (96 mmol/L)
White blood cells $14.8 \times 10^3/mm^3$ ($14.8 \times 10^9/L$)
Blood urea nitrogen 28 mg/dL (9.99 mmol/L)
Total bilirubin 1.8 mg/dL (30.8 mcg mol/L)
Serum creatinine 1.4 mg/dL (123.8 mcg mol/L)
Platelets $110 \times 10^3/mm^3$ ($110 \times 10^9/L$)
Glucose 77 mg/dL (4.27 mmol/L)
Aspartate aminotransferase 87 U/L (1.45 mcg kat/L)
Albumin 3.2 g/dL (32 g/L)
Alanine aminotransferase 94 U/L (1.57 mcg kat/L)
Blood smear (Giemsa stain): *P. falciparum*

- In view of the above information, what is your assessment of this patient?
- Identify your treatment goals and monitoring parameters.

Recent innovations for detecting malaria include DNA or RNA probes by polymerase chain reaction (PCR). These, however, are not widely available for clinical use. A rapid dipstick test (ParaSight F, Becton-Dickinson, Cockeyville, MD) reportedly has a sensitivity of 88% and a specificity of 97%, which is comparable to microscopy. However, ParaSight F can give false-positive results with rheumatoid factor; thus microscopy remains the optimal test.

Treatment

The primary goal in the management of malaria is the rapid identification of the *Plasmodium* species by blood smears (both thick and thin smears repeated every 12 hours for 3 days). Antimalarial therapy should be initiated promptly to eradicate the infection within 48 to 72 hours and avoid complications such as hypoglycemia, pulmonary edema, and renal failure.

Pharmacologic Therapy

The chemoprophylaxis regimen for malaria is outlined in Table 75–1.[3]

Chemotherapy for Malarial Infection

In an uncomplicated attack of malaria (for all plasmodia except chloroquine-resistant *P. falciparum and P. vivax*), the recommended regimen is chloroquine 600 mg (base) initially, followed by 300 mg (base) 6 hours later, and then 300 mg (base) daily for 2 days.[3] ❻ *In severe illness or falciparum malaria, patients should be admitted to an acute care unit and quinidine gluconate 10 mg salt/kg*

TABLE 75–1. Chemoprophylaxis for Malaria

Plasmodia-Sensitive	Drug	Dose	Pediatric Dose	Comments
Chloroquine-sensitive	Chloroquine phosphate (oral)[a]	300 mg (base) once weekly beginning 1 week prior to departure and continued for 4 weeks after leaving endemic area	5 mg (base)/kg of body weight once weekly (maximum 300 mg)	Hydroxychloroquine sulfate 310 (base) or 400 mg salt once a week may be used instead of chloroquine; regimen will be similar to chloroquine
When leaving an area endemic for *P. vivax* or *P. ovale*	Primaquine (oral)	30 mg base (52.6 mg salt) daily for 14 days after departure, in addition to the above	0.6 mg/kg base (1 mg/kg salt) daily for 14 days after departure	*Contraindicated* in those with G6PD deficiency and in pregnancy and lactation
Chloroquine-resistant *P. falciparum*	Atovaquone-proguanil (oral)	250 mg atovaquone and 100 mg proguanil (1 tablet) once daily	62.5 mg atovaquone and 25 mg proguanil once daily 11–20 kg: 1 tablet 21–30 kg: 2 tablets 31–40 kg: 3 tablets Greater than or equal to 40 kg: 1 adult tablet daily	Begin 1–2 days before departure and continue for 1 week after leaving high-risk area Recommended also for primary prophylaxis in mefloquine-resistant *P. falciparum*
	Alternatives Doxycycline (oral)	100 mg daily	Greater than or equal to 8 years of age 2 mg/kg (maximum 100 mg)	Effective for mefloquine-resistant *P. falciparum* Start 1–2 days before departure, continue through stay in endemic area, and continue regimen for 4 weeks after returning
	Mefloquine (oral)	228 mg (base) (250 mg salt) weekly	Less than or equal to 15 kg: 4.6 mg/kg base (5 mg/kg salt) once weekly 15–19 kg: ¼ tablet 20–30 kg: ½ tablet 31–45 kg: ¾ tablet Greater than or equal to 45 kg: 1 tablet	Start 1–2 wk before departure and continue for 4 wk after leaving endemic area; may start 3–4 wk earlier to assess tolerance *Contraindications*: History of seizure, psychiatric disorders (including depression and anxiety), or arrhythmias
	Primaquine (oral)	30 mg base (1 mg/kg salt for adult) daily	0.6 mg/kg base (1 mg/kg salt up to adult dose)	Alternative or second-line regimen; see above for contraindications

[a]Pediatric dose can be calculated and tablet pulverized and placed in gelatin capsules. Parents can be instructed to suspend dose in food, simple syrup, or drink.

For further information, see Eyers JE. Sources of information in tropical medicine. In: Cook GC, Zumla A, eds. Manson's Tropical Diseases. 21st ed. London: Saunders; 2003:1807–1816.

G6PD, glucose-6-phosphate dehydrogenase deficiency.

as a loading dose (maximum 600 mg) in 250 mL normal saline should be administered intravenously slowly over 1 to 2 hours. This should be followed by continuous infusion of 0.02 mg/kg per minute of quinidine for at least 24 hours until oral therapy can be started. In patients who have received either quinine or mefloquine, the loading dose of quinidine should be omitted. Oral quinine salt (650 mg every 8 hours) plus doxycycline 100 mg twice daily should follow the intravenous dose of quinidine to complete 7 days of therapy. The pediatric dose of intravenous quinidine gluconate is the same as the dose for adults. The pediatric dose of oral quinine is 25 mg/kg per day in three divided doses, while the dose of doxycycline (children greater than 8 years old) is 4 mg/kg in two divided doses for 7 days. An alternative to doxycycline is clindamycin 900 mg (20 mg/kg per day) three times daily for 3 days. The pediatric dose of clindamycin is the same as in adults.

In *P. falciparum, P. vivax, P. ovale* or *P. malariae* (chloroquine-resistant) infections, a dose of 750 mg mefloquine followed by 500 mg 12 hours later is recommended. The pediatric dose of mefloquine is 15 mg/kg (less than 45 kg) followed by 10 mg/kg 8 to 12 hours later. Mefloquine is associated with sinus bradycardia, confusion, hallucinations, and psychosis and should be avoided in patients with a history of cardiovascular problems or depression. Intravenous quinidine gluconate followed by quinine plus doxycycline or clindamycin should be administered for severe illness as indicated above. The intravenous quinidine regimen requires close monitoring of the electrocardiogram (QT-segment) and other vital signs (hypotension and hypoglycemia). An alternative oral treatment for *P. falciparum* infections in adults, especially those with history of seizures, psychiatric disorders, or cardiovascular problems, is the combination of atovaquone 250 mg and proguanil 100 mg (Malarone) (2 tablets twice daily for 3 days).[3,8] The pediatric dose of Malarone: less than 5 kg :not indicated; 9 to 10 kg:3 pediatric tablets/day × 3 days; 11 to 20 kg: one adult tablet/day × 3 days; 21 to 30 kg: 2 adult tablets/day × 3 days; 31 to 40 kg:3 adult tablets/day × 3 days; greater than 40 kg: 2 adults tablets twice daily × 3 days. ❼ *Since falciparum malaria is associated with serious complications, including pulmonary edema, hypoglycemia, jaundice, renal failure, confusion, delirium, seizures, coma, and death, careful monitoring of fluid status and hemodynamic parameters is mandatory.*



Patient Encounter, Part 3

Following treatment of falciparum malaria, TW has remained well for 2 months. However, 2 days ago, he started developing fever and chills, nausea, and abdominal pain. When seen in the emergency department he has a fever of 38.4°C and complains of severe headache. Examinations of a thick and thin blood smear of the patient's blood identified *P. vivax* infection. TW received a course of chloroquine and primaquine. In a follow-up 2 weeks later, a repeat blood smear was negative for parasites and the patient was asymptomatic.

Exchange transfusion that may be required in patients with *P. falciparum* malaria in whom parasitemia may be between 5% and 15% remains a questionable modality. Either peritoneal or hemodialysis may be indicated in renal failure.

Outcome Evaluation

When advising potential travelers on prophylaxis for malaria, be aware of the incidence of chloroquine-resistant *P. falciparum* malaria and the countries where it is prevalent. In patients who have *P. vivax* or *P. ovale* malaria (note that some patients can have *P. falciparum* and one of these species), following the treatment of the acute phase of malaria and screening for glucose-6-phosphate dehydrogenase deficiency, patients should receive a regimen of primaquine for 14 days to ensure eradication of the hypnozoite stage of *P. vivax* or *P. ovale*. For detailed recommendations for prevention of malaria go to www.cdc.gov/travel/.



Patient Care and Monitoring

- Acute *P. falciparum* malaria resistant to chloroquine should be treated with intravenous quinidine via central venous catheter and fluid status and the electrocardiogram (ECG) should be monitored closely.
- The loading dose of quinidine should be omitted in those patients who have received quinine or mefloquine.
- Hypoglycemia that is associated with both *P. falciparum* and quinidine administration, should be checked every 4 to 6 hours and corrected with dextrose infusions (5% to 10%).
- Quinidine infusions should be slowed temporarily or stopped if the QT interval is greater than 0.6 second, the increase in the QRS complex is greater than 25%, or hypotension unresponsive to fluid challenge results.
- The suggested quinidine levels should be maintained at 3 to 7 mg/dL (9.2 to 21.6 mcg mol/L).
- Blood smears should be checked every 12 hours until parasitemia is less than 1%.
- Resolution of fever should take place between 36 and 48 hours after initiation of the intravenous quinidine therapy, and the blood should be clear of parasites in 5 days.
- When parenteral therapy is required for more than 48 hours or the patient's renal function deteriorates, the dose of quinidine should be lowered by half.

Advice to Travelers

All travelers to endemic areas should be advised to remain in well-screened areas, to wear clothes that cover most of the body, and sleep in mosquito nets. Travelers should adhere to malaria chemoprophylaxis regimens and carry the insect repellant DEET (N, N,-diethylmetatoluamide) or other insect sprays containing DEET for use in mosquito-infested areas.

AMERICAN TRYPANOSOMIASIS

Etiology

Two distinct forms of the genus *Trypanosoma* occur in humans. One is associated with African trypanosomiasis (sleeping sickness) and the other with American trypanosomiasis (Chagas' disease). *T. brucei gambiense* and *T. brucei rhodesiense* are the causative organisms for the East African and West African trypanosomiasis, respectively. *T. brucei rhodesiense* causes the acute disease and is the more virulent of the two species. Both East and West African trypanosomiasis are transmitted by various species of tsetse fly belonging to the genus *Glossina*. Further discussion of this subject will focus on American trypanosomiasis.

T. cruzi is the agent that causes American trypanosomiasis. American trypanosomiasis is transmitted by a number of species of reduviid bugs *(Triatoma infestans* and *Rhodrium prolixus)* that live in wall cracks of houses in rural areas of North, Central, and South America.[9] The reduviid bug is infected by sucking blood from animals (e.g., opossums, dogs, and cats) or humans infected with circulating trypomastigotes. American trypanosomiasis is endemic in all Latin American countries and can be transmitted congenitally, by blood transfusion, and by organ transplantation.

Clinical Presentation and Diagnosis



Clinical Presentation of Trypanosomiasis

Acute
- Unilateral orbital edema (Romana's sign)
- Granuloma (chagoma)
- Fever, hepatosplenomegaly, and lymphadenopathy

Chronic
- *Cardiac: cardiomyopathy and heart failure*
- *ECG: first-degree heart block, right bundle-branch block, and arrhythmias*
- *Gastrointestinal: enlargement of the esophagus and colon ("mega" syndrome)*
- *Central nervous system: meningoencephalitis, strokes, seizures, and focal paralysis*

Diagnosis

Positive history of exposure and use of serology: indirect hemagglutination test, ELISA (Chagas EIA, Abbott Labs, Abbott Park, IL), and complement fixation (CF) test. (*Note:* CF may produce false-positive reactions in those exposed to leishmaniasis, syphilis, and malaria. PCR may be more definitive for diagnosis.)



Patient Care and Monitoring

- It is essential to identify *T. cruzi*–infected patients by serology and to monitor the cardiovascular status of these patients by electrocardiogram periodically.
- Some patients will benefit from implantation of pacemakers.
- All transplant candidates from areas endemic for Chagas' disease need to be screened for T. cruzi. Immunosuppression in these patients can lead to overwhelming infections.

Pharmacologic Therapy

The drugs used for *T. cruzi* include nifurtimox (Lampit) and benznidazole (Rochagan). Oral nifurtimox is available from the CDC, while benznidazole is only available in Brazil. The adult dose of nifurtimox is 8 to 10 mg/kg per day in divided doses for 120 days. Since children seem to tolerate the dose better than adults, the pediatric dose of nifurtimox in children 1 to 10 years old is 15 to 20 mg/kg per day, and the dose for children 11 to 16 years old is 12.5 to 15 mg/kg per day in divided doses. Symptomatic treatment for heart failure associated with Chagas' disease should be initiated. The gastrointestinal complications may require surgical revisions and reconstruction.

Outcome Evaluation

Treatment of the acute phase of the disease (i.e., fever, malaise, edema of the face, and hepatosplenomegaly) is nifurtimox. The congestive heart failure associated with cardiomyopathy of Chagas' disease is treated the same way as cardiomyopathy from other causes.

ECTOPARASITES

A parasite that lives outside the body of the host is called an ectoparasite. Approximately 6 to 12 million subjects become infested with pediculosis (lice infestation) yearly in the United States. Pediculosis is usually associated with poor hygiene, and infections are passed from person to person through social and sexual contact.

Lice

The two species that belong to this group include *Pediculus humanus capitis* (head louse) and *P. humanus corporis* (body louse). The eggs (or nits) remain firmly attached to the hair, and in about 10 days the lice hatch to form nymphs, which mature in 2 weeks. The lice become attached to the base of the hair follicle and feed on the blood of the host.[10] Pubic or crab lice are found on the hairs around the genitals, but may occur

in other parts of the body (e.g., eyelashes or axillae). Hypersensitivity to the secretions from lice can produce macular swellings and lead to secondary bacterial infections.

Treatment

❾ *The agent of choice for all three infections (body, head, and crab lice) is 1% permethrin (Nix).* Permethrin has both pediculicidal and ovicidal activity against *P. humanus capitis*. The cure rate is reported to be between 90% and 97%. A cream rinse of permethrin 1% (Nix-Crème Rinse) is also available. Individuals with a history of hypersensitivity to ragweed or chrysanthemum may react to permethrin and should avoid this preparation. An alternative agent is oral ivermectin 100 mcg/kg for 3 days (days 1, 2, and 10). Permethrin can cause itching, burning, stinging, and tingling with application. Permethrin 1% should be applied to the dry scalp after shampooing and be left on the scalp for 10 minutes. The application may need to be repeated. Because of the reports of resistance to permethrin, an alternative agent is 0.5% malathion (Ovide), which has to be left on the scalp for 90 minutes, has also been found to be effective. For the relief of pruritus, calamine lotion with 0.1% menthol or an equivalent agent may be used. ❾ *All individuals, including immediate family members and sexual partners of the primary host, should be treated. All bedding and clothes should be sterilized as previously indicated for enterobiasis.*

Scabies

Scabies is caused by the itch mite *Sarcoptes scabiei hominis*, which affects both humans and animals. Infection usually affects the interdigital and popliteal folds, axillary folds, the umbilicus, and the scrotum. The infection causes severe itching and excoriations in the interdigital web spaces, buttocks, groin, and scalp.[10] ❿ *Diagnosis is made by identifying the mite from skin scrapings on a wet mount.*

Treatment

❿ *The agent of choice for scabies is permerthrin 5% (Elimite) cream.* Alternative agents in subjects who cannot use permethrin are crotamiton 10% (Eurax) and oral ivermectin (Stromectal) 200 mcg/kg as a single dose. To initiate the treatment with permerthrin, the skin should be scrubbed in a warm soapy bath to remove the scabs. The permerthrin lotion should then be applied to the whole body, avoiding the face, mucous membranes, and eyes, and left on for 8 to 14 hours. A single application eradicates 97% of scabies. All close contacts should be treated appropriately. The pruritus associated with scabies may persist for 2 to 4 weeks because of the remnants of mite parts in the skin.

Outcome Evaluation

Infections due to arthropods can be controlled by preventing their access to the host. Improving living conditions and avoiding sharing common personal items like hats and hair brushes may minimize these infections due to arthropods. Permerthrin (1% to 5%) is an effective agent for all these infections.

ABBREVIATIONS

AIDS:	Acquired immunodeficiency syndrome
CDC:	Centers for Disease Control and Prevention
CF:	complement fixation
CT:	computed tomography
DEET:	N, N,-diethylmetatoluamide
ECG:	electrocardiogram
ELISA:	enzyme-linked immunosorbent assay
HIV:	human immunodeficiency virus
IgA:	immunoglobulin A
PCR:	polymerase chain reaction

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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76 Urinary Tract Infection

Brian A. Potoski



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Identify the diagnostic criteria for significant bacteriuria.
2. Describe the organism responsible for the majority of uncomplicated urinary tract infections.
3. Explain the three identified routes for bacteria to gain entry into the urinary tract.
4. Describe the signs and symptoms of urinary tract infections (UTIs) and how they differ in upper versus lower urinary tract disease.
5. Explain the laboratory tests that help in diagnosing patients with urinary tract infection.
6. Recommend an appropriate drug, dose, and duration for uncomplicated and complicated urinary tract infections.

Key Concepts

❶ Urinary tract infections are thought of as complicated and uncomplicated. Generally this refers to presence or absence, respectively, of functional or structural abnormalities within the urinary tract.

❷ The majority (85%) of **uncomplicated UTIs** are caused by *Escherichia coli*. The remaining 15% are caused by *Klebsiella* spp., *Staphylococcus saprophyticus*, *Enterococcus* spp., *Proteus* spp., and other organisms.

❸ Symptoms of lower UTIs include **dysuria**, urgency, frequency, **nocturia**, and suprapubic heaviness.

❹ Symptoms of upper UTIs include fever, nausea, vomiting, and often severe **flank pain**.

❺ The goals of antimicrobial treatment in UTIs are to eradicate the offending organism and prevent recurrence of infection.

❻ Uncomplicated UTIs may be managed with 3-day or even 1-day regimens, while complicated UTIs should be treated for at least 7 days, and sometimes up to 2 weeks.

Urinary tract infections (UTIs) are comprised of a diverse array of diseases. UTIs occur frequently, and are responsible for approximately 8 million patient visits annually.[1] In simplest of terms, a UTI is bacteria in the urinary tract seen either by wet prep or identified via bacterial culture, that does not represent contamination.

Bacteriuria, or bacteria in the urine, does not always represent infection. For this reason a number of quantitative diagnostic criteria have been created to identify the amount of bacteria in the urine that most likely represents true infection (hence the term "significant bacteriuria"). These are shown in Table 76–1. Furthermore, UTIs are classified as lower tract or upper tract disease. Patients will present differently with upper versus lower tract disease, and upper tract disease is thought of as a much more severe infection, as patients are more likely to be admitted to the hospital with upper urinary tract disease than lower tract disease. An example of lower tract infection is **cystitis.** Cystitis refers to the syndrome associated with a UTI involving dysuria, frequency, urgency, and occasional suprapubic tenderness. An example of upper urinary tract disease is pyelonephritis. Pyelonephritis is an inflammation of the kidney usually due to infection. Frequently, patients with uncomplicated UTI are treated as outpatients, while those patients with complicated UTIs are treated as inpatients.

EPIDEMIOLOGY AND ETIOLOGY

It is known that the prevalence of UTIs varies by age and gender. UTIs may occur at any age, even in the very young. Premature infants, for example, have a higher rate than full-term infants, and neonatal boys are five to eight times more likely to have

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Patient Encounter, Part 1

A 28-year-old female presents to her primary care physician's office with complaints of painful urination and frequent need to urinate which began 2 days ago. She denies vomiting, fever, nausea, or flank pain. Upon questioning she does admit that she is sexually active with only one partner and uses spermicidal jelly.

- What symptoms are suggestive of UTI?
- Does she have risk factors for UTI?
- What additional information do you need to know before creating a treatment plan for this patient?

UTIs than neonatal girls. In young children 1 to 5 years of age, **significant bacteriuria** occurs more in girls than boys, 4.5% compared to 0.5%, respectively.[2] Once adulthood is reached, bacteriuria increases in young, non-pregnant women (range, 1% to 3%), yet remains very low in men (up to 0.1%).[3] Symptomatic UTI affects 30% of women between the 20 and 40 years of age, which represents a prevalence that is 30 times greater than men of the same age group. With each year in adulthood, an equal number of bacteriuric women clear their bacteriuria, as do those who go on to develop a UTI. It is believed that upwards of 40% to 50% of the female population will experience a symptomatic UTI at sometime during their life.[4]

The etiology of UTIs has remained relatively unchanged over the past several decades. The frequency of causative organisms changes depending on whether the setting is a complicated or uncomplicated UTI. ❶ *There is a lack of consensus regarding the definition of what makes a UTI complicated, but in general a* ***complicated UTI*** *refers to a structural or functional abnormality of the urinary tract.* Patients with complicated UTIs are typically given longer treatment durations than those patients with uncomplicated infections. Those with complicated UTIs by definition are also prone to more frequent infections. It is important to note that an upper UTI does not necessarily imply complicated UTI, nor does lower UTI imply uncomplicated UTI.

❷ *Over 95% of uncomplicated UTIs are the result of a single causative organism. In 85% of the cases, this organism is* Escherichia coli.[5,6] *A variety of other organisms may cause uncomplicated UTIs, but represent the minority of pathogens. Other organisms may include gram-positives such as* Staphylococcus saprophyticus *and* Enterococcus *spp., and gram-negatives such as* Pseudomonas aeruginosa, Klebsiella pneumoniae, Proteus *spp., and* Enterobacter *spp*. The chances of isolating these organisms are higher in patients that have recurrent UTIs, particularly those patients whose UTI is complicated. It is also more common for organisms other than *E. coli* to cause UTIs in the hospitalized population.[7]

TABLE 76–1. Diagnostic Criteria for Significant Bacteriuria

Greater than or equal to 10^2 CFU coliforms/mL or greater than or equal to 10^5 CFU non-coliforms/mL in a symptomatic female
Greater than or equal to 10^3 CFU bacteria/mL in a symptomatic male
Greater than or equal to 10^5 CFU bacteria/mL in asymptomatic individuals on two consecutive specimens
Any growth of bacteria on suprapubic catheterization in a symptomatic patient
Greater than or equal to 10^2 CFU bacteria/mL in a catheterized patient

CFU, colony-forming unit.

PATHOPHYSIOLOGY

Routes of Infection

There are three potential ways for bacteria to enter into the urinary tract and cause infection. These routes or pathways include the ascending, hematogenous, and lymphatic pathways.

Ascending Pathway

The ascending pathway occurs when bacteria colonizing the urethra subsequently travel upwards, or ascend, the urethra to the bladder and cause cystitis (Fig. 76–1). The ascending route may help to explain why urinary tract infections occur more commonly in women than in men. Women have a shorter urethra than men, and colonization of the female urethra is likely due to its proximity to the perirectal area. It is also known that the use of spermicidal agents increases the colonization of the vagina with uropathogens.[8] Additionally, massage of the urethra in women as well as sexual intercourse may lead to bacteria gaining entrance into the bladder.[9,10] Once in the bladder, bacteria are not limited to causing cystitis. These bacteria may continue to ascend the urinary tract via the ureters and cause more complicated infections, such as pyelonephritis.

Hematogenous Pathway

The hematogenous route occurs through the seeding of the urinary tract with pathogens carried by the blood supply. These pathogens represent an infection at some other primary site in the body. *Staphylococcus aureus* bacteremia, for example, can cause renal abscesses via the hematogenous route, and pyelonephritis can be experimentally produced by intravenous injection of *Salmonella*, *Mycobacterium tuberculosis*, or even yeast (*Candida* spp.) into rabbits.[11] However, experimentally creating this pathway has not been successful with all organisms. Experimental hematogenous seeding of the kidneys could not be created with the intravenous injection of large innocula of *E. coli* or *P. aeruginosa* in a mouse model.[12]

Lymphatic Pathway

The lymphatic system, also known as the secondary circulatory system, connects the bladder to the kidney and may represent a way for bacteria to be transported and subsequently cause

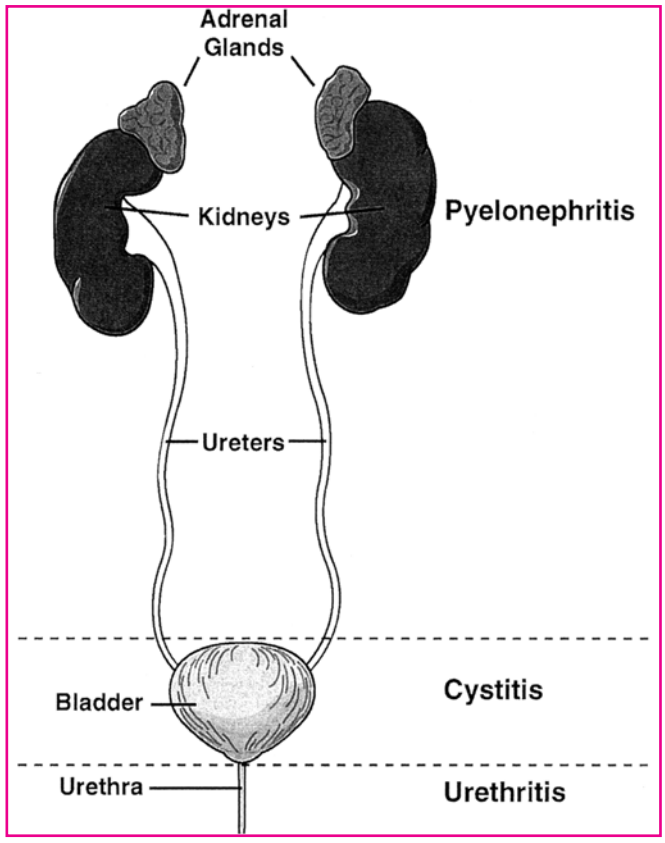


FIGURE 76–1. Anatomy and associated infections of the urinary tract. (From Sprandel KA, Lesch CA, Rodvold KA. Lower urinary tract infection. In: Schwinghammer TL, (ed.) *Pharmacotherapy Casebook: A Patient-Focused Approach*. 6th ed. New York: McGraw-Hill; 2005: 319, with permission.)

infection. Although this pathway is classically included as a route of infection, there is a lack of data showing the lymphatic pathway as a significant mechanism for development of infection. As a result this pathway is not believed to be a significant host mechanism.

Host Defense Mechanisms

Urine, although not an antimicrobial itself, does possess characteristics that are less than ideal for bacterial growth. Some of these characteristics include low pH, significant urea concentration, and high osmolality. Also, specifically in men, it is known that prostatic fluid secretions inhibit bacterial growth.[13] When they enter the bladder, bacteria stimulate an urge to urinate. This is yet another host defense mechanism targeted at preventing a bladder infection.

There are several other host factors present that should be mentioned that inhibit what are known as bacterial virulence factors. In general, these virulence factors are mechanisms that bacteria utilize to cause infection and/or ensure their survival. The first is glycosaminoglycan, a compound produced by the body that coats the epithelial cells of the bladder. This compound essentially separates the bladder from the urine by forming a protective layer against bacterial adhesion.[14] A second compound known as Tamm-Horsfall protein is secreted into the urine, and prevents *E. coli* from binding to receptors present on the surface of the bladder. Other factors implicated in contributing to host defense mechanisms include immunoglobulins, specifically IgA, and lactobacilli, bacteria that are part of the normal vaginal flora.[13,15]

Risk Factors

Several risk factors are known to exist in men and women. The common risk factors for UTI in women include sexual intercourse, lack of voiding after intercourse, use of a diaphragm, use of spermicidal jellies, diabetes, and pregnancy. In men, the risks are different, and are primarily centered on lack of circumcision, and at an older age include prostatic hyperplasia. Common risk factors for both men and women include urologic instrumentation, renal transplantation, neurogenic bladder, and urinary tract obstruction.[26]

CLINICAL PRESENTATION AND DIAGNOSIS



Clinical Presentation of Urinary Tract Infection

General

- Most women present with hematuria; however, this is not a presentation restricted only to UTIs.
- The elderly frequently will not present with common signs and symptoms of UTI, but may present with altered mental status.
- More than 95% of UTIs are caused by a single organism.
- Patients may present with **urosepsis.**

Signs and Symptoms of Lower UTI

❸ *Dysuria, suprapubic heaviness, gross hematuria, urinary frequency,* and nocturia

Signs and Symptoms of Upper UTI

❹ *Flank pain, fever, nausea, vomiting,* and *malaise*

Laboratory Tests

Urinalysis should show:

- **Pyuria** typically greater than 10 white blood cells/mm^3 urine
- Bacteriuria
- Nitrites present
- Leukocyte esterase present

Other Diagnostic Tests

- Bacterial quantitative culture, usually greater than 10^5 organisms/mL
- Upper UTI: presence of costovertebral tenderness



Patient Encounter, Part 2: The Medical History, Physical Exam, and Diagnostic Tests

PMH
None

FH
Father living with hypertension (controlled) and chronic obstructive pulmonary disease; mother living with hypertension (controlled)

SH
Works as a pharmacist at a local independent pharmacy

Allergies: Sulfa (patient states she breaks out in a rash that in some areas is "red and raised" and "red and flat")

Meds
None (occasional ibuprofen for headaches)

ROS
(+) dysuria, urinary frequency; (–) fever, nausea, vomiting, flank pain

PE
VS: Blood pressure 128/68 mm Hg, pulse 67 beats per minute, respiratory rate 16/minute, afebrile
CV: RRR, normal S1, S2; normal findings
Abd: Soft, non-tender, non-distended; (+) bowel sounds, no hepatosplenomegaly, heme (–) stool

Labs
Within normal limits

- Identify your treatment goals for the patient.
- What pharmacologic alternatives are available for the patient?

TREATMENT

Desired Outcomes

❺ *The goals of treatment are to eradicate the invading organism; to prevent or treat consequences of infection; and to prevent, if possible, recurrence of infection.* Therapy is directed at microbiologic eradication of the offending organism through antibiotics.

Pharmacologic Therapy

Antimicrobial therapy is the cornerstone of treatment in UTIs. This therapy should ideally be well tolerated, narrow in antimicrobial spectrum, lend itself to patient compliance (taken as infrequently as possible), have adequate concentrations at the site of the infection, and have good oral bioavailability. Table 76–2 reviews antibiotics frequently used to treat UTIs with comments on their use, and Table 76–3 reviews frequency, duration, and doses of those antibiotics.

Uncomplicated Cystitis

Uncomplicated cystitis represents the most common of UTIs. These are frequently managed in the outpatient setting, and occur in women of childbearing age. ❷ E. coli *is the most frequent (85%) of causal organisms in this setting, but in a minority of cases may be caused by* S. saprophyticus, K. pneumoniae, P. mirabilis, Enterococcus *spp., and a small percentage of others.*[16] As such, treatment in the outpatient setting is frequently relegated to a urinalysis and **empiric** therapy without a urine culture.[17] Patients are subsequently followed-up for resolution of signs and symptoms. ❻ *One significant benefit of treatment in the setting of uncomplicated cystitis is that treatment duration can be less than 7 days, and often may be 3 days or even 1 day.*

Although treatment duration of 1 day is advantageous because it strictly limits adverse events and drug interactions, and increases compliance, practitioners should know that 3-day courses of fluoroquinolones and trimethoprim-sulfamethoxazole are superior to single-doses in terms of cure rates in uncomplicated UTIs.[5,18] In the acute uncomplicated UTI, it is reasonable to pursue a 1-day course of therapy. Which agent to choose empirically partly hinges on known resistance rates in the geographic region, particularly *E. coli* resistance to trimethoprim-sulfamethoxazole.[19] Although no consensus has been reached on what percentage of *E. coli* isolates is resistant to trimethoprim-sulfamethoxazole should preclude its use, a model has recently been created that suggests that this threshold should be between 19% and 21% in the empiric setting.[20]

Acute Pyelonephritis

In contrast to patients that present with lower tract UTIs, those that present with pyelonephritis will have high-grade fever [greater than 38.3°C (100.9°F)] and severe flank pain. Select patients with pyelonephritis may be treated in the outpatient setting; however, patients whose infection is severe enough to cause vomiting, decreased food intake, and dehydration should be treated in an inpatient hospitalized setting. These patients will receive intravenous antibiotics at first before being switched to oral therapy.

Patients with pyelonephritis are traditionally given 14 days of therapy; however, there are limited data showing success in treating acute uncomplicated pyelonephritis for 7 to 10 days. More studies need to be conducted on treating for these shorter durations.[21] Gram stain and culture are important in ensuring appropriate antimicrobial coverage is selected. As stated above, a stratification exists for managing patients with acute pyelonephritis. Women who present with mild cases of pyelonephritis (defined as low-grade fever and a normal to slightly elevated peripheral white blood cell count, without nausea or vomiting) may be treated as outpatients.[21] Those women who exhibit more severe signs and symptoms will need to be admitted to an acute care setting for appropriate treatment. The same holds true for antibiotic selection in these patients. Those who are treated in an outpatient setting can be treated with trimethoprimsulfamethoxazole, fluoroquinolones, or even β-lactam/β-lactamase inhibitors, such as

TABLE 76–2. Commonly Used Antimicrobial Agents for the Treatment of Urinary Tract Infections

Agent	Comments
Oral Therapy	
Sulfonamides	These agents have been replaced by TMP-SMX.
Trimethoprim-sulfamethoxazole (TMP-SMX)	This combination is highly effective against most aerobic enteric bacteria except *P. aeruginosa*. High urinary tract tissue levels and urine levels are achieved, which may be important in complicated infection treatment. Also effective as prophylaxis for recurrent infections. Well tolerated, low cost. Patients with sulfa allergies may preclude its use.
Penicillins	
Ampicillin, amoxicillin, amoxicillin-clavulanic acid	Ampicillin is the standard penicillin that has broad-spectrum activity, and is the drug of choice for enterococci sensitive to penicillin. Amoxicillin is frequently used as well. Increasing *E. coli* resistance has limited amoxicillin use in acute cystitis. Amoxicillin-clavulanate is empirically preferred due to resistance.
Cephalosporins	
Cephalexin, cephradine, cefaclor, cefadroxil, cefuroxime, cefixime, cefzil, cefpodoxime	There are no major advantages of these agents over others in the treatment of UTIs, and they are more expensive. They may be useful in cases of resistance to amoxicillin and trimethoprim-sulfamethoxazole. These agents are not active against enterococci.
Tetracyclines	
Tetracycline, doxycycline minocycline	These agents have been effective for initial episodes of UTI; however, resistance develops rapidly, and their use is limited. Avoid in pregnancy.
Fluoroquinolones	
Ciprofloxacin, norfloxacin, levofloxacin	The newer quinolones have a greater spectrum of activity. These agents are effective for pyelonephritis. Avoid in pregnancy and children. Moxifloxacin is not listed due to lack of indication and efficacy data.
Nitrofurantoin	This agent is effective in treatment and prophylaxis in patients with recurrent UTIs. Contraindicated in patients with low creatinine clearances due to potential for neuropathy.
Azithromycin	Commonly used for sexually transmitted diseases (i.e., chlamydial infections) rather than UTIs.
Methenamine hippurate, methenamine mandalate	These agents are reserved for prophylactic therapy or suppressive use between episodes of infection.
Fosfomycin	Single-dose therapy for uncomplicated infections.
Parenteral Therapy	
Aminoglycosides	
Gentamicin, tobramycin, amikacin, netilmicin	Gentamicin and tobramycin are equally effective. Tobramycin has slightly better MICs to *Pseudomonas*. Amikacin generally is reserved for multi–drug resistant bacteria. Typically used as a short course of therapy followed by a switch to an oral agent.
Penicillins	
Ampicillin, ampicillin-sulbactam, ticarcillin-clavulanate, piperacillin, piperacillin-tazobactam	These agents are generally effective for susceptible bacteria. The extended-spectrum penicillins are more active against *P. aeruginosa* and enterococci and are preferred over cephalosporins. They are very useful in renally impaired patients or when an aminoglycoside is to be avoided.
Cephalosporins	
First-, second-, third-, and fourth-generation	Second- and third-generation cephalosporins have a broad spectrum of activity against gram-negative bacteria, but are not active against enterococci. Only ceftazidime and cefepime have activity against *P. aeruginosa*. They are useful for nosocomial infections and urosepsis due to susceptible pathogens.
Carbapenems	
Imipenem-cilastatin, meropenem, ertapenem	These agents have broad-spectrum activity, including gram-positive, gram-negative, and anaerobic bacteria. Imipenem and meropenem are active against *P. aeruginosa* and enterococci, but ertapenem is not. All may be associated with *Candida* superinfections. Rarely used for UTIs.
Fluoroquinolones	
Ciprofloxacin, levofloxacin	These agents have broad-spectrum activity against both gram-negative and gram-positive bacteria. They provide high urine and tissue concentrations and are actively secreted in reduced renal function. Switch to oral when possible due to excellent bioavailability.
Monobactam	
Aztreonam	Only active against gram-negative bacteria, including *P. aeruginosa*. Generally useful for nosocomial infections when aminoglycosides are to be avoided and in penicillin-susceptible patients.

MIC, minimum inhibitory concentration.

TABLE 76–3. Overview of Outpatient Antimicrobial Therapy for Lower Tract UTIs and Acute Pyelonephritis

Indications	Antibiotic	Dose	Frequency	Duration
Lower Tract Infections				
Uncomplicated	Trimethoprim-sulfamethoxazole	2 DS[a] tablets	Single dose	1 day
		or 1 DS[a] tablet	Twice a day	3 days
	Ciprofloxacin	250 mg	Twice a day	3 days
	Norfloxacin	400 mg	Twice a day	3 days
	Levofloxacin	250 mg	Once a day	3 days
	Amoxicillin	6 × 500 mg	Single dose	1 day
		500 mg	Twice a day	3 days
	Amoxicillin-clavulanate	500 mg	Every 8 hours	3 days
	Trimethoprim	100 mg	Twice a day	3 days
	Nitrofurantoin macrocrystals	50 or 100 mg	Every 6 hours	7 days
	Nitrofurantoin monohydrate	100 mg	Every 12 hours	7 days
	Fosfomycin	3 g	Single dose	1 day
Complicated	Trimethoprim-sulfamethoxazole	1 DS tablet	Twice a day	7–10 days
	Trimethorpim	100 mg		7–10 days
	Norfloxacin	400 mg		7–10 days
	Ciprofloxacin	250–500 mg	Twice a day	7–10 days
	Gatifloxacin	400 mg	Once a day	7–10 days
	Lomefloxacin	400 mg	Once a day	7–10 days
	Levofloxacin	250 mg	Once a day	10 days
	Amoxicillin-clavulanate	500 mg	Every 8 hours	7–10 days
	Nitrofurantoin macrocrystals	50 or 100 mg	Every 6 hours	6 months
Recurrent infections	Trimethoprim	100 mg	Once a day	6 months
	Trimethoprim-sulfamethoxazole	$^1/_2$ SS[b] tablet	Once a day	6 months
Acute pyelonephritis[c]	Trimethoprim- sulfamethoxazole	1 DS[a] tablet	Once a day	6 months
	Ciprofloxacin	500 mg	Twice a day	7 days
	Gatifloxacin	400 mg	Twice a day	14 days
	Norfloxacin	400 mg	Once a day	14 days
	Levofloxacin	250 mg	Twice a day	14 days
	Lomefloxacin	400 mg	Once a day	14 days
	Enoxacin	400 mg	Once a day	14 days
	Amoxicillin-clavulanate	500 mg	Twice a day	14 days
			Every 8 hours	14 days

[a]DS = double strength (160 mg trimethoprim/800 mg sulfamethoxazole).
[b]SS = single strength (80 mg trimethoprim/400 mg sulfamethoxazole).
[c]Doses listed for acute pyelonephritis are for oral regimens.

amoxicillin-clavulanate. In those patients that are admitted to the hospital, antibiotic therapy is usually broader in nature, especially in patients suspected of having bacteremia or urosepsis. These patients will typically receive intravenous therapy such as a fluoroquinolone, or a β-lactam plus an aminoglycoside.



Patient Encounter, Part 3: Creating a Care Plan

Based on the information presented, create a care plan for this patient's UTI. Your plan should include: (1) a statement of the drug-related needs and/or problems, (2) the goals of therapy, (3) a patient-specific detailed therapeutic plan including risk factor modification, and (4) a plan for follow-up to determine whether the goals have been achieved and adverse effects avoided.

Special Populations

Pregnant Women

Changes to the urinary tract in pregnant women predispose them to an increased incidence of bacteriuria, and subsequent urinary tract infections that may follow. These changes are not limited to amino acid and other nutrient concentrations in the urine, but extend to physiologic changes such as reduced bladder tone and dilation of the renal pelvis and ureters.[22,23]

It is known that an association exists between maternal UTI during pregnancy and fetal death, mental retardation, and developmental delay.[24] Because of this known association, and because up to 7% of pregnant women have an **asymptomatic bacteriuria** that may progress to pyelonephritis, screening is necessary. In patients with significant bacteriuria, whether symptomatic or asymptomatic, treatment is recommended to avoid the complications discussed above. In the majority

TABLE 76–4. Monitoring Parameters for Select Antibiotics Used in the Treatment of UTIs

Drug Class or Drug	What to Monitor	Frequency	Endpoint
Aminoglycosides	SCr	Every 24 hours	Prevention of nephrotoxicity manifested by a rise in SCr
	Aminoglycoside serum concentrations	At least once weekly; more frequently if evidence of changing renal function	Trough serum concentrations less than 2 mg/L (less than 3.42 mmol/L) to prevent nephrotoxicity (less than 8 mg/L or 13.68 mmol/L for amikacin)[a]
Nitrofurantoin	SCr	Only if renal function changing or unstable	Nitrofurantoin metabolites may accumulate in renal insufficiency and lead to neuropathy; avoid in CrCl less than 40 mL/minute

[a]Streptomycin concentrations are different than those listed here; because streptomycin is not used to treat UTIs, monitoring for this agent is not included.
CrCl, creatinine clearance; SCr, serum creatinine.

of patients, a sulfonamide (not in the third trimester due to concerns for hyperbilirubinemia), amoxicillin, amoxicillin-clavulanate, cephalexin, or nitrofurantoin are effective treatment options. Tetracyclines and fluoroquinolones should be avoided due to risk of teratogenicity and ability to inhibit cartilage and bone development, respectively. Follow-up usually consists of a urine culture 1 to 2 weeks after completion of therapy, and afterwards monthly until birth.

Catheterized Patients

An indwelling catheter is commonly used in various health care settings, and is associated with UTIs. Bacteria may be introduced into the bladder via the catheter in several ways. These include direct infection introduction during catheterization (via colonization and subsequently traveling the length of the catheter through bacterial motility or capillary action). UTIs as a result of an indwelling catheter are common and occur at a rate of 5% per day of catheter presence.[25]

The approach in the setting of a patient with bacteriuria and an indwelling urinary catheter follows two paths. The first, in asymptomatic patients with catheterization, is to hold antibiotics and remove the catheter if possible. The second as in the above-described patient who subsequently becomes symptomatic, antibiotics should then commence with removal of the catheter if possible. In both of the above situations, if discontinuation of the catheter is not possible, the patient should be re-catheterized with a new urinary catheter if the previous catheter is greater than 2 weeks old.

UTIs in Men

Although UTIs in men are not always complicated by definition, due to the relative infrequency of UTIs in men compared to women, an abnormality (structural or functional) should be suspected and therefore treated as a probable complicated infection until proven otherwise. For this reason, men should not be treated with a single dose or short course of therapy if diagnosed with a UTI. Typically these patients will receive 2 weeks of therapy, and in situations of failure may be treated up to 6 weeks, particularly if a prostatic source of infection is suspected. Prostatic enlargement, as previously mentioned, is a risk factor in men, and the prevalence of **benign prostatic hyperplasia** in the elderly population may predispose this population to UTIs.

OUTCOME EVALUATION

Outcome Parameters and Associated Goals

- Monitor the patient for resolution of symptoms (Table 76–4) Goal: 48 to 72 hours to resolution
- If possible, follow-up on susceptibilities of the infecting organism (urine culture)
- Repeat culture is necessary only if symptoms do not acutely abate or reinfection or recurrence occurs



Patient Care and Monitoring

1. Assess the patient's symptoms to determine response to the antimicrobial regimen you have chosen.
2. Review any microbiologic data:
   - Based on culture and Gram stain (if available), is your empiric selection reasonable?
   - Based on culture and susceptibility data (if available), are there any changes that need to be made from your initial empiric antimicrobial selection (i.e., resistance to the regimen initially selected)?
3. Determine if the patient would benefit from prophylactic therapy (recurrent UTIs secondary to, for example, chronic urinary catheterization due to paraplegia).
4. Evaluate the patient for the presence of adverse drug reactions, drug allergies, and potential drug interactions.
5. Stress the importance of complying with the prescribed antimicrobial regimen, and to follow-up with the health care provider if signs and symptoms recur.

ABBREVIATIONS

CFU: colony-forming units
CrCl: Creatinine clearance
SCr: Serum creatinine
UTI: Urinary tract infection

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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77 Sexually Transmitted Infections

Marlon Honeywell and Michael Thompson



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Analyze the behavioral considerations and assess the importance of contraception with regard to the contributing factors.
2. Apply the "expedited partner treatment" method when recommending treatment.
3. Identify the patient populations that are epidemiologically affected.
4. Identify causative organisms.
5. Devise a list of the clinical signs and symptoms corresponding to each disease state and classify patients based on recommended criteria.
6. Select appropriate diagnostic procedures.
7. Identify treatment regimens and recommend therapy when appropriate.
8. Design a patient care plan based on the monitoring parameters.

Key Concepts

❶ In order to yield positive results in terms of counseling a patient, intimate, friendly and knowledgeable clinician contact is vital. Additionally, patients, especially adolescents, should be counseled on the importance of using condoms properly.

❷ Generally, when treating a sexually transmitted infection (STI), the index patient should be provided with a sufficient quantity of medication for the partner to be treated, increasing the probability that the initial infection will be cured in both patients.

❸ When diagnosing and treating gonorrhea, assume co-infection with *Chlamydia trachomatis*; treatment recommendations should cover both organisms.

❹ Parenteral penicillin is the drug of choice for all stages of syphilis.

❺ The 5-nitroimidazoles are the standard therapy for trichomoniasis.

❻ Due to the variable appearance of genital warts, treatment may be based on the size, site, and morphology of the lesions. Additionally, switching to alternate therapy is appropriate if there has been no response after three treatment cycles.

❼ Therapy for genital herpes is generally based on patient compliance, host immunity, pregnancy, and observed symptoms.

❽ Bacterial vaginosis may be diagnosed according to the Amsel or Nugent criteria.

❾ With any suspicion of pelvic inflammatory disease, broad-spectrum coverage should be instituted immediately.

❿ Due to the low specificity of culture and clinical diagnosis, the multiplex polymerase chain reaction has been employed successfully in diagnosing *Haemophilus ducreyi*.

Though we have made many advances in medicine, age-old problems of infectious disease still plague us.[1] Even with the discovery of newly improved antibiotics, very few sexually transmitted infections (STIs) have been completely eliminated. Many have re-emerged secondary to modern social trends of promiscuity, and some as a result of the human immunodeficiency virus (HIV) epidemic, socioeconomic concerns, and the global lack of intimate preventive education. Educating the public has been shown to decrease the probability of infection in some individuals; however, this tactic alone may not be sufficient. *Globally, production of positive results, especially in younger patients and adolescents, may also require intimate, friendly, and knowledgeable clinician contact* ❶.

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BEHAVIORAL CONSIDERATIONS

The correlation between risky sexual behavior and STIs is well documented.[2] Inconsistent and incorrect condom use has attributed to a rise in new STIs. *Assuming that patients, especially adolescents, consistently use and understand how to use condoms can be detrimental and may contribute to nonpharmacologic mismanagement.*[3] ❶ In addition to the increasing number of adolescents engaging in unsafe sexual practices is a high incidence of men who have sex with men (MSM). Studies demonstrate that many MSM do not disclose their HIV status. This "don't ask, don't tell" theory has been linked to an upsurge in newly diagnosed HIV infections and STIs among previously non-infected people.[4]

GENERAL APPROACH

Optimally, both sex partners should be treated simultaneously for a STI; however, this is difficult to accomplish. *Clinics and health departments often proactively attempt dual treatment by providing a prescription for the partner to the* ***index patient****, a practice commonly known as expedited partner treatment* ❷.

GONORRHEA

Gonorrhea is a curable STI caused by the gram-negative diplococcus *Neisseria gonorrhoeae*. Proper therapeutic management with antimicrobial agents is essential to eradicate this infection and prevent the development of associated sequelae.

Epidemiology

In the United States, the highest rate of gonococcal infection is seen in both sexes within the 15- to 24-year-old age groups; more cases are reported in men. It is estimated that approximately 600,000 new cases occur annually in the United States.[5] A variety of factors is associated with an increased risk for this disease, including ethnicity, low socioeconomic status, and illicit drug use. The risk of a cervical infection after a single episode of vaginal intercourse is approximately 50% and increases with multiple exposure. Furthermore, rates of reinfection are significantly higher among minorities.

Pathophysiology

Attachment to mucosal epithelium, mediated in part by pili and opa, is followed by penetration of *N. gonorrhoeae* through epithelial cells to the submucosal tissue within 24 to 48 hours. A vigorous response by neutrophils begins with sloughing of the epithelium, development of submucosal microabscesses, and exudation of pus. Stained smears usually reveal large numbers of gonococci within a few neutrophils, whereas most cells contain no organisms.[6]



Patient Encounter, Part 1

LK is a 24-year-old African-American male who visits a clinic complaining of profuse urethral discharge for the past several days. He also complains of rectal itching that has been occurring since yesterday. The patient admits to having sexual intercourse, without protection, 10 days prior with a female he met at a party.

- What information is suggestive of gonorrhea?
- What potential risk factors for STIs are present?
- What information is needed prior to developing a treatment plan?

Diagnosis

Several laboratory tests are available to aid in the diagnosis of gonorrhea and include gram-stained smears, culture, or the DNA hybridization probe.



Patient Encounter, Part 2

PMH
Currently receiving no medications
Diagnosed and treated for syphilis 3 years ago
Allergic to penicillins (anaphylactic reaction 5 years ago)

FH
Noncontributory

SH
Smokes 2 packs per day; drinks alcohol (beer) daily
Admits to having unprotected sex frequently

ROS
c/o severe lower back pain, (+) for pain in testicles, (+) urethral discharge, (+) rectal itching and discharge

PE
VS: Blood pressure 140/72 mm Hg, pulse 77 bpm, temperature 37°C (98.6°F)
Exam: WNL except notable exudates oozing from urethral opening after urination

Labs
Urethral discharge swab revealed *N. gonorrhoeae*

- Given this additional information, what is your assessment of the patient's condition?
- Identify your treatment goals for the patient.
- What pharmacologic alternatives are available for patient?



Patient Encounter, Part 3

Unprotected sex is a major risk factor for contracting STIs and this patient's symptoms are consistent with gonorrhea, as purulent urethral discharge is suggestive of this infection. In addition, the incubation period is also evidence that the infection could be gonococcal. Infection with *C. trachomatis* is usually associated with a very watery discharge and this patient lacks the characteristic ulcerations commonly observed with other STIs such as syphilis and herpetic infection.

Rectal itching with anal discharge in a male patient is highly suggestive of homosexual activity. Heterosexual women may become infected rectally due to the spread of the infection into the anal area, but this typically does not occur in men. Prior to designing an adequate therapeutic regimen for this patient, a more detailed history reveals that he has experienced an anaphylactic reaction to penicillins in the past. This finding is significant because it may limit the ability to utilize a cephalosporin as the initial drug of choice since cross-allergic reactions may occur. If cephalosporin therapy is to be avoided, a fluoroquinolone may be beneficial. Levofloxacin 500 mg orally once daily for 7 days may be prescribed to treat *N. gonorrhoeae* and provide effective coverage for *C. trachomatis*.



Clinical Presentation of Gonorrhea[7,15]

General
- Purulent discharge

Signs
- Painful or swollen testicles
- Tubal scarring

Symptoms
Men:
- May be asymptomatic, though acute urethritis is the predominant manifestation
- Urethral discharge and dysuria, usually without urinary frequency or urgency
- When compared with nongonococcal urethritis, the discharge in gonococcal urethritis is generally more profuse and purulent
- Pain during urination

Women:
- Cervicitis, urethritis, increased vaginal discharge, dysuria and intermenstrual bleeding
- Pain during urination
- Abdominal pain

Treatment

Desired Outcome
The desired outcome is complete eradication of *N. gonorrhoeae.*

PharmacologicTherapy[7]
Patients infected with gonorrhea often are co-infected with Chlamydia trachomatis *and should receive therapy to eradicate both organisms concurrently.* ❸ Though fluoroquinolones and broad-spectrum cephalosporins have been effective in the treatment of gonorrhea, recent evidence suggests that resistant strains of *N. gonorrhoeae* have emerged. In far eastern countries, as many as 50% of gonococcal strains exhibit decreased susceptibility to fluoroquinolones. Therefore, monitoring for fluoroquinolone resistance is now essential to ensure proper treatment and to ascertain the maximum time that this class may be employed as a treatment option.

Treatment of gonorrhea may vary according to clinical presentation and is indicated as follows:

Recommended Regimens (All Regimens Are Given for One Dose Only)
- Ceftriaxone 125 mg intramuscularly
- Ciprofloxacin 500 mg orally
- Cefixime 400 mg orally

Coverage for Co-Infection with Chlamydia trachomatis
- Azithromycin 1 g orally as a single dose

or

- Doxycycline 100 mg orally twice daily for 7 days

Treatment of Gonorrhea in Special Situations
Uncomplicated infections of the cervix, urethra, and rectum can be treated with one of the following regimens in adults:

Recommendations During Pregnancy
- Ceftriaxone 125 mg intramuscularly as a single dose plus therapy recommended for co-infection with *Chlamydia*
- Spectinomycin 2 g intramuscularly as a single dose plus therapy recommended for co-infection with *Chlamydia*
- Doxycycline and fluoroquinolones are contraindicated

Recommendations for Disseminated Gonococcal Infection
- Ceftriaxone 1 g intramuscularly or intravenously every 24 hours for 24 to 48 hours

After improvement begins, therapy is then switched to *one* of the following 7-day oral regimens:

- Cefixime 400 mg orally twice daily
- Ciprofloxacin 500 mg orally twice daily

Uncomplicated Infections of the Cervix, Urethra, and Rectum in Children (less than 45 kg)
- Ceftriaxone 125 mg intramuscularly as a single dose
- Spectinomycin 40 mg/kg intramuscularly as a single dose

- Ceftriaxone 50 mg/kg intramuscularly or intravenously once daily for 7 days in children with bacteremia or arthritis

Gonococcal Conjunctivitis

- Ceftriaxone 1 g intramuscularly once for adults
- Ceftriaxone 25 to 50 mg/kg intravenously or intramuscularly as a single dose for ophthalmia neonatorum or infants born to mothers with gonococcal infection as prophylaxis

Patient Care and Monitoring

Monitoring is generally not required.

CHLAMYDIA

Epidemiology

Infection with *C. trachomatis* has increased dramatically in recent years. Presently, this bacterium is the most common cause of nongonococcal urethritis, accounting for as many as 50% of cases. More than half of men infected with *C. trachomatis* exhibit symptoms, whereas, approximately 70% to 80% of women are asymptomatic.

Pathophysiology

C. trachomatis possesses characteristics resembling both bacteria and viruses. Its major membrane is comparable to that of gram-negative bacteria, although it lacks a peptidoglycan cell wall and requires cellular components from the host for replication. Chlamydia transmission risk is thought to be less than that of gonorrhea.

Diagnosis

Tests used to diagnose *C. trachomatis* include culture, the enzyme immunoassay, the DNA hybridization probe, or the direct fluorescent monoclonal antibody test. Given the fact that most women are asymptomatic, an annual screening or physical is necessary, as early detection may reduce rates of transmission.



Clinical Presentation of Chlamydia[8]

General
- Asymptomatic

Signs
- Beefy red cervix which bleeds easily (women)

Symptoms
- When present, the urethral discharge is watery and less purulent than that seen with acute gonococcal urethritis. Complications resulting from lack of treatment or inadequate treatment include: epididymitis (in males), and pelvic inflammatory disease including associated complications in women.

Other Diagnostic Tests
- Culture is usually positive for both chlamydia and gonorrhea.

Treatment[8]

Uncomplicated urethral, endocervical, or rectal infection in adults:
Recommended:
- Azithromycin 1 g orally for one dose only

or
- Doxycycline 100 mg orally twice daily for 7 days

Urogenital infections during pregnancy:
Recommended:
- Erythromycin base 500 mg orally four times daily for 7 days

or
- Amoxicillin 500 mg orally three times daily for 7 days

Patient Care and Monitoring

Monitoring is generally not required.

SYPHILIS

Syphilis, caused by the spirochete *Treponema pallidum*, can have numerous and complex manifestations. Clinician familiarity, stage-specific diagnosis, and effective treatment are vital. Missed or inappropriately treated syphilis may result in cardiovascular complications, neurologic disease, or congenital syphilis.

Epidemiology

Since the 1940s, the incidence of syphilis declined drastically following the introduction of penicillin, but rose when HIV arrived from obscurity in the 1980s. From 1990 to 2000, the rate declined again by approximately 90%. Unfortunately, recent data confirm a new spike in diagnosed cases among MSM. The 2003 morbidity and mortality report reflects a 62% increase among men and a 53% decrease in women. The disparity among men and women has been observed across racial and ethnic groups and is highest in the South and among non-Hispanic Blacks.[9]

Pathophysiology

T. pallidum rapidly penetrates intact mucous membranes or microscopic dermal abrasions, and within a few hours, enters the lymphatics and blood to produce systemic illness. During the secondary stage, examinations commonly demonstrate abnormal findings in the cerebrospinal fluid (CSF). As the infection progresses, the parenchyma of the brain and spinal cord may subsequently be damaged.

Stages[10]

- *Primary syphilis:* Usually manifests as a solitary, painless chancre. Primary syphilis develops at the site of infection

approximately 3 weeks after exposure to *T. pallidum*; the chancre is highly infectious.

- *Secondary syphilis:* Without appropriate treatment, primary syphilis will advance to secondary syphilis, a stage usually apparent from its clinical symptomatology. Symptoms include fatigue, diffuse rash, fever, lymphadenopathy, and genital or perineal condyloma latum. Also, the skin is most often affected and a rash may present as macular, macropapular, or pustular lesions, or involve skin surfaces including the palms of the hands and soles of the feet.
- *Latent syphilis:*
  1. *Early latent:* Involves the first year after infection and may be established in patients who have seroconverted in the past year, who have had symptoms of primary or secondary syphilis in the past year, or who have had sex with a partner with primary, secondary, or latent syphilis in the past year.
  2. *Late latent:* Patients should be considered to have late latent syphilis if the aforementioned criteria (early latent) are not met. In both stages, patients are usually asymptomatic and the lesions noted in the primary and secondary phase usually resolve; however, individuals are still seropositive for *T. pallidum*.
  3. *Tertiary syphilis:* Develops years after the initial infection and may involve any organ in the body.

Congenital Syphilis

Congenital syphilis is a condition in which the fetus is infected with *T. pallidum* as a result of the hematogenous spread from an infected mother, although transmission may also occur from direct contact with the infectious genitalia of the mother. Since the primary stage of syphilis is characterized by spirochetemia, infectious rates of the fetus are nearly 100% if the mother has primary syphilis.[11]

Diagnosis

Diagnostic procedures include dark-field microscopy[12], nontreponemal exams[10] (i.e., the Venereal Disease Laboratory and the rapid plasma reagin test), and treponemal exams (i.e., enzyme immunoassay, the *T. pallidum* hemagglutination test, the fluorescent treponemal antibody test, and the enzyme-linked immunosorbent assay).

Treatment

Desired Outcome

After confirming the diagnosis of syphilis, the desired outcome is a four-fold decrease in quantitative non-treponemal titers over a 6-month period and within 12 to 24 months after treatment of latent or late syphilis. An algorithm for the treatment of syphilis is shown in Fig. 77–1.

With regard to neurosyphilis, a reduction in neurologic manifestations is desired, which may include seizures, paresis, hyperreflexia, visual disturbances, hearing loss, neuropathy, or loss of bowel and bladder function. In late neurosyphilis, vascular lesions (meningovascular neurosyphilis) may also be observed; thus, a reduction in the number of observed lesions is warranted. A diminution in CSF white blood cell (WBC) count (less than $10 \times 10^3/\mu L$ [$10 \times 10^9/L$]) or protein levels (0.05 g/dL [0.5 g/L]) is also preferred.

Pharmacologic Treatment

Parenterally administered penicillin is recommended for all stages of syphilis. ❹ Alternative agents may be used in allergic individuals and include doxycycline, minocycline, tetracycline, or erythromycin base or stearate. Some patients may not respond favorably to alternative modalities. Therefore, in patients who must be administered penicillin (i.e., patients who are pregnant or have central nervous system [CNS] involvement) or are allergic, **desensitization** must be performed before the drug is initiated.

Additionally, some patients may experience fever, chills, tachycardia, and tachypnea, a condition commonly known as the Jarisch-Herxheimer reaction. Postulated to occur secondary to spirochete lysis and proinflammatory cytokine cascades, this reaction may transpire as early as 2 hours after penicillin administration and usually resolves within 24 hours. Treatment is supportive and may include antipyretic and anti-inflammatory agents, as well as fluid resuscitation and bed rest.

Pertinent information related to benzathine penicillin G is found in Table 77–1.

Primary Syphilis

- ***Drug of choice:*** Benzathine penicillin, 2.4 million units intramuscularly as a single dose.
- ***Alternatives:*** Oral doxycycline 100 mg twice daily for 2 weeks or tetracycline 500 mg by mouth four times daily for 2 weeks. Limited literature also supports the use of ceftriaxone 1 g intramuscularly or intravenously once daily for 10 days or oral azithromycin as a single 2-g dose.[13]

Secondary and Early Latent Syphilis

Treatment modalities administered in primary syphilis are also effective in secondary syphilis and latent syphilis (less than 1 year duration).

Tertiary Syphilis

- *Drug of choice:* Benzathine penicillin 2.4 million units administered intramuscularly once weekly for 3 weeks.
- *Alternatives:* In non-pregnant patients with a penicillin allergy, alternative regimens include doxycycline 100 mg orally two times daily for 4 weeks or tetracycline 500 mg orally four times daily for 4 weeks.

Gummatous and Cardiovascular Syphilis

As long as no evidence of CNS involvement exists, antibiotic therapy for **gummatous** and cardiovascular syphilis is identical to that for tertiary syphilis.

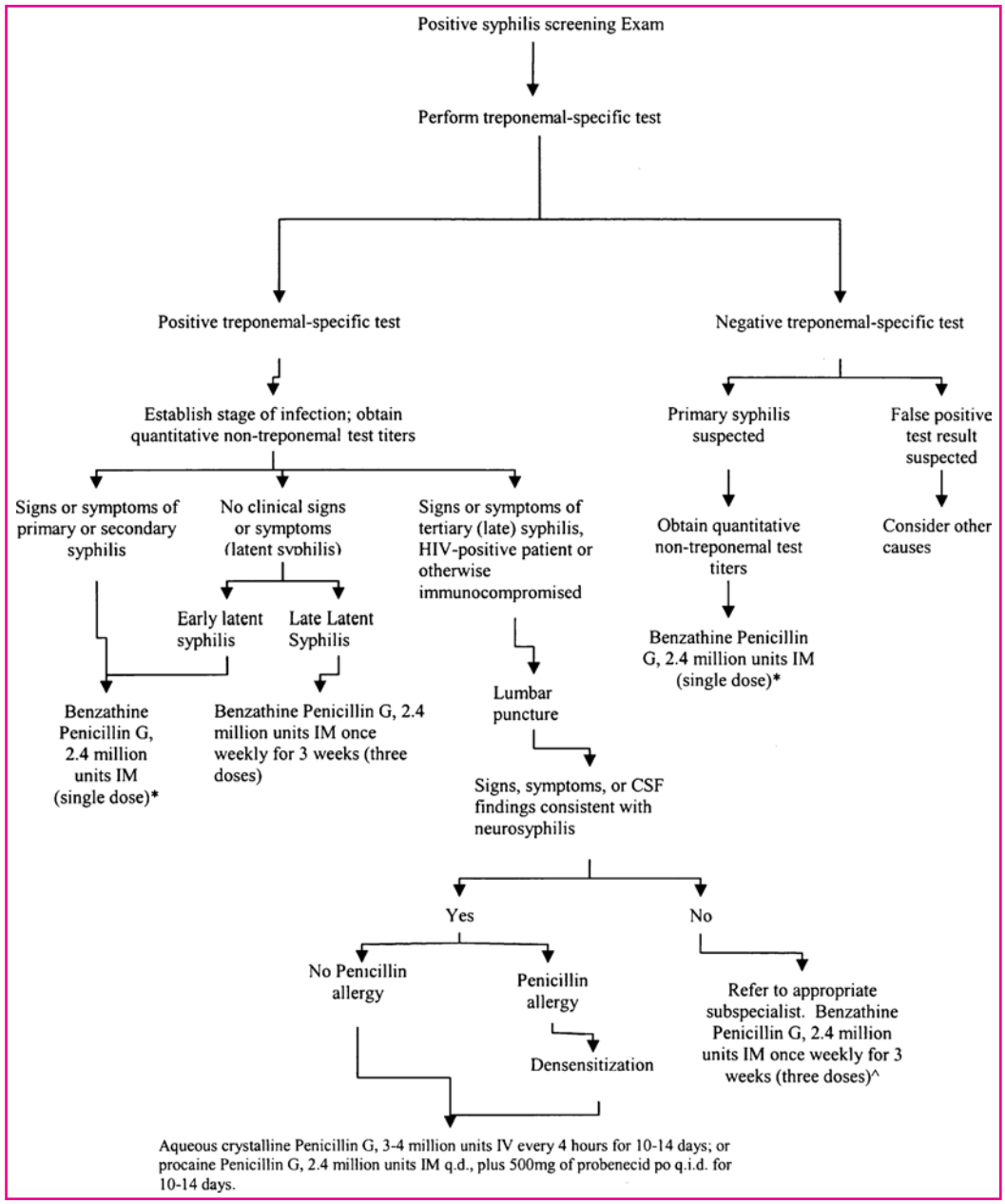


FIGURE 77–1. Treatment of syphilis.
*Alternative treatments for non-pregnant penicillin-allergic patients: doxycycline 100 mg orally twice daily for 2 weeks, or tetracycline 500 mg four times daily for 2 weeks; limited data support ceftriaxone 1 g once daily IM or IV for 8 to 10 days; or azithromycin, 2 g orally (single dose).
^Alternative treatments for non-pregnant penicillin-allergic patients: doxycycline, 100 mg orally twice daily for 4 weeks, or tetracycline 500 mg orally four times daily for 4 weeks.
CSF, cerebrospinal fluid; IM, intramuscularly.
Brown D, Frank J. Diagnosis and Management of Syphilis. American Family Physician. 2003;68(2):283–290.

Neurosyphilis

As an effective treatment for neurosyphilis, the Centers for Disease Control and Prevention (CDC) endorses two regimens of penicillin. Alternatively, ceftriaxone may also be prescribed.[13]

The regimens are as follows:

Drugs of choice:

- Aqueous penicillin G: 3 to 4 million units administered intravenously every 4 hours for 10 to 14 days
- Procaine penicillin G: 2.4 million units administered intramuscularly once daily, plus probenecid 500 mg orally four times daily for 10 to 14 days.

Congenital Syphilis

Maternal Syphilis After screening the mother, guidelines recommend that treatment decisions be based on:

- Diagnosing syphilis in the mother
- Confirming the adequacy of maternal treatment

TABLE 77–1. Benzathine and Procaine Penicillin G Informational Chart[a]

Categories	Benzathine Penicillin G	Procaine Penicillin G
Mode of action	Interferes with bacterial cell wall synthesis during active multiplication, causing cell wall death and resultant bactericidal activity	Inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins, which in turn inhibit the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls; bacteria usually lyse from ongoing autolytic enzyme activity
Pharmacodynamics	Duration: 1–4 weeks Absorption IM: slow Time to peak serum levels: 12–24 hours	Duration: 15–24 hours; Absorption IM: slow; Distribution: Poor blood–brain barrier penetration, enters breast milk; Metabolism: ≅30% hepatic inactivation; Protein binding: 65%; Time to peak serum levels: 1–4 hours; Excretion: Urine (60–90% as unchanged drug); Clearance: Renal
Adverse reactions	CNS: Convulsions, confusion, drowsiness, myoclonus, fever; Dermatologic: Rash; Metabolic: Electrolyte imbalance; Hematologic: Positive Coombs test, hemolytic anemia; Local: Pain, thrombophlebitis; Renal: Acute interstitial nephritis; Miscellaneous: Anaphylaxis, hypersensitivity, Jarisch-Herxheimer reaction	CNS: Seizures, confusion, drowsiness, myoclonus, CNS stimulation; Cardiovascular: Myocardial depression, vasodilation, conduction disturbances Hematologic: Positive Coombs test, hemolytic anemia, neutropenia; Local: Thrombophlebitis, sterile abscess at injection site; Renal: Interstitial nephritis; Miscellaneous: Pseudoanaphylactic reactions, hypersensitivity, Jarisch-Herxheimer reaction, serum sickness
Monitoring parameters	Observe for anaphylaxis during first dose	Periodic renal and hematologic function tests with prolonged therapy; fever, mental status, WBC count
Test interactions	Positive Coombs (direct) test, false-positive urinary and/or serum proteins, false-positive or false-negative urinary glucose using Clinitest	Positive Coombs (direct) test, false-positive urinary and/or serum proteins
Pregnancy category	B	B
Lactation	Enters breast milk	Enters breast milk
Stability	Refrigerate	Refrigerate
Nursing Implications	Monitor: CBC, urinalysis, renal function tests	Periodically evaluate renal and hematologic systems during prolonged therapy; do not inject into gluteal muscle in children less than 2 years of age
Availability	BiCillin® L-A: 600,000 U/mL (1, 2, 4 ml); Permapen® Isoject: 600,000 U/mL (2 mL)	Injection, suspension: 600,000 U/mL (1, 2 mL)
Combination	Bicillin® C-R: (1, 2, 4 mL) Bicillin® C-R 900/300: (2 mL)	Same

CBC, complete blood cell count; CNS, central nervous system; IM, intramuscular; WBC, white blood cell count.
Lacy C, Armstrong L, Goldman M, Lance L. Lexi-Comp's Drug Information Handbook, 12th edition. 2004:1128–1132.

- Ascertaining clinical, laboratory, or radiographic evidence of syphilis in the infant
- Comparing maternal non-treponemal titers (at delivery) with the infant's non-treponemal titers.

In treatment of maternal syphilis, recommend the following regimens:

- *Drug of choice:* Benzathine penicillin G 2.4 million units or 7.2 million units intramuscularly over 3 weeks if the duration of syphilis has been at least a year
- *Alternatives:* Procaine penicillin 0.6 to 0.9 million units intramuscularly for 10 to 14 days, or ceftriaxone 1 g daily intramuscularly or intravenously for 8 to 10 days.

In women that experience uterine cramping, pelvic pain, or fever, administer acetaminophen to combat these symptoms. Additionally, make certain that the patient is well hydrated and has the opportunity to rest.

Congenital Syphilis[14]

- *Asymptomatic neonates:* 50,000 U/kg of benzathine penicillin G in a single intramuscular dose

- *Symptomatic neonates:* 50,000 U/kg of aqueous crystalline penicillin G every 12 hours intramuscularly for the first 7 days of life, then every 8 hours for 3 days, or procaine penicillin G 50,000 IU/kg intramuscularly as a single dose daily for 10 days

Patient Care and Monitoring

The CDC has provided patient care monitoring guidelines for syphilis (Fig. 77–2).[10]

Primary and Secondary Syphilis

- After 6 and 12 months of treatment, re-examine the patient and recommend a follow-up non-treponemal titer. If the patient is asymptomatic, yet has a four-fold increase in non-treponemal titer or persistent or recurrent symptoms are observed, order an HIV test and a lumbar puncture; if the patient is HIV-positive, suggest an infectious disease consult.
- In patients who are both negative for HIV and the lumbar puncture, administer benzathine penicillin G 2.4 million units intramuscularly once weekly for 3 additional weeks. Perform a patient follow-up in 6 months including a clinical examination and another non-treponemal titer. In HIV-negative patients with lumbar puncture findings compatible with neurosyphilis, treat the patient accordingly for neurosyphilis.
- Six months after the original diagnosis, institute a standard clinical follow-up exam in patients who show no symptomatology and a four-fold decrease in non-treponemal titers. By testing and observing the patient for signs of remission, you

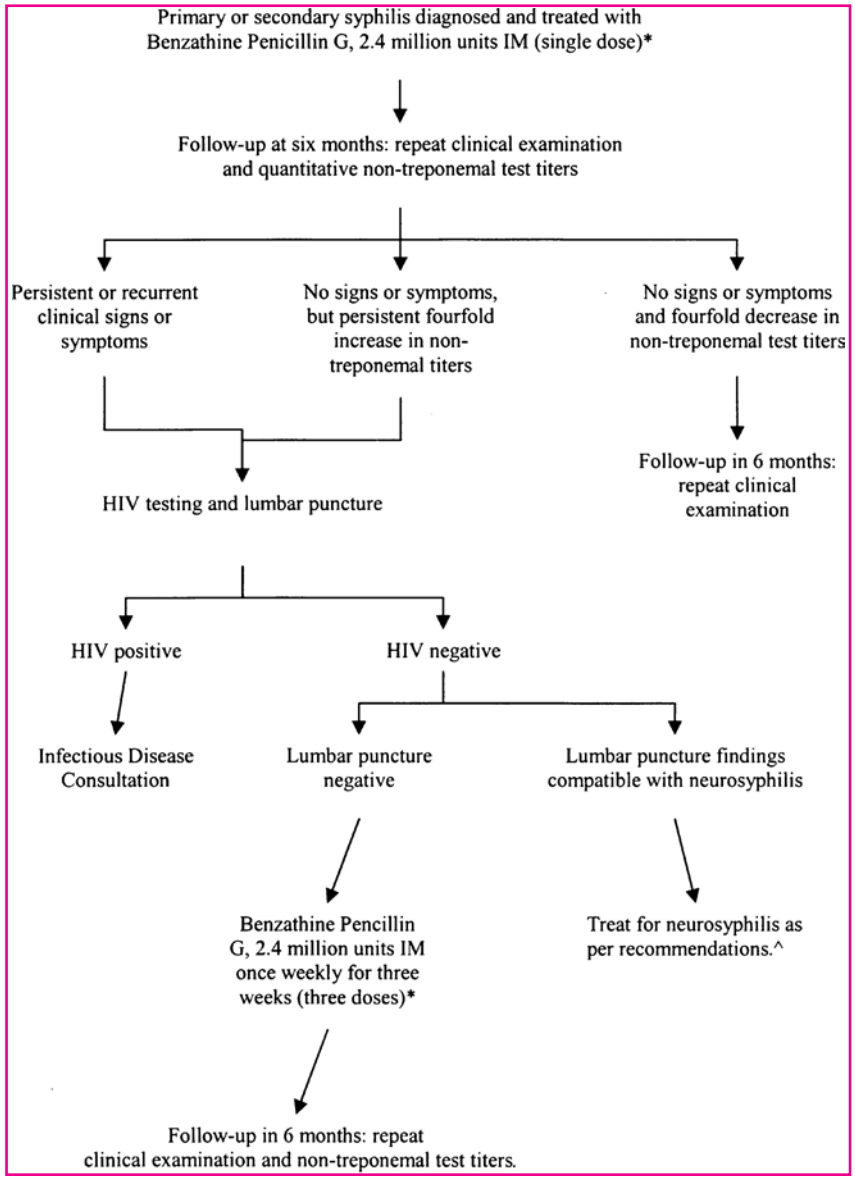


FIGURE 77–2. Patient care monitoring for syphilis.
*See text for alternative treatment recommendations for non-pregnant penicillin-allergic patients.
^See text for treatment recommendations for neurosyphilis.
HIV, human immunodeficiency virus; IM, intramuscularly.
Brown D, Frank J. Diagnosis and Management of Syphilis. American Family Physician. 2003;68(2):283–290.

may be able to initiate proper treatment or recommend a consult in a timely fashion, thereby decreasing the propensity of the patient's condition to advance to a higher stage.

Early and Late Latent Syphilis

- Order non-treponemal titers 6, 12, and 24 months after instituting treatment for early or late latent syphilis.
- Strongly consider neurosyphilis in individuals who show a four-fold increase in titers, patients who have an initially high titer (1:32 or greater) that fails to decline at least four-fold, HIV-positive patients, and those who develop symptoms consistent with neurosyphilis.

Neurosyphilis

- Follow-up is dependent on the CSF findings. If **pleocytosis** is present, re-examine the CSF every 6 months until the WBC count normalizes. Consider recommending a second course of treatment if the CSF white count does not decline after 6 months or completely normalize after 2 years.[15] Failure to normalize may require retreatment; most treatment failures occur in immunocompromised patients.

Congenital Syphilis

- Observe the patient for changes in clinical features; hepatomegaly, jaundice, and bone changes will usually resolve in 3 months.
- Monitor elevated serologic markers (non-treponemal exams) for reduction. Given effective treatment, clinical features will usually disappear after 6 months. On this basis, evaluate seropositive infants periodically for at least 6 months.[14]

TRICHOMONIASIS

Trichomoniasis is caused by the protozoan *Trichomonas vaginalis* and is far more prevalent than *C. trachomatis* or *N. gonorrhoeae*. In the United States, it is estimated that 5 million new cases appear annually, compared with 3 million chlamydial and 650,000 gonococcal cases annually.[16]

Pathophysiology

T. vaginalis may be isolated from the vagina, urethra, and Bartholin or Skene glands. After attachment to the host cells, it ignites an inflammatory response exhibited as a discharge containing elevated levels of polymorphonuclear leukocytes. The protozoal pathogen causes direct damage to the epithelium, leading to microulcerations.

Diagnosis

Diagnosis is usually performed with a wet mount or Papanicolaou smear.



Clinical Presentation of Trichomoniasis[16]

General
- Asymptomatic

Signs
- Strawberry cervix (women)
- Colpitis macularis (women)
- Prostatitis or epididymitis (men)

Symptoms
- Vaginal/vulvar erythema
- Excessive yellow-green discharge
- Vulvar itching
- Vaginal odor
- Urethral discharge or irritation
- Dysuria
- Vaginal pH greater than 4.5

Treatment

Desired Outcome

The desired outcome is the complete eradication of *T. vaginalis* in both partners and elimination of the signs and symptoms observed.

Pharmacologic

The 5-nitroimidazoles have been the standard therapy for trichomoniasis for over 40 years. ❺ Drugs included in this class are metronidazole, tinidazole, ornidazole, and secnidazole; metronidazole and tinidazole are the only drugs in this class available in the United States.

Metronidazole

Metronidazole may be administered orally as a single 2-g dose or 500 mg twice daily for 7 days.[17] Pregnant women should be prescribed the single dose of metronidazole. Cure rates are greater than 90% when metronidazole is administered as either a single 2-g dose or a 7-day regimen. Possible adverse effects include an unpleasant metallic taste, reversible neutropenia, urticaria, rash, flushing, dry mouth, darkened urine, and a disulfiram-like reaction.

Tinidazole

Tinidazole, a second-generation nitroimidazole with protozoal and anaerobic activity, has been available outside the United States for over 30 years.[18] Recently, the Food and Drug Administration (FDA) approved it for use in the United States. As a single 2-g dose, tinidazole has an efficacy equivalent to a 2-g dose of metronidazole. Tindazole also has a longer half-life than metronidazole, 14 and 7 hours respectively, and penetrates into male reproductive tissue better than metronidazole.

Various studies demonstrate the successful use of tinidazole for metronidazole-resistant trichomoniasis.[19] Possible side effects include a metallic taste, dizziness, loss of coordination, seizures, severe diarrhea, darkened urine, nausea, vomiting, and a swollen or discolored tongue.

Patient Care and Monitoring

Monitoring for *T. vaginalis* is generally not required.

GENITAL WARTS

Genital warts, caused by the human papillomavirus (HPV), are regularly encountered in primary care. Responsible for various visible, **keratotic,** and non-keratotic manifestations, HPV has nearly 120 noted strains, some of which have been linked to squamous cell carcinoma.[20]

Epidemiology

Affecting over 20 million Americans, HPV is one of the most common STIs in the United States, with an estimated prevalence of approximately 15%. Furthermore, among adolescent and college-aged women, HPV may be the most common STI.[15] The frequency of cervicovaginal HPV infection among sexually active women has been observed at 43%, with the greatest incidence noticed in men with three or more sex partners and women whose most recent regular sexual partner had two or more lifetime partners.

Pathophysiology

HPV replicates in terminally differentiated squamous cells in the intermediate layers of the genital mucosa. Hence, these effects of the viral early region genes on DNA synthesis are critical for viral survival. Genital warts are the clinical manifestation of active viral replication and virion production at the infection site.

Diagnosis

- Diagnosis is generally made from the clinical presentation and may be classified into several categories: classic condyloma acuminata, which are pointed or cauliform; keratotic warts with a thick, horny surface resembling common skin warts; and flat warts, frequently observed on the surface.
- Tissue **biopsy** or viral typing is only indicated if diagnosis is uncertain and is not recommended for patients with routine or typical lesions.
- Since HPV has been recently discovered to be highly associated with cervical cancer and since there are more than 20 different cancer-associated HPV types, patients who are diagnosed with HPV should be tested for cervical cancer.



Clinical Presentation of Genital Warts[21]

General
- Appear as rough, thick cauliflower-like lesions

Signs
- Black dots within warts
- Disrupted surface

Symptoms
- Anogenital pruritus
- Burning
- Vaginal discharge or bleeding
- Although rare, **dyspareunia** may occur with vulvovaginal condyloma

Treatment

Desired Outcome

Removal of visible warts and reduction of infectivity are the goals of treatment. According to the Department of Vaccines and Other Biologicals, a vaccine may be available in the near future to aid in reducing the spread of the disease.[22]

Pharmacologic

Currently, the choice of therapy is based on the size, site, and morphology of lesions, as well as patient preference, treatment costs, convenience, adverse effects, and patient experience. Assuming that the diagnosis is correct, switching to alternate therapy is appropriate if there has been no response observed after three treatment cycles. ❻ A comparison of adverse effects related to treatment options may be found in Table 77–2.

TABLE 77–2. Comparison of Adverse Effects Seen with Treatments for Genital Warts

Treatment	Adverse Effects
Podofilox	Burning at site of application, pain, inflammation
Imiquimod	Erythema, irritation, ulceration, pain, burning, edema, pigmentary changes
Podophyllin resin	Local irritation, erythema, burning, soreness at application site; possibly oncogenic
Bichloroacetic and trichloroacetic acid	Local irritation and pain, minimal systemic effects
Cryotherapy	Pain or blisters at application site
Surgical excision	Pain, bleeding, scarring; possible burning or allergic reaction to local anesthetic
Vaporization	Pain, bleeding, scarring; risk of HPV spreading via smoke plumes
Intralesional interferon	Burning, itching, irritation at injection site, systemic myalgia, headache, fever, chills, leukopenia, elevated liver enzymes, and thrombocytopenia

HPV, human papillomavirus.

[20]Kodner C, Nasraty S. Management of Genital Warts. American Family Physician. 2004;70(12):2335–2342, 2345–2346.
[41]McEvoy G eds. AHFS Drug Information. ASHP. Bethesda, MD. 2005.

Patient-Applied Treatment

Podofilox

- Available as a 0.5% gel or solution containing purified extract of the most active compound of podophyllin
- Arrests the formation of the mitotic spindle, prevents cell division, and may also induce damage in blood vessels within the warts
- The surface area treated must not exceed 10 cm^2, and a maximum of 0.5 mL should be used on a daily basis
- Treatment regimen:

Apply twice daily for three consecutive days followed by four consecutive days without treatment. This cycle may be repeated until there are no visible warts or for a maximum of 4 weeks.

- Side effects are generally local and may include erythema, swelling, and erosions.
- Podofilox is not recommended for use in the vagina, anus, or during pregnancy.

Imiquimod

- A cell-mediated immune response modifier, available as a topical 5% cream in single-dose application packets
- Two recommended dosage regimens:
  1. Apply at bedtime for 3 days, rest for 4 days.
  2. Apply every other day for three applications.
  3. Weekly cycles may be repeated for up to 16 weeks.
- Mild to moderate erythema has been noted with imiquimod use; however, this generally suggests that the drug is reaching a therapeutic range and may be clearing the lesion.[23]

Physician-Applied Treatments

Podophyllin Resin[21,24]

- A 10% to 25% solution of podophyllin resin has been the standard in-office treatment for genital warts.
- It is neurotoxic and due to its systemic absorption; a small amount (no more than 0.5 mL) should be applied.
- Affected area will likely become erythematous and painful within 48 hours of application.
- Treatment regimen:

Topical podophyllin is applied once weekly and the area should be allowed to dry. Immediately following treatment, the dried drug should be removed using alcohol or soap and water. Contraindicated in pregnant patients.

Bichloroacetic and Trichloroacetic Acid

- Excellent when used to treate a few, small, moist lesions.
- May be applied to both keratinized epithelial and mucosal surfaces.
- Available in 80% to 90% concentrations and is not systemically absorbed.
- May be used in pregnancy.
- A noted reaction to these medications is transient burning, and contact with surrounding epithelium may prove to be painful, producing significant local erythema and swelling. To avoid these effects, place petroleum jelly around the external lesion, including unaffected skin, and carefully apply the agent with a small applicator.

Other Treatments[21]

Other treatments may include fluorouracil/epinephrine/bovine collagen gel, an intralesional injection that has been proven effective in clinical trials for refractory patients, or an intralesional injection of interferon.

Ablative Therapy

Several ablative options have been employed in the treatment of genital warts and include cryotherapy, surgical removal, and vaporization.

Special Therapeutic Issues[21,22]

- *Large warts*: Treat warts greater than 10 mm in diameter with surgical excision. Use imiquimod for three to four treatment cycles to reduce the number of warts and improve surgical outcomes. Fifty percent reduction in wart size after four treatment cycles warrants continued use of imiquimod until warts clear or eight cycles have been completed; less than 50% reduction warrants surgical excision or other ablative therapy.
- *Subclinical warts*: Subclinical warts may be identified through colonoscopy, biopsy, acetic acid application, or laboratory serology. However, early treatment has not been linked to a favorable effect during the course of therapy in the index patient or the partner with regard to reduction of the transmission rate.
- *Pregnancy*: Agents contraindicated in pregnancy include podofilox, fluorouracil, and podophyllin. Imiquimod is not approved for use in pregnancy, although it has been considered after signed consent has been obtained. Bichloroacetic and trichloroacetic acid have been used without problems. Ablative therapy is also a viable option.

Patient Care and Monitoring

Monitor patients every 3 to 6 months for a reduction in lesions or disease remission. Monitoring parameters include patient compliance, disease remission, and benign or cancerous tumors.

GENITAL HERPES

Genital herpes, caused by herpes simplex virus (HSV) types 1 and 2, is a common STI for which there is no cure. Once latency is established, neither competent host immunity nor therapeutic agents can eradicate the virus. Currently, there is

no vaccine available for HSV, and it seems that the development of one is unlikely in the near future.

Epidemiology

Despite a decline in the number of bacterial STIs, HSV-2 in adults has increased from approximately 20% to 32%.[25] Prevalence of HSV-2 infection has grown by approximately 30% since the late 1970s, and currently it is believed that over 500,000 new cases of HSV-2 occur annually.

Pathophysiology

Since HSV is only found in humans, infection may only be transmitted from infectious secretions onto mucosal surfaces (i.e., cervix or urethra) or abraded skin. It has also been noted that the virus may survive for a limited amount of time on environmental surfaces.

Diagnosis

Laboratory confirmation is vital to effective treatment of HSV, especially in individuals in whom a clinical diagnosis cannot be obtained. There are several methods by which a definitive diagnosis may be acquired, and these include virologic typing, serologic diagnosis, rapid point-of-care antigen detection, enzyme-linked immunosorbent assay (ELISA), immunoblot, and DNA polymerase chain reaction.[27]

Treatment

Desired Outcome

The desired outcome is to curtail the number of episodic prodromes and to minimize any side effects experienced due to the antivirals.



Clinical Presentation of Genital Herpes[26]

General
- Asymptomatic

Classic Sign
- A cluster of painful vesicles on an erythematous base

Symptoms
- Itching
- Burning
- Tingling
- Groin lump
- Dysuria
- Dyspareunia
- Increased urinary frequency

Other Symptoms
- Ulcerative lesions, fissures, cervicitis

Pharmacologic

Treatment is based on several factors including likelihood of patient compliance, whether it is the first or a recurrent episode, host immunity, and pregnancy. ❼ However, patient response has been linked to the time it takes to initiate treatment after symptom onset.

First Episode

The first episode is a systemic illness associated with the vesicular lesions, may last up to 21 days, usually has an uncomplicated course of infection, and in severe cases may require hospitalization. Several agents have been found to be effective during this period (Table 77–3).[28,29] At the cited dosages, these agents have had excellent outcomes with regard to lesion healing time, viral shedding, and loss of pain. Common adverse effects are nausea, headache, and diarrhea.

Episodic Therapy

In a patient with a previous diagnosis of genital herpes, the appearance of new vesicular lesions is synonymous with HSV reactivation. For most patients, genital herpes recurrence is self-limiting and short-lived, lasting approximately 6 to 7 days.

Suppressive Therapy

Suppressive therapy is effective for controlling all symptoms related to the disease and may impact troublesome complications of infection. Before beginning suppressive therapy, discuss patient expectations. Encourage patients to record any breakthrough episodes, as this may require treatment re-evaluation and adjustment.

Preventive Therapy

Valacyclovir 500 mg orally once daily has been implicated to prevent the sexual transmission of HSV to an uninfected partner. In addition to pharmacologic therapy, counsel patients regarding safe sex practices.

Immunocompromised Patients

Foscarnet, cidofovir, and trifuridine have been administered in acyclovir-resistant patients.[30] These agents are usually reserved for use after other agents have failed because of their associated toxicities.

Pregnancy

Women who are pregnant may transmit the virus to the neonate during delivery. There are two management strategies: cesarean section and antiviral therapy. A few studies indicate that acyclovir 200 mg 4 times daily can be effective.

Neonates

Herpes simplex virus infections should be considered in all neonates who present with nonspecific symptoms such as

TABLE 77–3. Comparison of Antivirals used for Herpes Simplex Infection

Agent	Dose	Side Effects
First Episode		
Acyclovir	*200 mg PO q4hour × 7–10 days* 400 mg PO 3 times daily × 7–10 days[a] 200 mg PO q12hour × 7–10 days[e]	Headache, confusion, nausea, vomiting, thrombocytopenia, renal insufficiency, rash, pruritus, fever, arthralgias, myalgia, thrombotic thrombocytopenic purpura, hallucinations, somnolence, depression
Valacyclovir	*1 g PO 2 times daily × 7–10 days* 1 g PO daily × 7–10 days[d] **or** 500 mg PO daily × 7–10 days[d]	Refer to acyclovir
Famciclovir	250 mg PO 3 times daily × 7–10 days	Refer to acyclovir
Episodic		
Acyclovir	*200 mg PO q4hour × 5 days* **or** 400 mg PO q8hour × 5 days **or** 800 mg PO 2 times daily × 5 days	Refer to acyclovir
Valacyclovir	*500 mg PO 2 times daily × 5 days* 500 mg PO once daily × 5 days[d]	Refer to acyclovir
Famciclovir[c]	*125 mg PO 2 times daily × 5 days* 125 mg PO once daily × 5 days[d]	Refer to acyclovir
Suppressive		
Acyclovir	*400 mg PO 2 times daily up to 1 year* **or** 200 mg PO 3–5 × daily up to 1 year	Refer to acyclovir
Valacyclovir[b]	250 mg PO 2 times daily up to 1 year **or** 500 mg PO once daily up to 1 year **or** 1 g PO once daily up to 1 year	Refer to acyclovir
Famciclovir	*250 mg PO 2 times daily up to 1 year*	Refer to acyclovir
Reserved Agents		
Foscarnet	40 mg/kg IV q8–12hours × 2–3 wk or until clinical resolution is attained	Renal insufficiency, metabolic disturbances, hypophosphatemia
Cidofovir	0.3%, 1%, and 3% topical agent used on a compassionate basis for acyclovir-resistant herpes lesions (3–7 days)	Application site reactions, lesion recrudescence
Trifluridine	1% topical agent used for acyclovir-resistant herpes infections for 7–14 days	Transient burning or stinging, palpebral edema, superficial punctuate, keratopathy, changes in intraocular pressure

[a]The Centers for Disease Control and Prevention states that this dosage may be useful for immunocompromised patients.
[b]Dose is based on the number of symptomatic recurrences.
[c]If administered at the same frequency, there is no evidence that 250 mg or 500 mg will provide greater benefit than 125 mg.
[d]Dose for administration in renal impairment (CrCl 30 mL/minute or less).
[e]Dose for administration in renal impairment (CrCl 10 mL/minute or less).
Italicized data indicate recommended dosages.
CrCl, creatinine clearance; IV, intravenously; PO, orally.
McEvoy G eds. AHFS Drug Information. ASHP. Bethesda, MD. 2005.

fever, poor feeding, lethargy, or seizures in the first month of life. Infants suspected to have or who are diagnosed with an HSV infection should be treated parenterally. Acyclovir 60 mg/kg per day in three divided doses intravenously for 14 days for disease limited to skin, eyes, and mucous membranes, and 21 days for central nervous system or disseminated disease is suggested.

Patient Care and Monitoring

Re-evaluation of the patient's condition and therapy adjustment are key elements in effective monitoring. Parameters may include:

- The patient's psychosocial and psychosexual status
- Frequent reassessment of recurrent episodes and therapy adjustment

- Ordering tests for malignancy
- Yearly testing of HIV status
- Side effects of drugs.

BACTERIAL VAGINOSIS

Bacterial vaginosis (BV) is a very common infection and a recurrent cause of abnormal discharge in women of childbearing age. BV is categorized by an overgrowth of anaerobic organisms such as *Gardenella vaginalis*, *Prevotella* species, *Mycoplasma hominis*, and *Mobiluncus* species, leading to the replacement of lactobacillus and an increase in vaginal pH from 4.5 to 7.0.[31]

Epidemiology

BV has been found in 12% to 25% of women in routine clinic populations, 10% to 26% of women in obstetrics clinics, and 32% to 64% of women in clinics for STIs. BV infection usually results from sexual activity, although some cases have been reported in women who are not sexually active.

Pathophysiology

A complex and intricate balance of microorganisms maintains the normal vaginal flora (i.e., lactobacilli, corynebacteria, and yeast). The normal postmenarchal and premenopausal vaginal pH is 3.8 to 4.2. At this pH, growth of pathogenic organisms is usually inhibited; however, disturbance of the normal vaginal pH can alter the vaginal flora, leading to overgrowth of pathogens.

Diagnosis

BV is diagnosed according to the Amsel criteria. In order for diagnosis to be confirmed, three of the four criteria must be present ❽:

1. Thin, white, homogenous discharge
2. Clue cells on microscopy
3. pH of vaginal fluid greater than 4.5
4. Release of a fishy odor upon the addition of an alkali (10% potassium hydroxide) to a vaginal sample

Alternatively, a Gram stain vaginal smear may be used to diagnose BV using the Nugent criteria. ❾ This relies on estimating the proportions of bacteria morphotypes to provide a score between 0 and 10. A score of less than 4 is normal, 4 to 6 is intermediate, and greater than 6 is consistent with BV.

Isolation of *G. vaginalis* may not be diagnostic because it can be cultured from the vagina in some normal women, although a high concentration may be indicative of infection.



Clinical Presentation of Bacterial Vaginosis[32]

General
- Offensive fishy-smelling vaginal discharge

Signs
- Thin, white, homogenous discharge, coating the walls of the vagina

Symptoms
- Many women are asymptomatic; usually not associated with soreness, itching, or irritation

Treatment

Desired Outcome

Reduction in the number of causative bacteria, cessation of vaginal discharge, and decrease in vaginal pH are the desired outcomes.

Pharmacologic[33]

Recommended regimens include:

- Metronidazole 400 to 500 mg orally twice daily for 5 to 7 days
- Metronidazole 2 g orally in one dose

Alternative regimens include:

- Intravaginal metronidazole 0.75% gel once daily for 5 days
- Intravaginal clindamycin 2% cream once daily for 7 days
- Clindamycin 300 mg orally twice daily for 7 days

Pregnancy

- It is unclear whether treating pregnant women for BV is beneficial. If treatment is initiated, the drugs of choice are oral or intravaginal metronidazole or oral clindamycin.

Patient Care and Monitoring

A test to determine if the patient has been cured is generally not recommended. However, in patients with recurrent BV, a follow-up after the course of therapy may be warranted. If treatment has been prescribed during pregnancy to reduce preterm birth, perform a repeat exam in 1 month and advise further treatment for recurrent BV.

PELVIC INFLAMMATORY DISEASE

Pelvic inflammatory disease (PID) usually affects young, sexually active, reproductive-age women. In the majority of cases, the pathogens responsible are *C. trachomatis* and *N. gonorrhoeae,*

although anaerobes have also been implicated in the pathogenesis.[34] PID has been correlated with ectopic pregnancy, infertility, tubo-ovarian abscess, and chronic pelvic pain.

Pathophysiology

It has been postulated that *Chlamydia* may produce a heat shock protein that causes tissue damage through a delayed hypersensitivity reaction. *C. trachomatis* may also possess DNA evidence of toxin-like genes that code for high-molecular-weight proteins with structures similar to *Clostridium difficile* cytotoxins, enabling inhibition of immune activation. This may explain the observation of a chronic *C. trachomatis* infection in subclinical PID.

Diagnosis[34,35]

Minimum criteria

- Uterine tenderness
- Cervical motion tenderness
- No other cause of the aforementioned criteria

Additional criteria

- Oral temperature greater than 101°F
- Abnormal cervical or vaginal discharge
- White blood cell presence on saline microscopy of vaginal secretions
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein

Treatment

Desired Outcome

The removal of causative bacteria and reduction of any related sequelae are the desired goals of treatment.



Clinical Presentation of Pelvic Inflammatory Disease[35]

General
- Signs and symptoms may vary from mild to severe

Signs
- Vague

Symptoms
- Lower abdominal or pelvic pain
- Malodorous vaginal discharge
- Abnormal uterine bleeding
- Dyspareunia
- Dysuria
- Nausea and/or vomiting
- Fever

TABLE 77–4. Treatment Regimens for Pelvic Inflammatory Disease

Parenteral
Clindamycin 900 mg IV every 8 hours and gentamicin, loading dose IV or IM (2 mg/kg) followed by maintenance dose (1.5 mg/kg) every 8 hours (a single daily dose may be used)
Levofloxacin 500 mg IV every 24 hours with or without metronidazole 500 mg IV every 8 hours
Ampicillin-sulbactam, 3 g IV every 6 hours and doxycycline 100 mg PO or IV every 12 hours
Oral
Levofloxacin 500 mg PO daily for 14 days with or without metronidazole 500 mg PO twice daily for 14 days
Ceftriaxone 250 mg IM single dose and probenecid 1 g single dose, plus doxycycline 100 mg PO twice daily for 14 days with or without metronidazole, 500 mg PO twice daily for 14 days
Third-generation cephalosporin plus doxycycline 100 mg PO twice daily for 14 days with or without metronidazole 500 mg PO twice daily for 14 days

IM, intramuscularly; IV, intravenously; PO, orally.
Epperly A, Viera A. Pelvic Inflammatory Disease. Clin Fam Pract. 2005;7:67–78.

Pharmacologic

Providing broad-spectrum coverage for N. gonorrhoeae, C. trachomatis, Streptococcus *spp., and gram-negative facultative bacteria should be the main goal of pharmacologic therapy.* ❾ CDC-approved treatment regimens are shown in Table 77–4.[34,36] Optimal management of PID should be individualized based on clinical setting and patient characteristics. For some patients, hospitalizations, intravenous antibiotics, and surgical treatment of complications may be needed. Though outpatient management remains contentious, many feel that outpatient management should be limited to: those who remain afebrile, have WBC counts less than 11,000 mm^3, have minimal evidence of peritonitis, have active bowel sounds, and can tolerate oral nourishment. Nonetheless, outpatient therapy with a parenteral cephalosporin followed by doxycycline and metronidazole is recommended.

Patient Care and Monitoring

The goals of monitoring patients with PID are related to reducing long-term complications. To this end, the primary approach should be prevention and education of at-risk women. Secondary prevention may include screening by conducting a pelvic exam during a routine check-up.

CHANCROID

Haemophilus ducreyi, a gram-negative bacterium, has been isolated as the causative organism of chancroid, a genital ulcerative disease usually accompanied by inguinal lymphadenitis and bubo formation. Chancroid may possibly spread to other anatomic sites, a clinical feature first discovered by Ducrey in 1889.[37]

Epidemiology

In 2003, more than 50,000 patients were diagnosed with chancroid in the United States. The majority of cases were diagnosed in the South Atlantic region, which included Delaware, North and South Carolina, Georgia, and Florida.[38]

Pathophysiology

Transmission commences through direct contact with the skin, presumably through minor abrasions. The ulcer may be quite deep, and more than half of patients have multiple ulcers.

Diagnosis

The multiplex polymerase chain reaction has been used successfully in diagnosis, demonstrating approximately 75% specificity in studies employing genital ulcer swabs. ⑩ It offers an acceptable sensitivity in the detection of the three most common organisms involved in the etiology of genital ulcer disease: HSV, *T. pallidum*, and *H. ducreyi*.[37,39] Additionally, several amplification techniques have been created in hopes of improving the sensitivity of laboratory diagnosis.

Treatment

Management of the syndrome has been the accepted approach of the World Health Organization (WHO) in lieu of the limitations seen with most diagnostic procedures. The prevailing thought is that patients should be treated during the first visit with a combination of antibiotics to cover for probable etiologic organisms.[39]



Clinical Presentation of Chancroid[37]

General
- The ulcer edge is commonly ragged and poorly defined.

Signs
- Four to seven days after infection, a tender, erythematous papule usually develops and subsequently progresses to the pustular stage.[37] The pustules often rupture after 2 to 3 days.
- Lesions typically occur on the prepuce and frenulum in men and on the vulva, cervix, and perianal area in women. Some extragenital cases have been noted on the inner thighs, breasts, and fingers, though rarely seen in practice.

Symptoms
- Painful and tender lesions
- Painful shallow ulcers with granulomatous bases and purulent exudates.

TABLE 77–5. Recommended Treatment Regimens for Chancroid from the World Health Organization (WHO), and the Centers for Disease Control and Prevention (CDC)

Antimicrobial	Regimen	Recommending Body
Erythromycin	500 mg PO 3 times daily for 7 days **or** 500 mg PO 4 times daily for 7 days	WHO, CDC
Azithromycin	1 g PO as a single dose	CDC
Ceftriaxone	250 mg IM as a single dose	WHO, CDC
Ciprofloxacin	500 mg PO as a single dose **or** 500 mg PO 2 times daily for 3 days	WHO, CDC
Spectinomycin	2 g IM as a single dose	WHO

IM, intramuscularly; PO, orally.
Lewis D. Diagnostic Tests for Chancroid. Sex Transm Infect. 2000 Apr; 76(2):137–141.

Desired Outcome

The desired outcome is to effectively treat the ulceration and reduce the potential for spread of the disease by instigating overall syndromic management.

Pharmacologic

The WHO and CDC recommended treatment regimens are shown in Table 77–5.[37] There has been some debate about a suitable dosage of ciprofloxacin in the treatment of chancroid. Though the CDC recommends 500 mg orally three times daily, the WHO supports a single 500-mg oral dose. Ciprofloxacin has demonstrated an acceptable cure rate for a single dose (92%) when compared to erythromycin (91%).

Patient Care and Monitoring

Follow-up should include patient education, counseling, and repeated inspections of the ulceration to ensure healing.

PREVENTION STRATEGIES

Though previous literature suggests several prevention strategies, a combination of efforts may be more advisable. Alteration in sexual behavior should undoubtedly be the first counseling concern, as promiscuous sexual activity has been shown to augment the probability of infection.

Abstinence is the best course of action, especially in patients with herpes during lesional episodes. However, compliance in some may be minimal, in which case, appropriate condom use should always be recommended. To alleviate any possible misconceptions about condom application, either demonstrate how to apply a condom or ask the patient to demonstrate. During the demonstration, explicitly educate the patient with regard to application, storage, and the use of lubricants.[43]

CONCLUSION

STIs encompass a number of diseases that seem to be increasing with regard to newly documented infections. With proper education, effective drug therapy, and patient monitoring, clinicians may be able to drastically diminish the number of new infections and the overall disease burden.

ABBREVIATIONS

BV:	bacterial vaginosis
CDC:	Centers for Disease Control and Prevention
CNS:	central nervous system
CSF:	cerebrospinal fluid
FDA:	Food and Drug Administration
ELISA:	enzyme-linked immunosorbent assay
HPV:	human papillomavirus
HSV:	herpes simplex virus
HIV:	human immunodeficiency virus
IM:	Intramuscularly
IV:	Intravenously
MSM:	men who have sex with men
PID:	pelvic inflammatory disease
po:	Orally
STI:	sexually transmitted infection
WBC:	white blood cell
WHO:	World Health Organization

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

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78 OSTEOMYELITIS

Melinda M. Neuhauser and Susan L. Pendland



LEARNING OBJECTIVES

UPON COMPLETION OF THE CHAPTER, THE READER WILL BE ABLE TO:

1. Discuss the pathophysiology of osteomyelitis.
2. List common risk factors for osteomyelitis.
3. Compare and contrast the classic signs and symptoms of acute and chronic osteomyelitis.
4. Evaluate microbiology culture data and other laboratory tests utilized for the diagnosis and treatment of bone infections.
5. List the most common pathogens isolated in acute and chronic osteomyelitis.
6. Develop a treatment plan for osteomyelitis.
7. Recommend parameters to monitor antimicrobial therapy for efficacy and toxicity.
8. Educate patients regarding disease state and drug therapy.

KEY CONCEPTS

❶ Osteomyelitis, an infection of the bone, can be an acute or chronic process.
❷ Osteomyelitis is most often classified by route of infection and duration of disease.
❸ *Staphylococcus aureus* is the predominant pathogen seen in all types of osteomyelitis. However, the spectrum of potential causative pathogens varies with patient-specific risk factors and route of infection.
❹ Typical signs and symptoms of osteomyelitis include local pain and tenderness over the affected bone, as well as inflammation, erythema, edema, and decreased range of motion. Patients with acute hematogenous osteomyelitis may also present with fever, chills, and malaise.
❺ The gold standard for diagnosis is a bone biopsy with isolation of microorganism(s) from culture and the presence of inflammatory cells and osteonecrosis on histologic exam. However, more commonly, the diagnosis of osteomyelitis is based on clinical findings coupled with results from imaging studies and laboratory tests such as white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).
❻ The treatment goals for acute and chronic osteomyelitis are to eradicate the infection and prevent recurrence. Higher cure rates are seen with acute compared to chronic osteomyelitis. Therefore, in chronic osteomyelitis, a common treatment goal for many patients is to prevent complications such as amputation.
❼ Treatment of osteomyelitis is dependent on the extent of bone necrosis. For acute osteomyelitis with minimal bone destruction, an extended course of antimicrobial therapy should effectively treat the infection; however, in chronic osteomyelitis surgical intervention is also typically required.
❽ Empiric antimicrobial therapy should target likely causative pathogen(s) based on patient-specific risk factors and route of infection. However, therapy should be modified based on culture and sensitivity data.
❾ The total duration of antimicrobial therapy is typically 4 to 6 weeks. Therapy is often administered intravenously for 1 or 2 weeks and then switched to the oral route.
❿ Patients should be monitored for clinical response, development of adverse drug reactions, and potential drug-drug interactions.

❶ *Osteomyelitis is an infection of the bone that is associated with high morbidity and increased health care costs. The inflammatory response associated with acute osteomyelitis can lead to bone necrosis and subsequently chronic infections.* Bacterial pathogens, particularly *Staphylococcus aureus*, are the most common microorganisms implicated in these infections. Diagnosis and treatment are often difficult due to the heterogeneous

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nature of osteomyelitis. Medical management is the mainstay of treatment for acute infections; however, surgical intervention is necessary for chronic cases that involve bone necrosis. Outcomes may vary based on patient-specific risk factors, duration of disease, and site of infection.

EPIDEMIOLOGY AND ETIOLOGY

❷ *There are multiple classification schemes for osteomyelitis.*[1] *Due to the heterogeneity of bone infections, no single classification system has been universally accepted.*[1,2] *Two of the most common classification schemes are based on* route of infection *and* duration of disease.[1–5] In the classification scheme developed by Waldvogel and colleagues,[5] the route of infection is categorized as either hematogenous or contiguous (Fig. 78–1). Osteomyelitis secondary to a contiguous focus was further subdivided into infections with or without vascular insufficiency.

Historically, osteomyelitis has been classified as acute or chronic based on duration of disease (Fig. 78–2).[2,4] However, there are no established definitions for acute and chronic infections.[2–4] Acute infection has been defined as first episode or recent onset of symptoms (less than 1 week).[2,3] Chronic osteomyelitis is generally defined as relapse of the disease or symptoms persisting beyond 4 weeks.[2,3] Others describe chronic osteomyelitis as the presence of necrotic bone.[3]

An alternative classification, the Cierny-Mader staging system, is based on anatomic site and physiologic status of the patient.[1] This classification scheme was developed for chronic osteomyelitis involving long bones and has limited application for small bones and digits. The detailed stratification has the greatest utility in clinical trials since it would permit comparison of treatment regimens in patients with diverse comorbidities and infection sites.

The epidemiology of osteomyelitis has been changing over the past several decades.[6] The incidence of acute hematogenous osteomyelitis, which is most often seen in children, has been declining.[6,7] In contrast, the frequency of contiguous osteomyelitis has been increasing. This trend may be related to the rising rates of diabetes and peripheral vascular disease (PVD), as well as the increased presence of prosthetic implants and surgical interventions.[3,6,8]

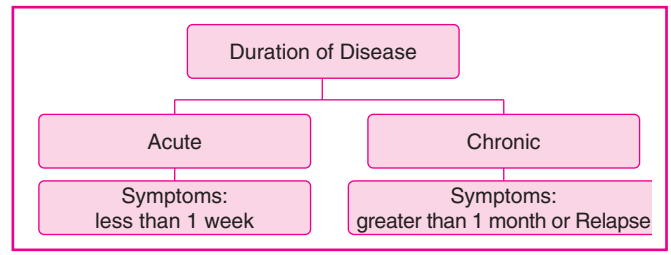


FIGURE 78–2. Classification by duration of disease.

PATHOPHYSIOLOGY

Healthy bone tissue is normally resistant to infection but may become susceptible under certain conditions.[9] Bone can become infected: (1) via the presence of bacteria in the bloodstream, (2) by direct inoculation from trauma or surgery, and (3) by spread from an adjacent site (e.g., soft-tissue infection).[9] The latter is particularly problematic in patients with foreign body implants (e.g., hip replacement) and chronic skin ulcers.[3,9,10] Microorganisms adhere to the bone and elicit an inflammatory response.[3] The subsequent release of leukocytes and cytokines leads to changes in vascular permeability (edema) and decreased oxygen tension (ischemia). In some cases, these processes can lead to bone necrosis.[2] Pieces of dead bone may become separated forming sequestra.[2,3] These areas typically cannot be penetrated by antimicrobials and phagocytic cells and thus require surgical intervention to eradicate the bacterial nidus (Fig. 78–3).[3]

Both microbial and host factors are important determinants in the development of osteomyelitis.[2,3,9] *Staphylococcus* species possess bacterial adhesions, which promote their attachment to tissues and foreign devices. ❸ *As such,* S. aureus

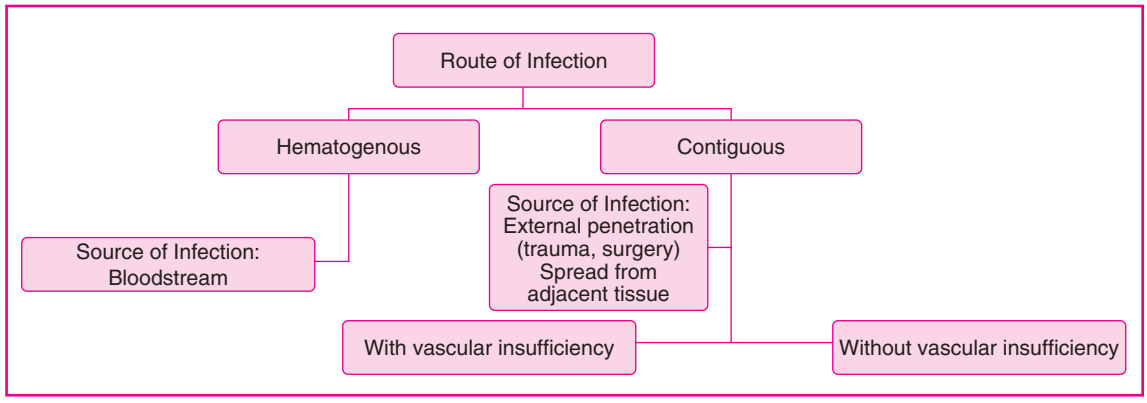


FIGURE 78–1. Classification by route of infection.

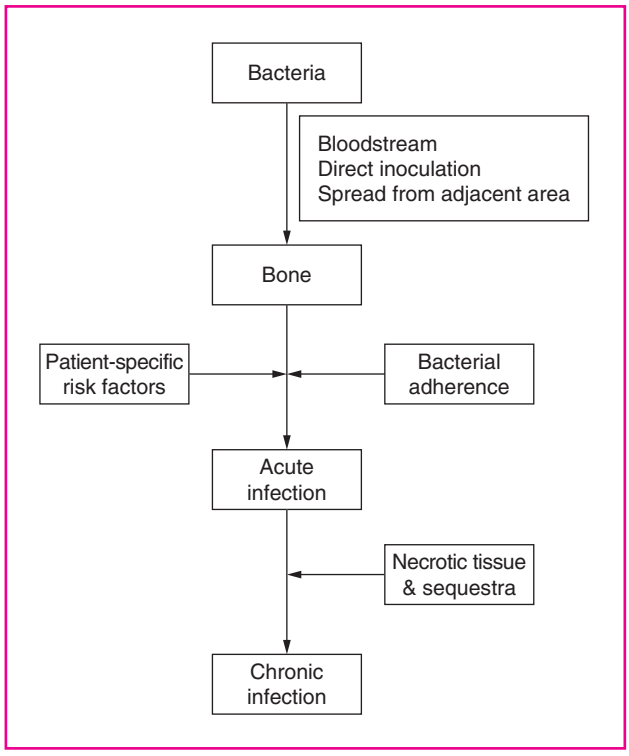


FIGURE 78–3. Pathogenesis of osteomyelitis.



Acute Hematogenous Osteomyelitis

- Single pathogen most often isolated
- *S. aureus* is the predominant pathogen
- Other pathogens based on risk factors:
  Neonates: *E. coli* or group B streptococci
  Elderly: *E. coli* [secondary to urinary tract infections (UTIs)]

is the predominant pathogen seen in all types of osteomyelitis.[11] *Host factors such as age, comorbidities, and presence of foreign devices can influence the spectrum of infection (i.e., bone and pathogen involvement)* (Table 78–1).[4,9] For example, patients with diabetes and PVD have poor wound healing and often present with non-healing skin ulcers. These wounds are typically colonized with a mixture of aerobic and anaerobic microorganisms, which can lead to polymicrobial osteomyelitis. Therefore, if a wound is deep or extensive, these patients should be evaluated for underlying osteomyelitis.[10] Other special populations that have a varied pathogen spectrum include intravenous drug abusers (IVDA) (*P. aeruginosa* and methicillin-resistant *S. aureus* [MRSA]), sickle cell patients

TABLE 78–1. Empiric Antimicrobial Therapy for Osteomyelitis[2,4,7,12,13,17]

Classification	Age of Onset	Infection Site	Risk Factors	Typical Pathogens	Antimicrobial Therapy
Hematogenous	Neonates	Long bones (femur, tibia)		*Staphylococcus aureus,*[a] *E. coli,* group B streptococci	Nafcillin[b] and cefotaxime
	Prepubertal children	Long bones (femur, tibia)		*S. aureus*[a]	Nafcillin[b] or cefazolin
	Elderly	Vertebra	UTI	*S. aureus,*[a] *E. coli*	Nafcillin[b] and cefotaxime/ ceftriaxone
Contiguous					
With Vascular Insufficiency	Adult (greater 50 years)	Feet, fingers	Diabetes, PVD, peripheral neuropathy	*S. aureus* (MRSA), Enterobacteriaceae, *P. aeruginosa, Enterococcus* spp., anaerobes	Several therapeutic options: Vancomycin **PLUS** (1) piperacillin/tazobactam (2) imipenem/cilastatin or meropenem (3) cefepime or ceftazidime and clindamycin or metronidazole (4) ciprofloxacin or levofloxacin and clindamycin or metronidazole
Without Vascular Insufficiency	Adult (greater 50 years)		Postoperative (e.g., hip fractures), soft-tissue infections	*S. aureus*[a]	Nafcillin[b] or cefazolin

[a]If the patient has risk factors for MRSA present, vancomycin should be substituted for nafcillin. MRSA risk factors may include: previous antimicrobial therapy, prolonged hospitalization, hemodialysis, presence of an indwelling catheter, intravenous drug abuse.
[b]Oxacillin can be substituted for nafcillin.
MRSA, methicillin-resistant *S. aureus;* PVD, peripheral vascular disease; UTI, urinary tract infection.



Contiguous Focus Osteomyelitis with Vascular Insufficiency

- Multiple pathogens often isolated
- Mixture of aerobic and anaerobic organisms:
  S. aureus, Enterococcus spp.
  Enterobacteriaceae, *P. aeruginosa*
  Anaerobes

(*Salmonella*), and individuals with prosthetic implants (coagulase-negative staphylococci).[3]

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation of osteomyelitis may vary depending on route and duration of infection, as well as patient-specific factors such as infection site, age, and comorbidities. ❹ *In hematogenous osteomyelitis, the patient typically experiences systemic and localized signs and symptoms.*[3,4,7,12,13] *In comparison, patients with chronic infection typically present with only localized signs and symptoms.*[4,6] A cardinal sign of chronic osteomyelitis is the formation of sinus tracts with purulent drainage.[2,3,6]

Common signs and symptoms of osteomyelitis include:
- Systemic: Fever, chills, malaise
- Localized: Pain or tenderness, edema, erythema, inflammation, decreased range of motion of infected area

❺ *The diagnosis of osteomyelitis is based on clinical findings, laboratory tests, and imaging studies.*[2,3] A thorough history and physical examination are especially important for diagnosis in patients with limited or atypical symptoms. *The gold standard for diagnosis is a bone biopsy with isolation of microorganism(s) from culture and the presence of inflammatory cells and osteonecrosis on histological exam.*[4,10] *Due to the invasive nature of this procedure, imaging studies and laboratory tests are generally used in making diagnoses.*



Contiguous Focus Osteomyelitis without Vascular Insufficiency

- Single or multiple pathogens isolated
- *S. aureus* is predominant pathogen
- Other pathogens based on source of infection:
  For example: Mandibular osteomyelitis (mixture of aerobic and anaerobic oral flora)



Patient Encounter, Part 1

A 62-year-old male with history of diabetes and PVD comes to the emergency department complaining of a "painful sore" on his left lower leg. After questioning him, you determine that the wound has been present for months and has not responded to oral antibiotic therapy. On physical examination, a large, deep wound with purulent drainage is seen.

- What information is suggestive of osteomyelitis?
- What risk factors, if any, does he have for osteomyelitis?

Non-specific inflammatory markers for infection include:[2,3,6,12]
- WBC, **ESR**, and **CRP** may be elevated or within normal limits.
- An elevated WBC is mostly seen in patients with acute osteomyelitis.
- CRP rises faster than ESR during early stages of infection.
- CRP returns to normal levels more quickly than ESR.

Imaging studies include:[2,3,4,6,8,10]
- Plain film radiographs
  -Most commonly used for initial screening
  -Bone destruction is not apparent for 10 to 21 days following infection
- **Magnetic resonance imaging (MRI)**
  -Most accurate for diagnosing bone infection
  -Can detect early infection
  -More expensive than radiograph
- Others
  -**Nuclear medicine scans:** useful for early detection
  -**Computed tomography (CT) scan:** useful for monitoring clinical improvement

Microbiologic evaluation:[2,3,6,10,12]
- Isolation of causative pathogen is essential for targeted antimicrobial therapy
- Bone biopsy can provide definitive diagnosis:
  Samples should be submitted for culture and histology
  Rarely performed due to invasive nature
- Blood cultures may be positive in patients with hematogenous osteomyelitis
- Superficial swabs should have limited role in directing therapy
  -May represent colonization rather than infecting organism(s)



Patient Encounter, Part 2

The medical resident suspected osteomyelitis and ordered plain film radiographs. He also swabbed the open wound and sent the swab to the microbiology laboratory for culture and sensitivity. The following result was reported:

Radiograph: lytic changes consistent with bone destruction

- How would you classify the infection in this patient?
- How should the results of the wound swab culture be utilized to target the patient's antimicrobial therapy?

TREATMENT

Desired Outcomes

❻ *The treatment goals for osteomyelitis are to eradicate the infection and prevent recurrence. Cure rates of greater than 85% have been reported for acute hematogenous osteomyelitis.*[7,13] *In contrast, chronic osteomyelitis is associated with higher failure rates largely due to the presence of necrotic bone.*[9] These patients typically require surgical intervention to remove the necrotic bone and tissue, and if applicable, to replace infected hardware.[3,14] Comorbidities such as vascular insufficiency can further contribute to the poor outcomes seen with chronic osteomyelitis. Due to the high failure rates, treatment in this patient population may require prolonged therapy with the primary goal of preventing amputation of infected areas.[3,6,10,15]

General Approach To Treatment

❼ *Antimicrobial therapy alone is the mainstay of treatment for acute osteomyelitis.*[7,12] *In comparison, treatment for chronic osteomyelitis typically requires a combination of antimicrobial therapy and surgical intervention.*[3,6,14,15] If the patient is not a candidate for surgical intervention, prolonged antimicrobial therapy is generally necessary.[6,10,16]

Pharmacologic Therapy

❽ *Empiric antimicrobial therapy should target likely causative pathogen(s) based on patient-specific risk factors and route of infection* (Table 78–1).[2] *Empiric antimicrobial coverage against* S. aureus *should be considered for all classifications of osteomyelitis. Specific recommendations may vary based on factors such as patient allergies, potential for harboring a resistant organism, institution formulary, and cost considerations.*

❽ *Antimicrobial therapy should be modified based on culture and sensitivity data of appropriately collected specimens (Table 78–2).*[2,17,18] ❾ *Typically, treatment is initiated with intravenous antimicrobials to ensure that therapeutic drug concentrations will be achieved in the bone.*[16] *Intravenous therapy can be administered in the inpatient or outpatient setting.*[15,19] *Following 1 to 2 weeks of intravenous therapy, a switch to oral antibiotics may be considered in patients with good adherence and outpatient follow-up.*[12,15,20,21] Oral agents should possess such characteristics as high bioavailability, good bone penetration, and long half-life (i.e., extended dosing interval).[16,20] Antimicrobials commonly used as oral therapy for osteomyelitis include fluoroquinolones, clindamycin, linezolid, and trimethoprim-sulfamethoxazole (TMP-SMX).[6,13,17,18,20,21] Additionally, oral rifampin may be



Patient Encounter, Part 3: The Medical History, Physical Exam, and Diagnostic Tests

PMH
Diabetes mellitus, PVD, hypertension

SH
Tobacco smoker (2 packs per day for the past 30 years), social drinker ("3 cans of beer per day"), non-employed with medical disability

Meds
Aspirin 81 mg orally once daily
Atorvastatin 40 mg orally once daily
Clopidogrel 75 mg orally once daily
Lisinopril 10 mg orally once daily
Insulin glargine 20 units every day at bedtime
Insulin lispro 7 units before breakfast and lunch; insulin lispro 9 units before dinner

PE
Gen: His general appearance is that of an obese male with tenderness and pain in the region of the non-healing skin ulcer
Skin: Large, deep ulcer with purulent drainage on his left lower leg
VS: Blood pressure 145/87 mm Hg, pulse 80 beats per minute, respiratory rate 18/minute, temperature 36.0°C (96.8°F), Ht 5'6" (165 cm), Wt 93 kg (205 lb)

Labs
WBC 13,000 cells/mm^3 (13 × 10^9 cells/L), blood urea nitrogen (BUN)/serum creatinine (Scr) 19/1.3 mg/dL (6.8/99.2 mmol/L), fasting blood glucose 156 mg/dL (8.7 mmol/L), ESR 80 mm/hour, CRP 2.1 mg/dL (0.02g/L)
Culture from wound swab: *Enterococcus*, coagulase-negative staphylococci, and *P. aeruginosa*
Culture from bone biopsy during débridement: MRSA and *Bacteroides fragilis*

- Against which organisms should the antimicrobial therapy be targeted?
- Based on the information presented, create a care plan for this patient's osteomyelitis. Your plan should include: (1) goals of therapy, (2) patient-specific detailed therapeutic plan, (3) nonpharmacologic interventions, and (4) follow-up plan to determine if outcomes have been achieved.

TABLE 78–2. Pathogen-Targeted Antimicrobial Therapy and Dosing Recommendations in Pediatrics and Adults[2,4,6,8,13,17,18]

Microorganism	Recommended Therapy	Alternatives
S. aureus		
MSSA	Antistaphylococcal penicillin: Nafcillin[a]/oxacillin Adult: 2 g IV every 4–6 hours Pediatric[b]: 100–200 mg/kg per day IV in divided doses every 4–6 hours First-generation cephalosporin: Cefazolin[c] Adult: 1–2 g IV every 8 hours Pediatric[b]: 50–100 mg/kg per day IV in divided doses every 6–8 hours	β-Lactam allergy: Vancomycin Linezolid
MRSA	Vancomycin[c]: Adult: 10–15 mg/kg per dose IV every 8–12 hours Pediatric[b]: 40 mg/kg per day IV in divided doses every 6 hours Linezolid: Adult: 600 mg IV/oral every 12 hours Pediatric[b]: 10 mg/kg per dose IV/oral every 8 hours	
Enterococcus spp.		
Ampicillin-sensitive	Ampicillin[c]: Adult: 2 g IV every 4–6 hours Pediatric[b]: 100–200 mg/kg per day IV in divided doses every 4–6 hours	β-Lactam allergy: Vancomycin
Ampicillin-resistant Vancomycin-resistant	Vancomycin Linezolid	
***Streptococcus* spp.**	Penicillin G[c]: Adult: 2–4 million units IV every 4–6 hours Pediatric[b]: 250,000–400,000 units/kg per day IV in divided doses every 4–6 hours	β-Lactam allergy: Vancomycin
Enterobacteriaceae	Third- or fourth-generation cephalosporin: Ceftriaxone[a] Adult: 1–2 g IV every 24 hours Pediatric[b]: 50–75 mg/kg per dose IV every 24 hours Cefotaxime[a,c]: Adult: 1–2 g IV every 8 hours Pediatric[b]: 50–200 mg/kg per day IV in divided doses every 8 hours Ceftazidime[c]: Adult: 1–2 g IV every 8 hours Pediatric[b]: 100–150 mg/kg per day IV in divided doses every 8 hours Cefepime[c]: Adult: 2 g IV every 8–12 hours Pediatric[b]: 50 mg/kg per dose IV every 8–12 hours Piperacillin/tazobactam[c]: Adult: 3.375 g IV every 4–6 hours **OR** 4.5 g IV every 6–8 hours Fluoroquinolones[e]: Ciprofloxacin[c] Adult: 400 mg IV every 12 hours; 500–750 mg oral twice daily Levofloxacin[c]: Adult: 500–750 mg IV/oral once daily Moxifloxacin[d]: Adult: 400 mg IV/oral once daily	Carbapenems: Imipenem/cilastatin[c] Adult: 500 mg IV every 6–8 hours Pediatric[b]: 60–100 mg/kg per day in divided doses every 6 hours Meropenem[c]: Adult: 1 g IV every 8 hours Pediatric[b]: 60–120 mg/kg per day in divided doses every 8 hours Ertapenem[c]: Adult: 1 g IV every 24 hours
P. aeruginosa	Antipseudomonal cephalosporin: Ceftazidime Cefepime Antipseudomonal fluoroquinolone[e]: Ciprofloxacin Levofloxacin	Piperacillin/tazobactam Carbapenems (only imipenem/cilastatin or meropenem)
Anaerobes	Clindamycin[d]: Adult: 600–900 mg IV every 8 hours 300–450 mg oral every 6–8 hours Pediatric[b]: 25–40 mg/kg per day IV in divided doses every 6–8 hours 10–30 mg/kg per day orally in divided doses every 6–8 hours Metronidazole[c,d]: Adult: 500 mg IV/oral every 8 hours Pediatric[b]: 30 mg/kg per day IV/oral in divided doses every 6–8 hours	

[a]Dosage adjustment necessary in patients with concomitant renal and hepatic dysfunction.
[b]Refer to specialized pediatric reference for maximum pediatric dose and neonatal recommendations and dosing.
[c]Dosage adjustment necessary in renal dysfunction.
[d]Dosage adjustment necessary in severe hepatic dysfunction.
[e]Fluoroquinolones: Not approved by the United States Food and Drug Administration for use in children except for anthrax (ciprofloxacin).
MRSA, methicillin-resistant *S. aureus;* MSSA, methicillin-sensitive *S. aureus*.

TABLE 78–3. Selective Toxicities and Drug Interactions Associated with Antimicrobials[6,12,17,18]

Antimicrobial	Adverse Events	Drug-Drug Interactions
β-Lactams Clindamycin	Hypersensitivity (rash, anaphylaxis) Nausea/vomiting (oral) Diarrhea (oral)	
Fluoroquinolones	Photosensitivity CNS disturbances (e.g., dizziness, confusion) particularly in the elderly QTc prolongation Use in children is generally avoided (assess individual patient risk versus benefit); studies conducted in immature dogs revealed signs of arthropathy	Separate administration from aluminum- or magnesium-containing antacids, calcium, iron, and carafate Ciprofloxacin is a moderate inhibitor of CYP1A2 Significant drug interactions may be seen with theophylline and methylxanthines
Linezolid	Myelosuppression: monitor CBC once weekly if more than 2 weeks of therapy Peripheral and/or optic neuropathy has been reported with long-term therapy	Mild MAO inhibitor; evaluate for potential drug-drug or drug-food interactions
Metronidazole	Nausea/vomiting Metallic taste	Refrain from using alcoholic beverages: potential for disulfiram-like reaction Substrate for CYP2C9 and inhibitor of CYP2C9, 3A3/4 and 3A5-7; potential interactions may include warfarin (enhanced prothrombin time) and lithium (increased concentrations)
Rifampin	Hepatic abnormalities: monitor LFTs Reddish-orange discoloration of secretions (e.g., urine, sweat, tears)	Potent inducer of CYP-mediated metabolism; evaluate for drug-drug interactions
TMP-SMX	Nausea/vomiting Myelosuppression: monitor CBC Hepatic abnormalities: monitor LFTs Rash including severe reactions such as Stevens-Johnson syndrome	Inhibitor of CYP2C9; evaluate for potential drug-drug interactions such as warfarin
Vancomycin	Infusion related toxicity (phlebitis, red man syndrome) Potential for additive renal toxicity if being coadministered with a nephrotoxic agent (e.g., aminoglycoside): monitor renal function (BUN/SCr) weekly in stable patients Consider vancomycin troughs to ensure therapeutic concentrations	

BUN, blood urea nitrogen; CBC, complete blood cell count; CNS, central nervous system; CYP, cytochrome P-450 isoenzyme; LFT, liver function test; MAO, monoamine oxidase; QTc, Q-T interval corrected for heart rate; SCr, serum creatinine; TMP-SMX, trimethoprim-sulfamethoxazole.



Patient Encounter, Part 4

The patient received 4 weeks of intravenous antimicrobial therapy following débridement. Due to clinical improvement, the physician contacts you for a recommendation for an oral antibiotic to complete a total of 6 weeks of therapy.

- What antimicrobial therapy would you recommend for this patient?
- Evaluate the patient's medication profile for drug-drug interactions.
- Counsel the patient regarding this drug therapy.

used in combination with another antibiotic in the treatment of chronic osteomyelitis, particularly in patients with foreign devices.[15,17,20]

❾ *The duration of treatment is typically 4 to 6 weeks for acute osteomyelitis.*[15] *Chronic osteomyelitis also requires 4 to 6 weeks of therapy; however, the total length of therapy should be counted after the date of the last major surgical intervention.*[8,15] Longer courses may be necessary for certain populations such as patients with vascular insufficiency.[3,6,10,16]

In addition to medical and surgical management, non-pharmacologic interventions that reduce risk factors for developing osteomyelitis should be communicated to the patient. Examples include smoking cessation, weight-control, exercise, and good nutrition.[2] Additionally, a diabetic patient

should be counseled regarding the necessity of controlled blood glucose, routine care and self-examination of lower extremities, and aggressive wound care.[10]

Outcome Evaluation

Therapeutic success is measured by the extent to which the care plan (1) resolves signs and symptoms, (2) eradicates the microorganism(s), (3) prevents relapses, and (4) prevents complications such as amputation. Patients should be evaluated for resolution of clinical signs and symptoms and normalization of laboratory tests (WBC, CRP, and ESR). Improvement in clinical manifestations should be seen within 48 to 72 hours of initiation of intravenous antimicrobial therapy.[10] A reduction in CRP should be seen within 1 week of therapy and should be monitored weekly throughout therapy for a continued downward trend. ESR can also be monitored weekly although normalization will be slower than for CRP. If poor response is noted, the following should be evaluated: (1) patient compliance, (2) significant drug-drug or drug-food interactions, (3) appropriate dosage to achieve therapeutic concentrations, (4) development of antimicrobial resistance, (5) need for additional imaging studies, and (6) diagnostic re-evaluation.[10] Due to high rates of relapse, patients should have medical follow-up for at least 1 year following resolution of symptoms.[10]



⑩ Patient Care and Monitoring

1. Assess the patient's symptoms and laboratory test results to determine if patient-directed therapy is appropriate.
2. Obtain a thorough history of prescription, non-prescription, and natural drug product use.
3. Educate the patient on lifestyle modifications that will reduce the risk of recurrent infections.
4. Develop a plan to assess the effectiveness of antimicrobial therapy.
5. Evaluate the patient for the presence of adverse drug reactions, drug allergies, and drug interactions (Table 78–3).
6. Stress the importance of adherence to the therapeutic regimen.
7. Provide patient education with regard to disease state and drug therapy. Explain the following:
   - Causes of osteomyelitis
   - Complications associated with osteomyelitis
   - The drug, dose, duration, and route of administration of the patient's antimicrobial regimen
   - Optimal medication administration time for the patient's lifestyle and other concurrent medications
   - Available options for missed dose(s)
   - Adverse effects that may occur
   - Provide patient education monographs for antibiotic(s)

ABBREVIATIONS

BUN:	Blood urea nitrogen
CBC:	complete blood cell count
CRP:	C-reactive protein
CT:	computed tomography
CYP:	cytochrome P-450 isoenzyme
ESR:	erythrocyte sedimentation rate
IVDA:	intravenous drug abuser
LFT:	liver function test
MAO:	monoamine oxidase
MRI:	magnetic resonance imaging
MRSA:	methicillin-resistant *S. aureus*
MSSA:	methicillin-sensitive *S. aureus*
PVD:	peripheral vascular disease
Scr:	serum creatinine
TMP-SMX:	trimethoprim-sulfamethoxazole
UTI:	urinary tract infection
WBC:	White blood count

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

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79 Sepsis and Septic Shock

S. Scott Sutton



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Compare and contrast the definitions used for sepsis.
2. Identify the pathogens that cause sepsis.
3. Discuss the pathophysiology of sepsis as it relates to endotoxin, peptidoglycan, and pro- and anti-inflammatory mediators.
4. Identify patient symptoms as early or late sepsis and evaluate diagnostic and laboratory tests for patient treatment and monitoring.
5. Assess complications of sepsis and discuss their impact on patient outcomes.
6. Design desired treatment outcomes for septic patients.
7. Formulate a treatment and monitoring plan (pharmacologic and nonpharmacologic) for septic patients.
8. Evaluate patient response and devise alternative treatment regimens for non-responding septic patients.

Key Concepts

❶ Sepsis represents a continuum of physiologic stages that is defined by categories that describe the sepsis process.

❷ Gram-positive and gram-negative bacteria, fungal species, anaerobes, and viruses cause sepsis.

❸ Inflammation is the key factor in the development of sepsis. Patients with severe infections, trauma, debilitating conditions, or an immunocompromised status may experience an imbalance between inflammatory mediators that progresses to sepsis.

❹ The cumulative burden of sepsis complications is the leading factor of mortality. The risk of death increases 20% with failure of each additional organ. Severe sepsis averages two failed organs, with a mortality rate of 40%.

❺ Treatment is aimed at early goal-directed resuscitation; reducing or eliminating organ failures; treating and eliminating the source of infection; avoiding adverse reactions of treatment; and providing cost-effective therapy.

❻ Appropriate empiric anti-infective therapy decreases 28-day mortality. Appropriate therapy administered within 1 hour of the recognition of sepsis decreases complications and mortality.

❼ Drotrecogin alfa may be utilized for patients at a high risk of mortality, and is not utilized for patients at a low risk of mortality (as defined by APACHE II scores).

Sepsis is a continuum of physiologic stages characterized by infection, systemic inflammation, and hypoperfusion with widespread tissue injury.[1] ❶ The American College of Chest Physicians and the Society of Critical Care Medicine developed definitions to utilize for sepsis (Table 79–1).[2] ❶ They provide physiologic parameters categorizing patients as having: bacteremia, infection, systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, or multiple-organ-dysfunction syndrome (MODS).[2] Standardized definitions have been developed for infections in critically ill patients.[3]

EPIDEMIOLOGY AND ETIOLOGY

Sepsis is the leading cause of morbidity and mortality for critically ill patients, and the tenth leading cause of death overall.[1,4] Sepsis causes 660,000 to 750,000 cases annually, a four-fold increase from 1979.[1,4,5] Care of septic patients costs $17 billion in the United States annually ($22,000 to $50,000 per patient).[4,6]

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❶ **TABLE 79–1. Definitions Related to Sepsis[2]**

Bacteremia (fungemia): Presence of viable bacteria or fungi in the bloodstream.
Infection: Inflammatory response to invasion of normally sterile host tissue by microorganisms.
Systemic Inflammatory Response Syndrome (SIRS): A systemic inflammatory response to a variety of clinical insults which can be infectious, but can have a noninfectious etiology. The response is manifested by two or more of the following conditions: temperature greater than 38°C (100.4°F) or less than 36°C (96.8°F); pulse greater than 90 beats/minute; respiratory rate greater than 20 breaths/minute or $PaCO_2$ less than 32 torr; WBC greater than 12,000 cells/mm^3, less than 4,000 cells/mm^3, or greater than 10% immature (band) forms.
Sepsis: The systemic inflammatory response syndrome and documented infection (culture or Gram stain of blood, sputum, urine, or normally sterile body fluid positive for pathogenic microorganisms
Severe sepsis: Sepsis associated with organ dysfunction, hypoperfusion, or hypotension (systolic blood pressure less than 90 mm Hg). Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or acute alteration in mental status.
Septic shock: Sepsis with hypotension, despite fluid resuscitation, along with the presence of perfusion abnormalities. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time perfusion abnormalities are measured.
Multiple-Organ Dysfunction Syndrome (MODS): Presence of altered organ function requiring intervention to maintain homeostasis.

$PaCO_2$, partial pressure of carbon dioxide; WBC, white blood cell count.

Risk factors for sepsis include: age, cancer, immunodeficiency, chronic organ failure, genetic factors (male, and nonwhite ethnic origin in North America), bacteremic patients, and polymorphisms in genes that regulate immunity.[4,7–10] Pulmonary, gastrointestinal, genitourinary, and bloodstream infections account for the majority of sepsis cases.[4,7,8]

❷ Gram-positive and gram-negative bacteria, fungal species, anaerobes, and viruses cause sepsis (Table 79–2). Gram-positive infections account for 30% to 50% of sepsis and septic shock cases.[4,7,8] The percentages of gram-negative, polymicrobial, and viral sepsis cases are 25%, 25%, and 4%, respectively.[4,7-8,11] Multi–drug resistant bacteria are responsible for approximately 25% of sepsis cases, are difficult to treat, and increase mortality.[7,8] The rate of fungal infections increased 200% from 1979 to 2000.[4] ❷ *Candida albicans* is the most common fungal species; however, non-albicans species (*C. glabrata*, *C. krusei*, and *C. tropicalis*) have increased from 24% to 46%.[4,11–12] Other fungi identified as causes of sepsis include *Cryptococcus*, *Coccidioides*, *Fusarium*, and *Aspergillus*.

PATHOPHYSIOLOGY

The development of sepsis is complex and multifactorial. The normal host response to infection is designed to localize and control bacterial invasion and initiate repair of injured tissue through **phagocytic** cells and inflammatory mediators.[1] Sepsis results when the inflammatory response becomes systemic and extends to normal tissue distant from the initial tissue site.

❷ **TABLE 79–2. Pathogens in Sepsis[4–7]**

Organism	Frequency (%)
Gram-positive bacteria	30–50
Methicillin-susceptible *Staphylococcus aureus*	14–24
Methicillin-resistant *S. aureus*	5–11
Other *Staphylococcus* species	1–3
Streptococcus pneumoniae	9–12
Other *Streptococcus* species	6–11
Enterococcus species	3–13
Anaerobes	1–2
Other gram-positive bacteria	1–5
Gram-negative bacteria	25–30
Escherichia coli	9–27
Pseudomonas aeruginosa	8–15
Klebsiella pneumoniae	2–7
Enterobacter species	6–16
Haemophilus influenzae	2–10
Anaerobes	3–7
Other gram-negative bacteria	3–12
Fungi	
Candida albicans	1–3
Other *Candida* species	1–2
Parasites	1–3
Viruses	2–4

Pro- and Anti-Inflammatory Mediators

❸ The key factor in the development of sepsis is inflammation. Inflammation is intended to be a local and contained response to infection or injury. Infection or injury is controlled through pro- and anti-inflammatory mediators. Proinflammatory mediators facilitate clearance of the injuring stimulus, promote resolution of injury, and are involved in processing of damaged tissue.[1,13–16] In order to control the intensity and duration of the inflammatory response, anti-inflammatory mediators are released that act to regulate proinflammatory mediators.[15–16] ❸ The balance between pro- and anti-inflammatory mediators localizes infection/injury of host tissue.[13–16] However, systemic responses ensue when equilibrium in the inflammatory process is lost.

The inflammatory process in sepsis is linked to the coagulation system. Pro-inflammatory mediators may be procoagulant and antifibrinolytic, whereas anti-inflammatory mediators may be fibrinolytic. A key factor in the inflammation of sepsis is activated protein C, which enhances fibrinolysis and inhibits inflammation. Protein C levels are decreased in septic patients.

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation of sepsis varies and the rate of development of clinical manifestations may differ from patient to



Clinical Presentation of Sepsis

The signs and symptoms of septic patients are referred to as early and late sepsis.

Signs and Symptoms

The initial clinical signs and symptoms represent early sepsis, and they include: fever, chills, and change in mental status. Other signs and symptoms include:

- **Tachycardia**
- **Tachypnea**
- Nausea and vomiting
- Hyperglycemia
- Myalgias
- Lethargy and malaise
- **Proteinuria**
- **Leukocytosis**
- **Hypoxia**
- **Hyperbilirubinemia**

Septic patients may have an elevated, low, or normal temperature. The absence of fever is common in neonates and elderly patients. Hypothermia is associated with a poor prognosis. Hyperventilation may occur before fever and chills and may lead to respiratory alkalosis. Disorientation and confusion may develop early in septic patients, particularly in the elderly and patients with preexisting neurologic impairment. Disorientation and confusion may be related to the infection or due to sepsis signs and symptoms (e.g., hypoxia).

Late sepsis represents a slow process that develops over several hours of hemodynamic instability. Signs and symptoms of late sepsis include:

- **Lactic acidosis**
- **Oliguria**
- **Leukopenia**
- **Thrombocytopenia**
- Myocardial depression
- Pulmonary edema
- Hypotension
- Hypoglycemia
- Gastrointestinal hemorrhage

Oliguria often follows hypotension because of decreased perfusion. Metabolic acidosis ensues because of diminished clearance by the kidneys and liver of lactic acid.

patient. Certain disease states or bacterial organisms may cause progression to late sepsis more rapidly; examples include patients with immunosuppression, meningococcemia, and *Pseudomonas aeruginosa* infections.



Physical Examination Results in Sepsis

HEENT: Scleral icterus, dry mucous membranes, pinpoint pupils, dilated and fixed pupils, nystagmus

Neck: Jugular venous distention, carotid bruits

Lungs: Crackles (rales), consolidation, egophony, absent breath sounds

CV: Irregular rhythm, S_3 gallop, murmurs

Abd: Tense, distended, tender, rebound, guarding, hepatosplenomegaly

Rectal: Decreased tone, bright red blood

Exts: Swollen calf, disparity of blood pressure between upper extremities

Neurologic: Agitation, confusion, delirium, obtundation, coma

Skin: Cold, clammy, or warm; hyperemic skin; rashes

Physical Examination

The physical examination should be performed rapidly and efficiently, with efforts directed toward uncovering the most likely cause of sepsis. The patient may or may not provide any medical history; therefore historical data may be obtained from medical records and/or family. The patient's medical condition, recent illnesses, infections, or activities may provide valuable information about the cause of sepsis.

Diagnostic and Laboratory Tests

Microbiologic cultures should be obtained before anti-infective therapy is initiated. However, cultures take 6 to 48 hours and may be negative (no growth of bacterial organisms). Negative cultures do not rule out infection.

Two sets of blood cultures should be obtained, because two sets of cultures are required to rule out contamination. At least one should be drawn percutaneously and one drawn through each vascular access device, unless the device was recently (less than 48 hours) inserted.

Cultures to obtain if clinical situation dictates:

- Urine culture and urinalysis, respiratory secretions, cerebrospinal fluid, wounds

Laboratory tests to evaluate infection or complications of sepsis:

- Complete blood count with differential
- Coagulation parameters



Patient Encounter, Part 1

A 67-year-old man with a history of chronic obstructive pulmonary disease presents to the emergency department with high fevers, shaking chills, severe chest pain, and shortness of breath. His family members state that he has been confused all day. He started having a severe cough 2 days ago, with excessive sputum production. He received doxycycline 100 mg twice daily for an upper respiratory tract infection 7 days ago.

- What information is suggestive of infection and/or sepsis?
- Does this patient have factors that could lead to the development of sepsis?
- What information do we need in order to confirm or diagnose sepsis in this patient?

- Basic metabolic panel
- Serum lactate concentration
- Arterial blood gas

Biomarkers of sepsis have been controversial. The routine use of endotoxin, procalcitonin, or other markers is not routinely recommend. Concentrations of procalcitonin in serum are usually increased in sepsis, but fail to differentiate between infection and inflammation. However, procalcitonin has a high negative predictive value and could allow for the discontinuation of antibiotics.

Complications of Sepsis

❹ Recognition and treatment of sepsis complications is essential for improving outcomes. The cumulative burden of sepsis complications is the leading factor of mortality. The risk of death increases 20% with failure of each additional organ. Severe sepsis averages two failed organs, with a mortality rate of 40%. The most common complications are: disseminated intravascular coagulation, acute respiratory distress syndrome, acute renal failure, and hemodynamic compromise.

Disseminated Intravascular Coagulation

❹ Disseminated intravascular coagulation (DIC) complicates 25% to 50% of septic patients, and is an independent predictor of mortality.[17] DIC is a syndrome characterized by coagulation and activation and production of pro-inflammatory **cytokines**, culminating in intravascular fibrin formation and deposition in the microvasculature. Bleeding results from consumption and exhaustion of coagulation proteins and platelets, because of continued activation of the coagulation system.[17] DIC may produce acute renal failure, hemorrhagic necrosis of the gastrointestinal mucosa, liver failure, acute pancreatitis, ARDS, and pulmonary failure.[17]

Acute Respiratory Distress Syndrome

❹ Acute respiratory distress syndrome (ARDS) is an acute and persistent lung inflammatory process with increased vascular permeability leading to severe hypoxia. ARDS can affect 20% of septic shock patients.[18–19] Lung deterioration is a multi-phase process that begins after infection, injury, or exacerbation of the medical condition. The patient appears stable; however, the chest radiograph reveals parenchymal infiltrates. At this time the patient has pulmonary edema and may be hyperventilating.[18–19] During the next phase the patient develops respiratory insufficiency and pulmonary edema can be seen on chest radiographs. Severe hypoxia may ensue, leading to mechanical ventilation.

Acute Renal Failure

❹ Acute renal failure (ARF) occurs in 19% of septic patients, 25% of severe septic patients, and 51% of septic shock patients.[20] Sepsis and acute renal failure have a 70% mortality, compared to 45% among patients with ARF alone.[20] ARF leads to fluid in the extravascular space, including the lungs, followed by impairment in gas exchange and severe hypoxemia. The hypoxemia will exacerbate ischemia and organ damage. Renal replacement therapy with the use of continuous venovenous hemofiltration and intermittent hemodialysis can be used to facilitate volume and electrolytes.[20]

Hemodynamic Compromise

❹ Arterial vasodilatation is the hallmark of hemodynamic effects related to sepsis. High cardiac output and low systemic vascular resistance characterize arterial vasodilation. Tumor necrosis factor-α (TNF-α) and endotoxin directly depress cardiovascular function. Persistent hypotension offsets the delivery of oxygen to tissues (D_{O_2}) and oxygen consumption by tissues (V_{O_2}).[21] Certain tissues may receive adequate oxygen during sepsis; however, in other tissues oxygen demands may not be met because of decreased perfusion. This perfusion defect is accentuated by increased precapillary atrioventricular shunt. If perfusion decreases, oxygen extraction increases, and the atrioventricular oxygen gradient widens. Cellular D_{O_2} is decreased, but V_{O_2} remains unchanged. If perfusion decreases significantly, reserve D_{O_2} will be exceeded, and tissue ischemia results. Tissue ischemia leads to organ failure. Therefore, increasing oxygen delivery or decreasing oxygen consumption in a hypermetabolic patient should optimize systemic D_{O_2} relative to V_{O_2}.[21]

TREATMENT AND OUTCOME EVALUATION

Desired Outcomes

❺ The primary treatment goal of sepsis is to prevent morbidity and mortality. Treatment is aimed at early goal-directed resuscitation; reducing or eliminating organ failures; treating and eliminating the source of infection; avoiding adverse reactions of treatment; and providing cost-effective therapy.[22–28]

General Approach to Treatment

The speed and appropriateness of therapy administered in the initial hours after sepsis develops influences outcome, as is the case for acute myocardial infarction and cerebrovascular accidents.[22]

Pertinent issues in the management of septic patients are (Fig. 79–1):[24]

1. Early goal-directed resuscitation of septic patients during the first 6 hours after recognition.
2. Early administration of broad-spectrum anti-infective therapy.
3. Activated protein C in patients with severe sepsis and high risk of death (Acute Physiology, Age, and Chronic Health Evaluation II [APACHE II] score greater than 25).
4. Hydrocortisone for septic shock patients refractory to resuscitation and vasopressors, with adrenal insufficiency.
5. Glycemic control via infusion of insulin and glucose to maintain a glucose level between 80 and 110 mg/dL (4.4 and 6.1 mmol/L).
6. Adjunctive therapies: nutrition, deep vein thrombosis prophylaxis, stress ulcer prophylaxis, and sedation for mechanically ventilated patients.

Pharmacologic Therapy

Treatment for sepsis focuses on infection, inflammation, hypoperfusion, and widespread tissue injury. Septic patients may require

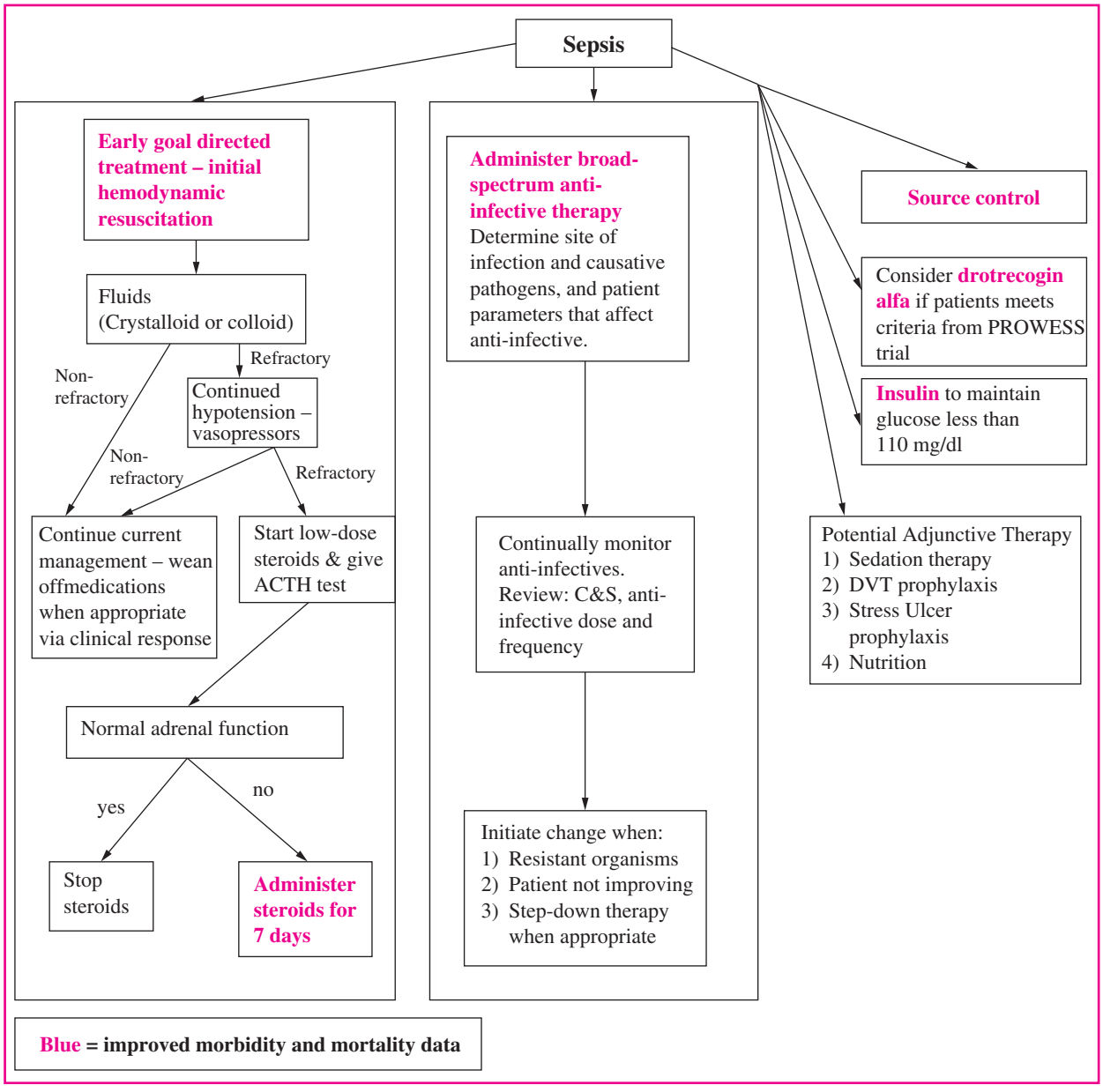


FIGURE 79–1. Therapeutic approach to sepsis. C&S, culture and sensitivity.



Patient Encounter, Part 2: The Medical History, Physical Exam, and Diagnostic Tests

PMH
Chronic obstructive pulmonary disease
Hypertension
Diabetes mellitus
Chronic renal insufficiency (baseline serum creatinine 1.6 mg/dL [141.44 µmol/L])

FH
Father had stroke at age 59; mother has history of hypertension and diabetes mellitus

SH
Construction worker; smoker with 35 pack-year history

Meds
No known drug allergies
Albuterol/ipratropium inhaler 2 puffs every 6 hours
Glipizide 10 mg once daily
Hydrochlorothiazide 25 mg once daily
Lisinopril 20 mg once daily

ROS
Unable to obtain; patient has become more confused

PE
VS: Blood pressure 87/53 mm Hg, pulse 97 bpm, respiratory rate 34/minute, temperature 39.3°C (102.7°F)
Lungs: decreased breath sounds

Labs
Serum creatinine 2.7 mg/dL (238.68 µmol/L); glucose 298 mg/dL (16.54 mmol/L); white blood cells: leukocytosis with left shift
Cultures: Blood, urine, and respiratory cultures pending
Radiology: Chest x-ray shows infiltrates in left lower lobe

- According to the patient's parameters what does he have (i.e., systemic inflammatory response syndrome, sepsis, or septic shock)?
- Identify treatment goals (nonpharmacologic and pharmacologic).

multiple simultaneous treatment regimens to achieve desired outcomes of decreased morbidity and mortality.

Initial Resuscitation

❺ Early goal-directed resuscitation decreases 28-day mortality in septic patients. The treatment goals of sepsis-induced hypoperfusion (hypotension or lactic acidosis) during the first 6 hours include:[24,27–29]

- Central venous pressure: 8 to 12 mm Hg (12 to 5 mm Hg for intubated patients)
- Mean arterial pressure greater than or equal to 65 mm Hg
- Urine output greater than or equal to 0.5 mL/kg per hour
- Central venous or mixed venous oxygen saturation greater than or equal to 70%

❺ Crystalloid or colloid fluids are used for resuscitation and clinical studies comparing the fluids found them to be equivalent.[29] Crystalloids require more fluids, which may lead to more edema (utilize caution in patients at risk for fluid overload, e.g., congestive heart failure and ARDS); however, colloids are significantly more expensive. Most patients require aggressive fluid resuscitation during the first 24 hours because of persistent venodilation and capillary leak.[24]

Monitoring parameters and alternative treatment for resuscitation:[24,27–29]

- An elevated serum lactate concentration may be an early marker for tissue hypoperfusion.
- Administer a fluid challenge to hypovolemic patients (hypotension or lactic acidosis): crystalloids 500 to 1,000 mL; colloids 300 to 500 mL. Administer over 30 minutes and repeat based on response (increase in blood pressure and urine output).
- Patients may require maintenance fluid therapy.

Anti-Infective Therapy

❻ Appropriate empiric anti-infective therapy decreases 28-day mortality compared to inappropriate empiric therapy (24% versus 39%).[22–23,30] ❻ Additionally, appropriate therapy administered within 1 hour of sepsis recognition also decreases complications and mortality.[22–23,30] Empiric anti-infective therapy should include one, two, or three drugs, depending on the site of infection and causative pathogens (Table 79–3). Anti-infective clinical trials in sepsis and septic shock patients are scarce and have not demonstrated differences among agents; therefore, factors that determine selection are:

- Site of infection
- Causative pathogens
- Community- or nosocomial-acquired infection
- Immune status of patient
- Antibiotic susceptibility and resistance profile for the institution
- Patient history (underlying disease, previous cultures or infections, and drug intolerance)
- Adverse reactions
- Cost

❻ Anti-infective regimens should be broad-spectrum since there is little margin for error in critically ill patients.

Monitoring and treatment strategies to maximize efficacy and minimize toxicity for anti-infectives:

- Administer broad-spectrum anti-infectives for initial therapy.
- Administer antibiotics that concentrate at the site of infection.
- Monitor patient parameters to ensure adequate dosing.

- Abnormal renal and hepatic function will increase drug concentration and predispose the patient to toxicity.
- Septic patients may have altered volume of distribution due to initial resuscitation.
- Re-evaluate the initial regimen in 48 to 72 hours by reviewing microbiologic and clinical data.
- Initiate step-down therapy based on microbiologic cultures to: prevent resistance and reduce toxicity and cost.
- Monotherapy is equivalent to combination therapy once a causative pathogen has been identified. Empiric therapy should include combination regimens to ensure coverage of causative organisms.

Selection of Antimicrobial Agents

Urinary Tract Infections

Septic patients with a community-acquired urinary tract infection should be treated with a third-generation cephalosporin or a fluoroquinolone. ❷ The causative pathogen is commonly a enteric gram-negative bacilli (i.e., *Escherichia coli*). ❷ Nosocomially-acquired urinary tract infections are often related to catheters and are caused by fermenting and nonfermenting (*Pseudomonas*) gram-negatives, and *enterococci* (see Table 79–3). β-Lactam/β-lactamase inhibitors (i.e., piperacillin-tazobactam), an antipseudomonal cephalosporin (i.e., cefepime or ceftazidime), or a carbapenem, plus an aminoglycoside are recommended treatment options (see Table 79–3).[31]



Clinical Parameters for Aminoglycosides

Tobramycin is more active against *Pseudomonas aeruginosa* than gentamicin, whereas gentamicin is more active against *Serratia* species. Amikacin is the most potent aminoglycoside against the Enterobacteriaceae; however, it should be reserved for bacterial organisms resistant to gentamicin and tobramycin. Select an aminoglycoside based on:

- Local sensitivity patterns
- Patient parameters (infection and microbiologic culture history)
- Cost

Aminoglycosides may be administered by traditional methods (1.5 to 2 mg/kg every 8 hours) or by an extended dosing interval method (4 to 7 mg/kg every 24 hours). The extended dosing method maximizes the pharmacodynamic properties of aminoglycosides (concentration-dependent killing and post-antibiotic effect) and reduces the incidence of nephrotoxicity. Extended dosing interval aminoglycosides have prolonged drug-free periods, during which the saturable uptake of aminoglycosides into the proximal renal tubular cells can be completed. Extended dosing interval aminoglycosides should not be used in pediatric patients, burn victims, pregnant patients, patients with preexisting or progressive renal insufficiency, or for synergy with gram-positive organisms.[32]

TABLE 79–3. Empirical Intravenous Antimicrobial Regimens in Sepsis[31,33–35,38–40]

Infection (Site or Type)	Community-Acquired	Hospital-Acquired
Urinary tract	Third-generation cephalosporin (ceftriaxone) **OR** Fluoroquinolone (levofloxacin or ciprofloxacin)	Antipseudomonal penicillin **OR** Antipseudomonal cephalosporin **OR** Antipseudomonal carbapenem plus aminoglycoside
Community-acquired pneumonia	Third-generation cephalosporin **plus** a macrolide or doxycycline	
Health care–associated, ventilator-asociated, or nosocomial pneumonia (Early onset; no risk factors for MDR pathogens)		Third-generation cephalosporin **OR** Fluoroquinolone **OR** Ampicillin-sulbactam **OR** Ertapenem
Health care–associated, ventilator-associated, or nosocomial pneumonia (Late onset and/or MDR pathogen risk factors)		Antipseudomonal penicillin **OR** Antipseudomonal cephalosporin **OR** Antipseudomonal carbapenem **plus** Aminoglycoside **OR** Antipseudomonal fluoroquinolone **plus** Vancomycin or linezolid
Intra-abdominal	Ampicillin-sulbactam **OR** Fluoroquinolone + metronidazole	Piperacillin-tazobactam **OR** Imipenem or meropenem **OR** Cefepime **plus** metronidazole **OR** Ciprofloxacin or levofloxacin **plus** metronidazole
Skin and soft tissue	Nafcillin or cefazolin	Ceftriaxone +/– vancomycin
Catheter-related		Vancomycin
Unknown source of infection		Antipseudomonal penicillin **OR** Antipseudomonal cephalosporin **OR** Antipseudomonal carbapenem **plus** Aminoglycoside **plus** Vancomycin

MDR, multi–drug resistant.

Community-Acquired Pneumonia

Septic patients with community-acquired pneumonia (CAP) are treated with a third-generation cephalosporin plus a macrolide or doxycycline, or a respiratory fluoroquinolone (see Table 79–3).[33] ❷ The causative organisms for CAP are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and atypical organisms (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*). *S. pneumoniae* accounts for 60% of the deaths associated with CAP, and is resistant to penicillin and macrolides (multi–drug resistant *S. pneumoniae*; MDRSP) 30% to 40% of the time.[33–34] Controversy exists relating to the clinical significance of this resistance for non-meningitis infections. Respiratory fluoroquinolones are indicated for MDRSP; however, clinical data have not shown them to be superior to cephalosporins plus a macrolide or doxycycline. The Centers for Disease Control and Prevention recommends reserving fluoroquinolones as last-line options in order to maintain their broad-spectrum antibacterial activity.[34]

Hospital-, Ventilator-, and Health Care–Associated Pneumonia

Treatment for septic patients with hospital-acquired, ventilator-acquired, and health care–associated pneumonia is dependent on risk factors for multi–drug resistant (MDR) organisms (Fig. 79–2). Recommended treatment for patients with no MDR risk factors are: third-generation cephalosporins, fluoroquinolones, ampicillin-sulbactam, or ertapenem (see Table 79–3).[35] Recommended treatment for patients with MDR risk factors are: β-lactam/β-lactamase inhibitors (piperacillin-tazobactam), antipseudomonal cephalosporin, or carbapenem, plus an aminoglycoside, plus vancomycin or linezolid (see Table 79–3).[35] If an aminoglycoside is undesirable, a antipseudomonal fluoroquinolone may be utilized with a β-lactam/β-lactamase inhibitor.



❷ Clinical Dilemma about Methicillin-Resistant *Staphylococcus aureus*

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a common hospital-acquired pathogen and is also increasing in the community. MRSA has presented a problem in the past because it required treatment with vancomycin. Community-acquired MRSA presents a major therapeutic challenge. MRSA can cause pneumonia, cellulitis, and other infections. Clinicians should be aware of the rate of hospital and community MRSA in your geographic area. New treatment options are available for MRSA. They include linezolid, tigecycline, and daptomycin. Prospective clinical trials have not demonstrated benefits of these agents over vancomycin.[36–37]



Patient Encounter, Part 3

Treatment and Outcome Evaluation

The patient has continued hypotension despite previous intervention. Continued hypoxia has led to mechanical ventilation. The patient's serum creatinine has risen to 6.8 mg/dL. Blood cultures reveal gram-positive cocci and lactose-negative oxidase-positive gram-negative rods.

- Design a therapeutic regimen for this patient. Include all necessary medications.

Skin and Soft Tissue Infections

❷ Community-acquired skin and soft tissue infections are caused by *Streptococcus pyogenes* and *Staphylococcus aureus.* Treatment with nafcillin or cefazolin is recommended (see Table 79–3).[38] Soft tissue infections caused by *Streptococcus pyogenes* can lead to streptococcal toxic shock syndrome. Although penicillins and cephalosporins are efficacious, experimental models show clindamycin to be more effective than penicillin.[31] ❷ Hospital-acquired skin and soft tissue infections are caused by *Streptococcus pyogenes, Staphylococcus aureus,* and enteric gram-negatives. Recommended treatment is a third-generation cephalosporin, ampicillin-sulbactam, or ertapenem, plus vancomycin (see Table 79–3).[38]

Intra-Abdominal Infections

❷ Intra-abdominal infections are polymicrobial, including enteric aerobes and anaerobes. Patients with community-acquired infections of mild to moderate severity should be administered antibiotics with activity against enteric gram-negative bacilli, gram-negative anaerobes, and gram-positive cocci. Recommended treatment for mild to moderate community-acquired intra-abdominal infections are: ampicillin-sulbactam; cephalosporins plus metronidazole; fluoroquinolones plus metronidazole; and ertapenem (see Table 79–3).[39] Patients with nosocomial-acquired or high severity intra-abdominal infections or immunosuppression should receive empiric treatment with broad-spectrum antibiotics. Broad-spectrum antibiotics such as antipseudomonal β-lactam/β-lactamase inhibitors, carbapenems, antipseudomonal cephalosporins plus metronidazole, or antipseudomonal fluoroquinolones plus metronidazole are recommended (see Table 79–3).[39]

Antifungal Therapy

Septic patients not responding to conventional antibiotics should be evaluated for fungal infections. ❷ *Candida albicans* is the most common fungal species; however, the prevalence of non-albicans species is increasing. Amphotericin B is utilized in septic patients with fungal or suspected fungal infections

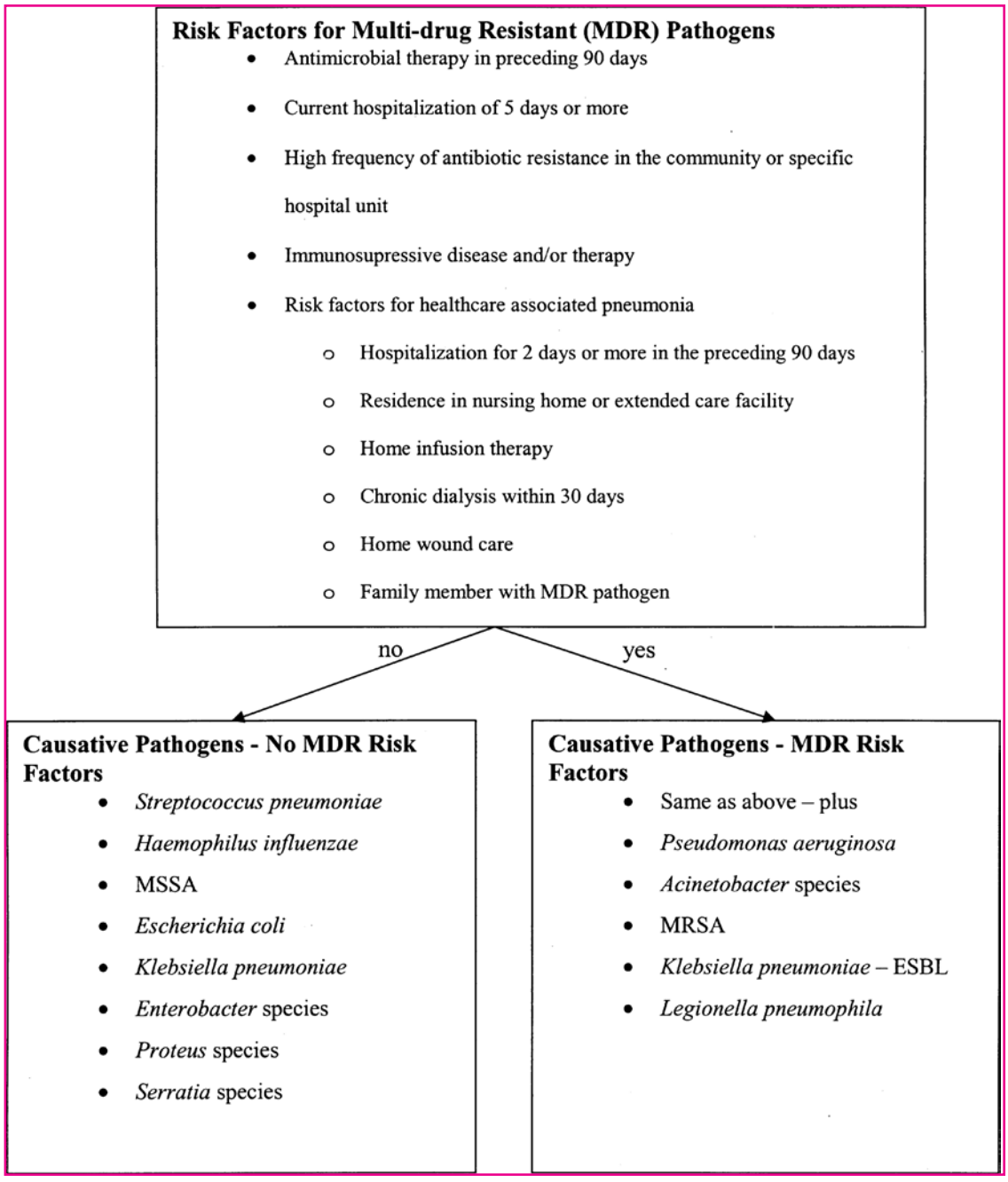


FIGURE 79–2. Risk factors for multi–drug resistant pathogens and causative pathogens for hospital-acquired, ventilator-acquired, and health care–associated pneumonia.[35] ESBL, extended spectrum β-lactamase; MDR, multi–drug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

because of greater activity against non-albicans *Candida* compared to fluconazole.[40] However, amphotericin B has a significantly higher rate of adverse reactions. Lipid formulations of amphotericin B are available that are less nephrotoxic and have decreased infusion-associated side effects. Efficacy among the amphotericin products is equivalent, but the lipid formulations are significantly more expensive. Lipid products are recommended for patients intolerant of conventional amphotericin. Other alternatives for treatment of fungal infections include voriconazole and echinocandins (caspofungin). Data are lacking that demonstrate clinical superiority between agents.

Duration of Therapy

Average duration of anti-infective therapy for septic patients is 7 to 10 days. However, the durations vary depending on the site of infection and response to therapy. Step-down therapy from intravenous to oral anti-infectives is recommended for:

- Hemodynamically stable patients
- Patients afebrile for 48 to 72 hours
- Patients with normalized white blood cell count
- Patients able to take oral medications



Clinical Controversy

Enterococcus species are normal inhabitants of the gastrointestinal tract, but should empiric treatment of intra-abdominal infections have activity against *Enterococcus* species? Empiric treatment that covered *Enterococcus* species in intra-abdominal infections was equivalent to empiric treatment that lacked enterococcal coverage. Routine coverage for *Enterococcus* is not necessary for patients with community-acquired intra-abdominal infections. However, in patients with nosocomial or high-severity infections, enterococcal coverage may be warranted.[39]

Vasopressors and Inotropic Therapy

When fluid resuscitation does not provide adequate arterial pressure and organ perfusion, vasopressors and/or intropic agents should be initiated. Vasopressors are recommended in patients with a systolic blood pressure less than 90 mm Hg or mean arterial pressure (MAP) lower than 60 to 65 mm Hg, after failed treatment with crystalloids.[24,27–28] Vasopressors and inotropes are effective in treating life-threatening hypotension and improving cardiac index, but complications such as tachycardia and myocardial ischemia require slow titration of the adrenergic agents to restore MAP without impairing stroke volume. Vasopressor therapy may also be required transiently to sustain life and maintain perfusion in the face of life-threatening hypotension, even when fluid resuscitation is in progress and hypovolemia has not yet been corrected. Agents commonly considered for vasopressor or inotropic support include dopamine, dobutamine, norepinephrine, phenylephrine, and epinephrine. Norepinephrine or dopamine are first-line vasopressors to correct hypotension in septic shock.[24,27–28]

Norepinephrine is a potent α-adrenergic agent with less pronounced β-adrenergic activity. Doses of 0.01 to 3 mcg/kg per minute can reliably increase blood pressure with small changes in heart rate or cardiac index. Norepinephrine is a more potent agent than dopamine in refractory septic shock.[24,27–28]

Dopamine is a α- and β-adrenergic agent with dopaminergic activity. Low doses of dopamine (1 to 5 mcg/kg per minute) maintain renal perfusion, higher doses (greater than 5 mcg/kg per minute) exhibit α- and β-adrenergic activity and are frequently utilized to support blood pressure and to improve cardiac function. Low doses of dopamine should not be used for renal protection as part of the treatment of severe sepsis.[24,27–28]

Dobutamine is a β-adrenergic inotropic agent that can be utilized for improvement of cardiac output and oxygen delivery. Doses of 2 to 20 mcg/kg per minute increase cardiac index; however, heart rate increases significantly. Dobutamine should be considered in septic patients with adequate filling pressure and blood pressure, but low cardiac index. If used in hypotensive patients, dobutamine should be combined with vasopressor therapy.[24,27–28]

Phenylephrine is a fast-acting, short-duration α_1 agonist. Phenylephrine has primarily vascular effects, and does not impair cardiac or renal function. Phenylephrine is useful when tachycardia limits the use of other vasopressors.[24,27–28]

Epinephrine is a nonspecific α- and β-adrenergic agonist. Epinephrine can increase cardiac index and produce significant peripheral vasoconstriction. However, it can also increase lactate levels and impair blood flow to the splanchnic system. Because of these undesirable effects, epinephrine should be reserved for patients who fail to respond to traditional therapies.[24,27–28]

Vasopressin levels are increased during hypotension to maintain blood pressure by vasoconstriction. However, there is a vasopressin deficiency in septic shock. Low doses of vasopressin increase MAP, leading to the discontinuation of vasopressors. However, routine use of vasopressin is not recommended because of lack of evidence of efficacy. Vasopressin is a direct vasoconstrictor without inotropic or chronotropic effects and may result in decreased cardiac output and hepatosplanchnic flow. Vasopressin use may be considered in patients with refractory shock despite adequate fluid resuscitation and high-dose vasopressors.[24,27–28]

Recombinant Human Activated Protein C

❼ Recombinant human activated protein C (drotrecogin alfa) is recommended for patients at a high risk of death (APACHE II score greater than or equal to 25, multiple organ failure, septic shock, or ARDS) and no absolute contraindications related to bleeding.[41] Drotrecogin alfa has antithrombotic, anti-inflammatory, and profibrinolytic properties. The Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial evaluated the effects of a 96-hour continuous infusion of drotrecogin alfa. Drotrecogin alfa decreased 28-day mortality compared to placebo (30.8% versus 24.7%). A higher incidence of serious bleeding occurred during the 28-day period in the drotrecogin alfa group (3.5%) than in the placebo group (2.0%). An analysis of secondary endpoints suggested that the incidence of multiple organ dysfunction was lower in patients treated with drotrecogin alfa, and that therapy was associated with more rapid recovery of cardiac and pulmonary function. A second study of patients with severe sepsis (ENHANCE trial) noted that 28-day all cause mortality for patients treated with drotrecogin alfa was similar to that observed in PROWESS. ENHANCE also found that patients treated within the first 24 hours of their first sepsis-induced organ dysfunction had significantly lower mortality than those treated after 24 hours (22.9% to 27.4%). Cost-effectiveness models have found that for septic patients with a APACHE II score greater than or equal to 25, the cost per year of life saved with drotrecogin alfa is $24,000 to $27,000, suggesting that this is a cost-effective therapy in patients with severe sepsis and septic shock. The effect of drotrecogin alfa on long-term

survival was evaluated in a retrospective analysis of patients in PROWESS. The mortality benefit of drotrecogin alfa persisted up to hospital discharge; however, there were no mortality differences between drotrecogin alfa and placebo thereafter.[42]

❼ Drotrecogin alfa is not recommended for severe sepsis patients at low risk for death. The Drotrecogin Alfa (Activated) for Adults with Severe Sepsis and a Low Risk of Death (ADDRESS) trial evaluated the effects of a 96-hour continuous infusion of drotrecogin alfa. There were no statistically significant differences between drotrecogin alfa and placebo in 28-day mortality (18.5% versus 17.0%).[43] The rate of serious bleeding was higher for drotrecogin alfa during the 96-hour infusion and the 28-day study period.

Steroids

Stress-induced adrenal insufficiency complicates 9% to 24% of septic patients and is associated with increased mortality. Adrenal-insufficient patients are identified by a adrenocorticotropic hormone (ACTH) stimulation test. Patients are given 250 mcg ACTH and a cortisol level is checked within 30 to 60 minutes. Responders are defined as a greater than 9-mcg/dL increase in cortisol and non-responders as a less than 9-mcg/dL increase in cortisol. Septic shock patients refractory to resuscitation and vasopressors, and with adrenal insufficiency (non-responders to the ACTH test) should be administered intravenous hydrocortisone 200 to 300 mg per day in three divided doses for 7 days.[24,44]

Sedation and Neuromuscular Blockade

Patients with progressive hypoxia leading to ARDS require mechanical ventilation. Critically ill patients may require sedation when high ventilator settings are used or when patients fight the ventilator. Mechanically ventilated patients should receive sedation by a protocol that includes a daily interruption or lightening of a sedative infusion until the patient is awake.[24] The utilization of sedation protocols decreases the duration of mechanical ventilation, length of hospitalization, and tracheostomy rates.

Paralysis usually is reserved for cases in whom sedation alone does not improve the effectiveness of mechanical ventilation. Neuromuscular blockers may lead to prolonged skeletal muscle weakness and should be avoided if possible. Patients requiring neuromuscular blockade are to be monitored and intermittent boluses should be utilized.



Patient Encounter, Part 4

During medical rounds, you are asked to discuss clinical trials.

- What antibiotics are found to be superior in septic patients?
- What are the results of the PROWESS and ADDRESS trials?
- Is this patient a candidate for drotrecogin alfa?

Glucose Control

Glycemic control improves survival in postoperative surgical patients and is recommended in septic patients. Following initial stabilization of septic patients, maintain blood glucose levels between 80 and 110 mg/dL (4.4 and 6.1 mmol/L).[24,45] Septic patients with high glucose levels should receive insulin and glucose with frequent blood glucose monitoring (every hour initially, then every 2 to 4 hours once glucose levels have stabilized).

Adjunctive Therapies

Enteral nutrition is recommended in septic patients to meet the increased energy and protein requirements. Protein requirements are increased to 1.5 to 2.5 g/kg per day. Nonprotein caloric requirements range from 25 to 40 kcal/kg per day.[24]

Deep vein thrombosis prophylaxis is recommended for septic patients. Low-dose unfractionated heparin or low-molecular-weight heparin may be utilized. Graduated compression stockings or an intermittent compression device is recommended for patients with a contraindication to heparin products (thrombocytopenia, severe coagulopathy, active bleeding, or recent intracerebral hemorrhage).[24]

Stress ulcer prophylaxis is recommended in septic patients. Patients at greatest risk for stress ulcers are: coagulopathic, mechanically ventilated, and hypotensive. Histamine-receptor antagonists are more efficacious than sucralfate, and proton pump inhibitors have not been compared to histamine-receptor antagonists. However, they do demonstrate equivalence in the ability to increase gastric pH.[24]

Nonpharmacologic Therapy

❺ Evaluate septic patients for the presence of a localized infection amenable to source control measures. Common source control measures include:[24–26]

- Drainage and débridement
- Device removal
- Prevention

❺ Implementation of source control methods should be instituted as soon as possible following initial fluid resuscitation. The selection of optimal source control methods must weigh benefits and risks of the intervention. Source control measures may cause complications (bleeding, fistulas, and organ injury), therefore the method with the least risk should be employed.[24]

Prognosis

Short-term mortality from sepsis has decreased in recent years. There are various factors that influence outcome. Gram-negative bacteria are more likely to produce septic



Patient Care and Monitoring

1. Evaluate patient parameters and classify as infection, SIRS, sepsis, severe sepsis, septic shock, or MODS.
2. Review available diagnostic and laboratory data.
3. Evaluate early goal-directed resuscitation therapy. Understand what parameters define efficacy and failure of initial therapy. Recommend alternative resuscitation therapy if the patient does not respond to initial fluid challenge.
4. Evaluate the source of infection and make recommendations to remove potential source(s).
5. Analyze anti-infective therapy (dose, frequency, and duration) and revise as necessary based on clinical response and culture and sensitivity reports. Prepare an appropriate step-down therapy for the patient.
6. Determine the risk of sepsis complications and construct recommendations for treatment and monitoring.
7. Formulate appropriate doses of medications involved in patient therapy and revise as needed. Patient parameters may change frequently, thus requiring different doses and/or medications. Examples include: antibiotic therapy, sedatives, insulin, fluids, or vasopressors.
8. Continually monitor patient parameters to ensure optimal therapy to maximize outcomes.

shock than gram-positive bacteria (50% versus 25%) and have a higher mortality than other pathogens. This may be related to the severity of the underlying condition. Patients with rapidly fatal conditions, such as leukemia, aplastic anemia, and burn patients have a worse prognosis than patients with nonfatal underlying conditions, such as diabetes mellitus or chronic renal insufficiency. Other factors that worsen the prognosis of septic patients are: advanced age, malnutrition, resistant bacteria, utilization of medical devices, and immunosuppression. Data for long-term mortality are lacking (it is estimated that the mortality for sepsis survivors within the first year is 20%).[5] Patients may have prolonged physical disability related to muscle weakness and post-traumatic stress.

CONCLUSION

Sepsis is a leading cause of morbidity and mortality and has a significant financial impact in our health care system. Treatment for sepsis should begin as soon as sepsis is recognized and key therapeutic priorities are:

- Provide supportive measures that counter physiologic abnormalities such as hypoxemia, hypotension, and impaired tissue oxygenation.
- Focus efforts on distinguishing sepsis from systemic inflammatory response syndrome, since identification and treatment of an infection should be initiated as soon as possible (with antibiotics or surgical drainage).

Septic patients must be monitored closely in order to assess their response to therapy. A combination of clinical and laboratory tests should be evaluated daily and decompensating patients should be rapidly and thoroughly re-evaluated.

ABBREVIATIONS

ACTH:	adrenocorticotropic hormone
APACHE II:	Acute Physiology, Age, and Chronic Health Evaluation II
ARDS:	acute respiratory distress syndrome
ARF:	acute renal failure
CAP:	community-acquired pneumonia
DIC:	disseminated intravascular coagulation
Do_2:	delivery of oxygen to tissues
ESBL:	extended spectrum β-lactamase
MAP:	mean arterial pressure
MDR:	multi–drug resistant
MDRSP:	multi–drug resistant *Streptococcus pneumoniae*
MODS:	multiple-organ-dysfunction syndrome
MRSA:	methicillin-resistant *Staphylococcus aureus*
MSSA:	methicillin-sensitive *Staphylococcus aureus*
$Paco_2$:	partial pressure of carbon dioxide
PROWESS:	Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (study)
SIRS:	systemic inflammatory response syndrome
TNF-α:	tumor necrosis factor-α
WBC:	white blood cell
Vo_2:	oxygen consumption by tissues

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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80 Superficial Fungal Infections

Lauren S. Schlesselman



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Explain the underlying pathophysiology of vulvovaginal candidiasis, oropharyngeal candidiasis, esophageal candidiasis, and fungal skin infections.
2. Identify symptoms of vulvovaginal candidiasis, oropharyngeal candidiasis, esophageal candidiasis, and fungal skin infections.
3. Identify the desired therapeutic outcomes for patients with uncomplicated and complicated vulvovaginal candidiasis, oropharyngeal candidiasis, esophageal candidiasis, and fungal skin infections.
4. Recommend appropriate lifestyle modifications and pharmacotherapy interventions for patients with vulvovaginal candidiasis, oropharyngeal candidiasis, esophageal candidiasis, and fungal skin infections.
5. Recognize when long-term suppressive therapy is indicated for a patient with vulvovaginal candidiasis.
6. Recognize when topical versus oral treatment is indicated for a patient with oropharyngeal candidiasis, esophageal candidiasis, and fungal skin infections.
7. Educate patients about the disease state, appropriate lifestyle modifications, and medication therapy required for effective treatment of vulvovaginal candidiasis, oropharyngeal candidiasis, esophageal candidiasis, and fungal skin infections.

Key Concepts

❶ The predominant pathogen associated with vulvovaginal candidiasis is *Candida albicans*, although a small percentage of cases are caused by *Candida glabrata, Candida tropicalis, Candida krusei,* and *Candida parapsilosis.*

❷ A variety of factors may increase the risk of developing symptomatic vulvovaginal candidiasis, including antibiotic use, diabetes, and immunosuppression. No risk factors are consistently associated with all cases of vulvovaginal candidiasis.

❸ Asymptomatic vaginal colonization of *Candida albicans* is not diagnostic of vulvovaginal candidiasis since 10% to 20% of women are asymptomatic carriers of *Candida* species. Asymptomatic vaginal colonization does not require treatment.

❹ Selection of antifungal agents to treat uncomplicated vulvovaginal candidiasis is influenced by patient preference, including route of administration, duration of therapy, cost, risk of adverse effects, and potential for medication interactions.

❺ Recurrent vulvovaginal candidiasis, defined as four or more infections per year, requires long-term suppressive therapy for 6 months.

❻ The occurrence of oropharyngeal and esophageal candidiasis is an indicator of immune suppression, often developing in infants, the elderly, and the immunocompromised.

❼ Topical agents are first-line therapy for oropharyngeal candidiasis, although oral agents may be used for severe or unresponsive cases.

❽ Representing a severe form of extension of oropharyngeal candidiasis, esophageal candidiasis requires oral antifungal therapy.

❾ Since dermatophyte hyphae seldom penetrate into the living layers of the skin, instead remaining in the stratum corneum, most infections can be treated with topical antifungals. Infections

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covering large areas of the body or infections involving nails or hair may require oral therapy.

⑩ Onychomycosis, fungal infections involving the nails, requires oral antifungal therapy. Topical agents do not adequately penetrate the nail.

VULVOVAGINAL CANDIDIASIS

Vulvovaginal candidiasis (VVC), whether symptomatic or asymptomatic, refers to infections in women whose vaginal cultures are positive for *Candida* species.

Epidemiology and Etiology

Vulvovaginal candidiasis, also known as moniliasis, is a common form of vaginitis, accounting for 20% to 25% of vaginitis cases. Although VVC is uncommon prior to **menarche**, nearly 50% of women will experience one or more episodes by the age of 25 years.[1] A survey of women in the United States found that 6.5% of women over the age of 18 years reported experiencing at least one episode of vaginitis during the previous 2 months.[2]

According to the treatment guidelines of the Centers for Disease Control and Prevention (CDC),[3] VVC can be classified as uncomplicated or complicated. Uncomplicated infections are typically infrequent and cause mild to moderate symptoms. Complicated infections, including recurrent or severe infections, may be caused by azole-resistant fungal organisms. Immunocompromise, including immunosuppression, uncontrolled diabetes, pregnancy, or debilitation, is a risk factor for developing recurrent infection. Recurrent VVC, defined as four or more infections per year, occurs in less than 5% of women.[4] Recurrent infection is distinguishable from a persistent infection by the presence of a symptom-free interval between infections.

Pathophysiology

❶ *Candida albicans* is the primary pathogen responsible for vulvovaginal candidiasis, accounting for more than 90% of cases.[5] A small percentage of cases are caused by non-albicans species including *Candida glabrata, Candida tropicalis, Candida krusei,* and *Candida parapsilosis*. In patients with recurrent vaginitis, the causative *Candida* is twice as likely to be non-albicans.[6] Some research suggests that the incidence of non-albicans VVC is increasing, possibly due to overuse of over-the-counter vaginal antifungal products, short-course treatments, and long-term suppressive therapy with antifungals.[7]

Risk Factors

❷ *Although no risk factors are consistently associated with conversion to symptomatic infection, a variety of factors may*



Patient Encounter, Part 1

A 28-year-old woman with a history of diabetes presents to your clinic complaining of what she calls "itching in my private areas." After questioning her, you determine that she has vaginal burning and itching, accompanied by a curd-like discharge. On examination, she has erythema of the labia and a non-odorous discharge.

- What information is suggestive of VVC?
- What additional information do you need to know before creating a treatment plan for this patient?



Clinical Presentation and Diagnosis of Vulvovaginal Candidiasis

Patients with vulvovaginal candidiasis may present with vulvar and/or vaginal symptoms. Symptoms often develop the week before menses and resolve with the onset of menses.
Symptoms include:

- Itching
- Soreness
- Burning
- Irritation
- External dysuria
- **Dyspareunia**

Signs include:

- Non-odorous discharge (may vary from watery to curd-like)
- Erythema and edema of the labia and vulva
- Fissures
- Pustulopapular lesions
- Normal cervix

Diagnostic Testing

- Microscopic investigation for the presence of **blastospores** or **pseudohyphae**; saline wet mount has a sensitivity of 40% to 50%, while a potassium hydroxide (KOH) preparation has a sensitivity of 50% to 70%.[7] ❸ *Asymptomatic vaginal colonization of* Candida albicans *is not diagnostic of VVC since 10% to 20% of women are asymptomatic carriers of* Candida *species. Asymptomatic vaginal colonization does not require treatment; therefore the presence alone of* Candida *should not determine care.*
- Vaginal pH less than or equal to 4.5; pH should remain normal in cases of fungal infection, while an elevated pH suggests bacterial infection.
- *Candida* cultures should be obtained only if signs and microscopy are inconclusive or in cases of recurrent VVC.

TABLE 80–1. Possible Risk Factors Associated with Vulvovaginal Candidiasis (VVC)

Risk Factor	Proposed Mechanism
Broad-spectrum antibiotic use	Altered vaginal flora allowing overgrowth of *Candida* organisms; risk increases with duration of antibiotic use
Systemic corticosteroid or immunosuppressant use	Reduced vaginal protection by immunoglobulins
Sexual activity	A small percentage of male partners have penile or oral colonization of identical strains; VVC is often associated with the onset of sexual activity
Tight-fitting and non-absorbent clothing	Promotes warm, moist environment for fungus growth
Elevated estrogen levels, hormonal contraceptives, and pregnancy	Estrogen enhances *Candida* adherence to vaginal epithelial cells and yeast-mycelial transformation; this is supported by the fact that infection rates are lower before menarche and after menopause (except in women taking hormone replacement therapy), while rates are higher during pregnancy
Vaginal pH	Changes in glycogen and lactic acid levels
Gastrointestinal reservoir of *Candida* organisms	Transfer of organism from rectum to vagina; irritation of the vulvovaginal area during sexual intercourse may enhance invasion of organisms
Diabetes	Enhanced binding of *Candida* to epithelial cells due to hyperglycemia; asymptomatic colonization is more common in patients with diabetes; elevated sugar levels may cause conversion to symptomatic infection

increase the risk of developing symptomatic VVC in certain women (Table 80–1).

Treatment

The goals of treatment of VVC are:

- Relief of symptoms
- Eradication of infection
- Re-establishment of normal vaginal flora
- Prevention of recurrent infections in complicated infections

Nonpharmacologic Treatments

In combination with pharmacologic treatment, the practitioner should recommend basic nonpharmacologic approaches to treatment and prevention of VVC:

- Keep the genital area clean and dry
- Avoid prolonged use of hot tubs
- Avoid constrictive clothing
- Wear underwear made of breathable materials, such as cotton
- To reduce vulvar irritation, avoid soaps and perfumes in the genital area
- Although study results are conflicting, the daily consumption of active *Lactobacillus acidophilus* may reduce recurrence. One study found that the daily ingestion of 8 ounces of yogurt produced a threefold reduction in the incidence of infection,[8] while other studies found no difference in infection rates in women who ingested yogurt.[9,10]

Pharmacologic Treatment of Uncomplicated VVC

Most cases of uncomplicated VVC will resolve with a single course of antifungal therapy. Treatment with an oral or vaginal antifungal agent, either prescription or nonprescription, is appropriate for most uncomplicated cases. Nonprescription azole antifungal products are available as 1-night, 3-night, and 7-night regimens in a variety of formulations, including cream, suppository, and vaginal tablets (Table 80–2).

To avoid inappropriate use of over-the-counter (OTC) products, the practitioner should only recommend them to women who have previously been diagnosed with VVC. Estimates of how

TABLE 80–2. Treatment Options for Uncomplicated VVC

1-Day Therapies
Butoconazole 2% sustained-release cream, 5 g intravaginally as a single application
Fluconazole 150 mg, one tablet orally as a single dose
Tioconazole 6.5% ointment, 5 g intravaginally as a single application

3-Day Therapies
Butoconazole 2% cream, 5 g intravaginally for 3 nights
Clotrimazole 100-mg vaginal tablet, two tablets for 3 nights
Miconazole 200-mg vaginal suppository, one suppository for 3 nights
Terconazole 0.8% cream, 5 g intravaginally for 3 nights
Terconazole 80-mg vaginal suppository, one suppository for 3 nights

7 to 14-Day Therapies
Clotrimazole 1% cream, 5 g intravaginally for 7–14 nights
Clotrimazole 100-mg vaginal tablet, one tablet for 7 nights
Miconazole 2% cream, 5 g intravaginally for 7 nights
Miconazole 100-mg vaginal suppository, one suppository for 7 nights
Nystatin 100,000-unit vaginal tablet, one tablet for 14 nights
Terconazole 0.4% cream, 5 g intravaginally for 7 nights

accurately women self-diagnose VVC are difficult to assess. One study found that only one-third of women accurately diagnosed an episode of vaginitis.[11] Women with a previous clinically based diagnosis of VVC are no more accurate at self-diagnosing than women without prior clinical diagnosis.[11]

❹ *Due to the numerous treatment options available, a variety of factors can influence product selection, with patient preference playing a significant role.* To improve adherence with therapy, the practitioner should discuss with the patient what options are available and what her preferences are.

Route of Administration

Adherence rates are greater with oral treatment than with vaginal therapy. This may be due to the ease of administration, short duration, and flexibility on time of administration. Vaginal creams provide rapid relief of itching and burning. The need to clean the vaginal applicator for reuse is unappealing for some women. Many OTC vaginal products are now packaged with sufficient disposable applicators to prevent the need for reuse with subsequent doses.

Duration of Therapy

Available regimens range from 1 to 7 days. Cure rates are similar among different durations of therapy.[12]

Cost

Most OTC products cost $10 to $20 per course of therapy. The cost of prescription products can vary based on if and what type of insurance coverage the patient has.

Risk of Adverse Effects

Systemic adverse effects associated with vaginal azoles are less frequent than with oral products. Local discomfort such as burning may occur with the first application. Fifteen percent of patients experience gastrointestinal side effects with orally administered antifungal agents.[13] Oral ketoconazole is associated with hepatic toxicity at a rate of 1 in 15,000.[14]

Risk of Medication Interactions

Oral azoles are associated with significant interactions, particularly due to cytochrome P-450 isoenzymes. Medications that interact with azoles include warfarin, phenytoin, theophylline, rifampin, cyclosporine, and zidovudine. For patients receiving only a few doses, these interactions do not pose a significant risk. These interactions may pose a risk for patients receiving long-term suppressive therapy for recurrent infections.

Inability to resolve an infection may indicate a mixed infection, infection due to a non-albicans strain, or an infection that is not fungal. Difficulty treating VVC can also be indicative of serious underlying conditions, such as diabetes or human immunodeficiency virus (HIV) infection. For these reasons, if infection does not resolve easily with a single course of antifungal therapy or if symptoms return within 2 months, practitioners should check cultures and further evaluate the patient's health status or refer the patient to a physician.

Treatment of Recurrent VVC

The goal of treating recurrent VVC is control of the infection, rather than cure. First, any acute episodes are treated, followed by maintenance therapy. For the treatment of acute episodes, intravaginal or oral azoles can be utilized. Although acute episodes of recurrent VVC will respond to azole therapy, some patients may require prolonged therapy in order to achieve remission. To achieve remission, a second dose of oral fluconazole 150 mg repeated 3 days after the first dose or 14 days of topical azole therapy can be used. The practitioner should consider that non-albicans infections are more common in recurrent VVC; therefore fluconazole and itraconazole resistance may make these agents less effective.

❺ *After achieving remission, recurrent VVC requires long-term suppressive therapy for 6 months* (Table 80–3). To improve adherence to long-term suppressive therapy, oral therapy, typically with fluconazole, is preferred. Studies have shown that fluconazole 150 mg weekly for 6 months will prevent recurrence of infection in 90% of women.[15] Cessation of suppressive therapy is associated with resurgence of symptomatic infection in 50% of women.[16]

Treatment of Non-Albicans Infections

Response rates are lower for non-albicans infections. Although an optimal regimen is unknown, use of intravaginal azole therapy for 7 to 14 days is recommended. Terconazole may prove more effective than other azoles in the treatment of non-albicans infections since *C. glabrata* and *C. tropicalis* are more susceptible to terconazole.[17] For second-line therapy, boric acid 600 mg in a gelatin capsule administered vaginally twice daily for 2 weeks followed by once daily during menstruation is effective.[18] Local irritation often limits the use of boric acid. Topical 4% flucytosine is also effective but use should be limited due to the potential for resistance.

VVC during Pregnancy

During pregnancy, VVC may prove difficult to treat due to elevated estrogen levels, accompanied by concern about harm to the fetus. Response rates are lower and recurrences are frequent during pregnancy. Vaginal antifungals remain the preferred treatment during pregnancy, although therapy should continue for 1 to 2 weeks to ensure effectiveness.[16] Most topical

TABLE 80–3. Treatment Options for Maintenance Therapy

Daily
Boric acid 600 mg in gelatin capsule vaginally daily during menses (5 days)
Itraconazole 100 mg orally once daily
Ketoconazole 100 mg orally once daily
Weekly
Clotrimazole 500 mg vaginal suppository once weekly
Fluconazole 100 or 150 mg orally once weekly
Terconazole 0.8% cream 5 g vaginally once weekly
Monthly
Fluconazole 150 mg orally once monthly
Itraconazole 400 mg orally once monthly



Patient Care and Monitoring

1. Assess the patient's symptoms to determine if self-treatment with OTC antifungal therapy is appropriate or whether the patient should be evaluated by a practitioner or physician. OTC preparations should only be recommended for patients who have previously been diagnosed with VVC. Patients who experience more than four episodes per year should be referred to a physician for culturing and initiation of maintenance therapy.
2. Review any available diagnostic data, including cultures and KOH preps.
3. Obtain a thorough history of prescription, nonprescription, and natural drug product use. Is the patient taking any medications, such as steroids or immunosuppressants, that may contribute to VVC? Is the patient taking any medications that may interfere with treatment?
4. If the patient has had VVC previously, determine what treatments were helpful to the patient in the past.
5. Educate the patient on lifestyle modifications that may prevent recurrence, including decreased consumption of sucrose and refined carbohydrates, increased consumption of yogurt containing live cultures, and wearing cotton underwear.
6. Develop a plan to assess effectiveness of antifungal therapy.
7. Determine if long-term suppressive therapy is necessary.
8. Evaluate the patient for the presence of adverse drug reactions, drug allergies, and drug interactions.
9. Stress the importance of adherence with the antifungal regimen, including lifestyle modifications.
10. Provide patient education pertaining to vulvovaginal candidiasis and antifungal therapy.
    - Causes of vulvovaginal candidiasis
    - How to administer vaginal antifungal creams
    - Vaginal antifungal creams' and suppositories' adverse effects on latex condoms and diaphragms
    - Potential adverse effects that may occur with antifungal therapy
    - Medications which may interact with antifungal therapy
    - Warning signs to report to a physician (recurrent or difficult-to-cure infections, infections with malodorous discharge)

antifungals are classified as risk category C, while clotrimazole is classified as risk category B. The primary reason for the risk category C classification is the lack of studies, rather than increased risk. Fluconazole is also classified as risk category C. Despite oral fluconazole's classification, studies have not demonstrated an increased risk to the fetus when the pregnant mother was exposed to fluconazole,[19,20] although case studies have reported congenital limb deformities.[21]

Outcome Evaluation

Patients should notice relief of itching and discomfort within 1 to 2 days. The volume of discharge should also begin to decrease within a few days. The entire course of therapy should be continued even if symptoms have resolved. If the condition does not resolve or worsens, the patient should be referred to a physician for aggressive therapy. If the condition recurs within 4 weeks or more than four times per year, the patient should be further evaluated or referred to a physician for evaluation of possible non-*Candida* infections, resistant organism, or other complicating factors, along with assessment of need for long-term suppressive therapy.

OROPHARYNGEAL AND ESOPHAGEAL CANDIDIASIS

Oropharyngeal candidiasis (OPC) is a common fungal infection, usually associated with immune suppression. If left untreated, it will progress to more serious oral disease. Esophageal candidiasis, representing a serious progression of oropharyngeal candidiasis, is associated with increased morbidity.

Epidemiology and Etiology

❻ *The occurrence of oropharyngeal and esophageal candidiasis is an indicator of immune suppression, often developing in infants, the elderly, and the immunocompromised.* One-third to one-half of geriatric inpatients develop oropharyngeal candidiasis. Denture stomatitis is present in 24% to 60% of denture wearers,[22] more commonly in women than men. Oral candidiasis is the most commonly reported adverse drug event reported by patients receiving inhaled corticosteroids.[23] Recent studies have reported the prevalence of esophageal candidiasis as 37% among patients treated with inhaled corticosteroids.[24] The incidence is highest among patients receiving high doses of corticosteroids or those with diabetes.

The prevalence of HIV infection plays a significant role in the incidence of oropharyngeal and esophageal candidiasis. In the 1980s, the incidence of oropharyngeal candidiasis increased fivefold, in association with the spread of HIV infections.[25] Although HIV infection remains a risk factor for candidiasis, the introduction of highly active antiretroviral therapy precipitated a decline in the incidence of both infections by 50% to 60%.[26]

Oropharyngeal candidiasis remains the most common opportunistic infection in patients with HIV. Eighty to ninety percent of HIV-positive patients develop oropharyngeal candidiasis.[27] For 70% of these patients, it is the first manifestation of HIV infection.[28] The incidence of oropharyngeal infection increases with decreasing CD4 lymphocyte counts, with an incidence of 60% in patients with a CD4 count less than 200 cells/mm^3.

Although esophageal candidiasis represents the first manifestation of HIV infection in less than 10% of cases, it is the second most common acquired immunodeficiency syndrome (AIDS)-defining disease.[29] As with oropharyngeal candidiasis, the incidence of esophageal candidiasis increases with decreasing CD4 counts.

Pathophysiology

Candida albicans accounts for 80% of cases of OPC and esophageal candidiasis. Over the last 20 years, an increasing incidence of *C. albicans* resistance has been accompanied by an increased incidence of non-albicans species infections, including *Candida glabrata, Candida tropicalis, Candida krusei*, and *Candida parapsilosis*. In patients with cancer, non-albicans *Candida* species account for almost half of all cases.[29]

Risk Factors

Risk factors for OPC can be found in Table 80–4.

Clinical Presentation and Diagnosis



Oropharyngeal Candidiasis

Oropharyngeal candidiasis is often a presumptive diagnosis based on signs and symptoms, along with the resolution of them after treatment with antifungal agents.

Symptoms

- Sore, painful mouth and tongue
- Burning tongue
- **Dysphagia**
- Metallic taste

Signs

Signs vary depending on the type of oropharyngeal candidiasis.

- Diffuse erythema on the surface of buccal mucosa, throat, tongue, and gums
- White patches on tongue, gums, or buccal mucosa; removal of patches reveals erythematous and bloody tissue; ability to remove patches distinguishes OPC from oral hairy leukoplakia
- Angular cheilitis presents with small cracking lesions, erythema, and soreness at the corners of the mouth; associated with vitamin and iron deficiency
- Denture stomatitis presents with flat, red lesions on mucosa beneath dentures; signs of chronic erythema and edema on mucosa
- Hyperplastic OPC presents with discrete, transparent raised lesions on the inner mucosa of the cheek; typically found in men who smoke
- Pseudomembranous OPC presents with yellow-white plaques that may be small and discrete or confluent; most common form found in HIV patients

Diagnostic Testing

Diagnosis is primarily based on identification of characteristic lesions. Although rarely necessary, diagnostic testing is possible if a definitive diagnosis is required.

- Cytology, although presence of *Candida* is not diagnostic since colonization is common
- Culture to identify species of yeast or presence of resistance
- Biopsy



Esophageal Candidiasis

Symptoms

- Fever
- Odynophagia
- Dysphagia
- Retrosternal pain

Signs

- Fever
- **Hyperemic** or edematous white plaques
- Ulceration of esophagus
- Increased mucosal friability
- Narrowing of lumen

Diagnostic Testing

Unlike OPC, diagnosis of esophageal candidiasis is not based solely on clinical presentation, instead requiring endoscopic visualization of lesions and culture confirmation. Due to the invasive nature of these procedures, most practitioners opt to treat the infection presumptively, reserving endoscopic evaluation for patients who fail therapy.

- Cytology and culture to identify species of yeast or presence of resistance
- Barium esophagogram
- Endoscopy revealing whitish plaques with progression to superficial ulceration of the esophageal mucosa
- Mucosal biopsy

Treatment

Along with selecting an effective treatment, selection of an appropriate antifungal agent requires consideration of location and severity of infection, medication adherence, potential drug



Patient Encounter

A 35-year-old woman presents to your clinic complaining of "burning and soreness in my mouth" along with a metallic taste and "this funny white stuff." On initial examination, she has white patches on her tongue, gums, and buccal mucosa. These patches are easily removed, revealing erythematous tissue underneath.

This is the woman's first visit to your clinic, therefore no medical history is available in her chart.

- What additional information do you need to know before creating a treatment plan for this patient?
- What underlying medical conditions might make her susceptible to fungal infections?
- How is the treatment care plan altered if the patient has a history of frequent and severe OPC? if the patient is HIV-positive? If the patient is neutropenic?

TABLE 80–4. Risk Factors for Oropharyngeal and Esophageal Candidiasis

Factor	Proposed Mechanism
Extremes of age	Immature immunity in infants and reduced immunity in the elderly
Impaired mucosal integrity	Breaks in the protective barrier allows fungal invasion; often due to radiation, surgery, or mucositis
Dentures	Adherence of fungus to dentures, along with reduced salivary flow under dentures; ill-fitting dentures may impair mucosal integrity
Xerostomia	Reduced cleansing and defense factors of saliva
Use of antibiotics	Altered flora of mucosa allowing fungal overgrowth
Use of steroids	Suppression of immunity
Use of immunosuppressants	Suppression of immunity
HIV infection	Decreased CD4 T lymphocytes
Diabetes mellitus	Elevated glucose levels and defense factors in saliva
Nutritional deficiencies	Altered defense mechanisms, impaired mucosal integrity, or enhanced pathogenic potential of fungus

interactions, concomitant medical conditions, and presence of sucrose or dextrose. Topical agents require frequent dosing and prolonged contact time with oral mucosa. Rough surfaces of tablets and troches may irritate sensitive mucosa. Patients with **xerostomia** may have inadequate saliva to dissolve troches. Topical agents containing sucrose or dextrose may increase the risk of caries or cause elevated blood sugar in patients with diabetes. Along with being expensive, oral azoles exhibit an increased risk of toxicity and drug interactions due to cytochrome P-450.

Since oropharyngeal and esophageal candidiasis are signs of immunocompromise, the immune status of the patient should be considered in the therapeutic care plan. For HIV-infected patients, this should also include an evaluation of the patient's antiretroviral therapy since fungal infections may represent deterioration in immune status.

❼ *For low-risk patients, topical agents are first-line therapy for oropharyngeal candidiasis, although systemic agents may be used for severe or unresponsive cases.* For patients with severe OPC, oral fluconazole remains the agent of choice. Oral fluconazole administered for 2 weeks exhibits a mycological cure rate of 48% and a **clinical cure** rate of 84% in HIV patients.[30] Response occurs within 5 days in patients receiving 100 to 200 mg daily.[16] Doses as low as 50 mg are effective, but clinical response is slow and potentially leads to resistance. Two weeks of oral itraconazole solution is as effective as fluconazole but is less well tolerated. Due to variable absorption, risk of toxicity, and potential for drug interactions, ketoconazole and itraconazole capsules are considered second-line alternatives to fluconazole.

For non–HIV-infected patients who have suppressed immune systems, the practitioner must consider the patient's risk of dissemination. Patients with cell-mediated immune deficiency but near-normal granulocyte function, such as patients with diabetes, solid organ transplant, or solid tumors, are at low risk for dissemination. The risk of dissemination is higher for patients who develop neutropenia, including patients with leukemia or bone marrow transplant. These patients should be treated aggressively to prevent invasive fungal infection.

For the treatment of OPC in HIV-infected individuals, initial episodes can be adequately controlled with topical agents, such as clotrimazole troches, so long as symptoms are not severe and no esophageal involvement is suspected.[26] Topical nystatin is the least effective agent, especially in severely immunocompromised patients.[31] Topical clotrimazole appears to be the most effective topical antifungal, exhibiting clinical responses equivalent to oral fluconazole and itraconazole solution, but **mycological cure** rates are lower and relapse rates higher with clotrimazole.[29]

❽ *Representing a severe extension of oropharyngeal candidiasis, esophageal candidiasis requires systemic antifungal therapy.* The significant morbidity associated with esophageal candidiasis warrants aggressive treatment. The diagnosis of esophageal candidiasis requires endoscopic evaluation, but rather than employing invasive procedures, patients can be treated with an appropriate course of antifungal based on clinical presentation. If patients do not respond, endoscopy should be considered.

Two to three weeks of fluconazole or itraconazole solution are highly effective and demonstrate similar clinical response rates.[32] Doses of 100 to 200 mg are effective in immunocompetent patients but doses up to 400 mg are recommended for immunocompromised patients. Due to variable absorption, ketoconazole and itraconazole capsules should be considered second-line therapy. In severe cases, oral azoles may prove ineffective, warranting the use of amphotericin B for 10 days. Although echinocandins and voriconazole are effective in treatment of esophageal candidiasis, experience remains limited.



Patient Care and Monitoring

1. Assess the patient's symptoms to determine if symptoms are consistent with oropharyngeal or esophageal candidiasis. All patients with suspected oropharyngeal or esophageal candidiasis should be referred to a practitioner or physician since no antifungal products appropriate for oral use are available without a prescription.
2. Review any available diagnostic data, including cultures.
3. Obtain a thorough history of prescription, nonprescription, and natural drug product use. Is the patient taking any medications that may contribute to candidiasis? Is the patient taking any medications that may interfere with treatment?
4. If the patient has had oropharyngeal or esophageal candidiasis previously, determine what treatments were helpful to the patient in the past.
5. If the patient has had oropharyngeal or esophageal candidiasis previously, determine if the patient has risk factors for recurrent infection.
6. Develop a plan to assess effectiveness of antifungal therapy.
7. Determine if long-term suppressive therapy is necessary.
8. Evaluate the patient for the presence of adverse drug reactions, drug allergies, or drug interactions.
9. Stress the importance of adherence with the antifungal regimen.
10. Provide patient education pertaining to oropharyngeal or esophageal candidiasis and antifungal therapy.
    - Causes of oropharyngeal or esophageal candidiasis
    - Risk factors for developing candidiasis
    - How to administer topical antifungal agents, including cleaning the oral cavity prior to administration, administering after meals, how to dissolve troches, and how to swish suspensions
    - Importance of completing the course of therapy
    - Potential adverse effects that may occur with antifungal therapy
    - Medications that may interact with antifungal therapy
    - Warning signs to report to a physician (recurrent or difficult-to-cure infections, or worsening symptoms)

Fluconazole-Resistant Infections

Twenty percent of HIV-infected patients develop fluconazole-resistant *Candida albicans* isolates after repeated exposure to fluconazole.[33] To treat fluconazole-resistant oropharyngeal candidiasis, daily itraconazole for 2 to 4 weeks may be used. Oral itraconazole solution exhibits a mycological cure rate of 88% and a clinical cure rate of 97% in immunocompromised patients.[34] Fluconazole-resistant esophageal candidiasis should be treated with intravenous amphotericin B or caspofungin.

Recurrent Infections

If immunocompromised patients experience frequent or severe recurrences, particularly of esophageal candidiasis, chronic maintenance therapy with fluconazole 100 to 200 mg daily should be considered. In patients with infrequent or mild cases, secondary prophylaxis is not recommended. The rationale for not giving prophylaxis includes availability of effective treatments for acute episodes, risk of developing resistant organisms, potential for drug interactions, and the cost of therapy.

Outcome Evaluation

- Patients should notice symptomatic relief within 2 to 3 days of initiating therapy. Complete resolution typically occurs within 7 to 10 days. The entire course of therapy should be continued even if symptoms have resolved. If the condition does not resolve or worsens, the patient should be referred to a specialist for aggressive therapy.
- Short courses of oral azoles are associated with gastrointestinal upset, while courses lasting longer than 7 to 10 days are associated with increased risk of hepatotoxicity. In patients receiving prolonged therapy lasting more than 3 weeks, periodic monitoring of liver function tests should be considered.
- Immunocompetent patients generally do not require reassessment after treatment. Patients with neutropenia exhibit an increased risk of dissemination of infection, and therefore should be monitored for signs of systemic fungal infection. Due to an increased risk of recurrence, HIV-positive patients should routinely be evaluated for recurrence at each visit.

MYCOTIC INFECTIONS OF THE SKIN, HAIR, AND NAILS

Tinea infections are superficial fungal infections in which the pathogen remains within the keratinous layers of the skin or nails. Typically these infections are named for the affected body part, such as tinea pedis (feet), tinea cruris (groin), and tinea corporis (body). Tinea infections are commonly referred to as ringworm due to the characteristic circular lesions. In actuality, tinea lesions can vary from rings to scales and single or multiple lesions.

Epidemiology and Etiology

Tinea infections are second only to acne in frequency of reported skin disease.[35] The common tinea infections are tinea pedis, tinea corporis, and tinea cruris. Tinea pedis, the most prevalent cutaneous fungal infection, afflicts more than 25 million people annually in the United States.

Pathophysiology

Fungal skin infections are primarily caused by **dermatophytes** such as *Trichophyton, Microsporum,* and *Epidermophyton*. *Trichophyton rubrum* accounts for more than 75% of all cases in the United States.[36] To a lesser extent, *Candida* and other fungal species cause skin infections. With tinea infections, the causative dermatophyte typically invades the stratum corneum without penetration into the living tissues, leading to a localized infection.

Risk Factors

- Prolonged exposure to sweaty clothing
- Excessive skin folds
- Sedentary lifestyle
- Warm, humid climate
- Use of public pools
- Skin trauma
- Poor nutrition
- Diabetes mellitus
- Immunocompromise
- Impaired circulation

Nonpharmacologic Therapy

- Since fungi thrive in warm, moist environments, the practitioner should encourage patients to wear loose-fitting clothing and socks, preferably garments made of cotton or other fabrics that wick moisture away from the body. Avoid clothing made with synthetic fibers or wool.
- Clean the infected area daily with soap and water.
- The infected area should be dried completely prior to dressing, paying particular attention to skin folds.
- To prevent spread, towels, clothing, and footwear should not be shared with other persons.
- Wear protective footwear in public showers and pool areas.



Clinical Presentation and Diagnosis

Symptoms and Signs (Table 80–5)

Diagnostic Testing

- KOH prep
- Wood's ultraviolet lamp
- Microscopic examination
- Fungal cultures
- Periodic acid-Schiff (PAS) staining of nail

Treatment of Skin and Hair Infections

The goals of treatment include:

- Providing symptomatic relief
- Resolution of infection
- Preventing spread of infection

Pharmacologic Therapy

❾ *Since dermatophyte hyphae seldom penetrate into the living layers of the skin, instead remaining in the stratum corneum, most infections can be treated with topical antifungals. Infections covering large areas of the body or infections involving nails or hair may require systemic therapy.* Patients with chronic infections or infections that do not respond to topical therapy are also candidates for systemic therapy.

Treatment is typically initiated based on symptoms, rather than on microscopic evaluation. Since several species can cause tinea infections, the choice of antifungal agent is not always clear. For infections accompanied by inflammation, combination therapy with a topical steroid can be considered.

The selection of vehicle is based on the type of lesion and location of the infection. Solutions are recommended for hairy areas and oozing lesions, while creams are better for moderately scaling and non-oozing lesions. For hyperkeratotic lesions, ointments can be considered. The selected formulation should be applied to the affected area after it is cleaned and dried. The medication should be rubbed into the infected area for improved penetration. Since most patients do not rub in sprays and powders, penetration of the epidermis is minimal, making them less effective than other formulations. Sprays and powders should be considered as adjuvant therapy with a cream or lotion or as prophylactic therapy to prevent recurrence.

Tinea pedis requires treatment one to two times daily for 4 weeks, while tinea corporis and tinea cruris require treatment one to two times daily for 2 weeks. Due to the severity of infection and inflammation, tinea capitis does not adequately respond to topical agents. Oral agents for 6 to 8 weeks are recommended for eradication of tinea capitis. Griseofulvin has long been considered the treatment of choice due to its ability to achieve high levels within the stratum corneum. Itraconazole has also demonstrated effectiveness. Due to its lipophilicity, itraconazole achieves high levels in the skin. These levels are maintained for 4 weeks after medication is discontinued. Some practitioners recommend adjunct therapy with the oral agent to decrease dissemination, including ketoconazole or selenium sulfide shampoos. Treatment of any infection should continue at least 1 week after resolution of symptoms.

Treatment of Onychomycosis

Onychomycosis is a chronic infection that rarely remits spontaneously. Adequate treatment is essential to prevent spread to other sites, secondary bacterial infections, cellulitis, or gangrene. ❿ *Due to the chronic nature and impenetrability of nails, topical agents have low efficacy rates for treating onychomycosis.* Oral agents that can penetrate the nail matrix and nail base, such as itraconazole and terbinafine, are more effective than ciclopirox lacquer. Itraconazole and terbinafine demonstrate mycological cure rates of 62%[37] and 76%,[38] respectively, while ciclopirox has a cure rate of 29% to 36%.[39]

Itraconazole can be administered continuously (200 mg daily) or as pulse therapy (200 mg twice daily for 1 week per

TABLE 80–5. Signs and Symptoms of Superficial Fungal Infections

Infection	Symptoms and Signs
Tinea pedis	• Involves plantar surface and interdigital spaces of foot • Interdigital infections produce itching; presents as fissures, scaling, or macerated skin; can occur between any toes but most often between fourth and fifth toes; may cause foul smell due to superinfection with *Pseudomonas* or diphtheroids • Hyperkeratotic infections present with slivery white scales on a thickened, red base; usually covers entire foot; occasionally may also affect hand • Vesiculobullous tinea pedis presents as pustules or vesicles on soles of feet; associated with maceration, itching, and thickening of sole; may cause lymphangitis and cellulitis; most common during summer months • Ulcerative tinea pedis presents as macerated, denuded, and weeping ulcers on soles; may produce extreme pain and erosion of interdigital spaces; typically complicated by opportunistic gram-negative infections • Risk factors include occlusive footwear and foot trauma
Tinea manuum	• Infection of the interdigital and palmar surfaces • Presents as white scales in palmar folds; may also develop scales on remainder of palm; may present as singular plaque • More commonly affecting only one hand • Presents with hyperkeratotic skin
Tinea cruris	• Presents with follicular papules and pustules on the medial thigh and inguinal folds • Ringed lesions may extend from inguinal fold over adjacent inner thigh • Lesions usually spare the penis and scrotum, in contrast to candidiasis • Frequency increases during summer • Primarily develops in young men • Risk factors include tight-fitting clothing • Commonly referred to as jock itch
Tinea corporis	• Presents with circular, scaly patch with enlarged border • Lesions may have red papules or plaque in center that clears, leaving hypopigmentation or hyperpigmentation • Itching may be present • Commonly referred to as ringworm of the body
Tinea versicolor	• Characterized by skin depigmentation but can present as hyperpigmentation, particularly in dark-skinned patients • Typically occurs in areas with sebaceous glands, including neck, trunk, and arms • Depigmentation may persist for years • Primarily develops in young and middle-aged adults • Risk factors include application of oil, greasy skin, high ambient temperature, high relative humidity, tight-fitting clothing, immunodeficiency, malnutrition, hereditary predisposition
Tinea barbae	• Infection of beard area
Tinea capitis	• Infection of the head and scalp • May be asymptomatic initially, then progress to inflammatory alopecia • "Black dot" alopecia may develop due to breakage of hair at the root • May form kerions (nodular swellings) • Scaling or favus may develop on scalp • Cervical lymphadenopathy is common • Primarily found in infants, children, and young adolescents, often in African-American and Hispanic populations • Can be spread from person to person or animal to person
Onychomycosis (tinea unguium)	• Infection of nail plate and bed • Nail becomes opaque, thick, rough, yellow, and friable; nail may separate from bed • Toenails affected more frequently than fingernails • Prevalence increases with advanced age

month). Terbinafine is administered 250 mg per day as continuous therapy. Whether administered continuously or as pulse therapy, oral treatment for toenail infections should continue for at least 3 months, while treatment for fingernail infections should continue for at least 2 months. Treatment with itraconazole or terbinafine for prolonged periods requires laboratory monitoring of liver function tests before initiation of therapy and at monthly intervals. Griseofulvin is also effective for the treatment of onychomycosis, but therapy must be continued for 4 months for fingernail infections or 6 months for toenail infections. For patients with liver disease or who are unable to use oral agents, ciclopirox nail lacquer remains a reasonable alternative, although it requires 48 weeks of therapy.

Outcome Evaluation

For infections of the skin, patients should notice relief of symptoms, including pruritus, scales, and inflammation, within 1 to 2 weeks. Therapy should be continued at least 1 week after complete resolution of symptoms. If the condition worsens or does not resolve within 4 weeks, the patient should be treated with oral therapy.

For onychomycosis, relief of symptoms is slow. The infected nail will need months to grow out. The practitioner should advise the patient not to become frustrated by the slow resolution. Despite the slow progress, the antifungal agent is curing the infection. The practitioner should also advise the patient that even after the infection is cured, the nail may not look "normal."

ABBREVIATIONS

AIDS: acquired immunodeficiency syndrome
CDC: Centers for Disease Control and Prevention
HIV: human immunodeficiency virus
KOH: potassium hydroxide
OPC: oropharyngeal candidiasis
OTC: over-the-counter
PAS: periodic acid-Schiff test
VVC: vulvovaginal candidiasis

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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Patient Care and Monitoring

1. Assess the patient's symptoms to determine if self-treatment with OTC antifungal therapy is appropriate or whether the patient should be evaluated by a practitioner. Exclusions for self-treatment include infection of nails or hair, unsuccessful initial treatment, worsening condition, signs of secondary bacterial or systemic infection, or chronic medical conditions such as diabetes, immunosuppression, or impaired circulation.
2. Review any available diagnostic data, including cultures and KOH preps.
3. Obtain a thorough history of prescription, nonprescription, and natural drug product use.
4. If the patient has had a mycotic infection previously, determine what treatments were helpful to the patient in the past.
5. Educate the patient on lifestyle modifications that will prevent recurrence, including keeping the area dry, wearing shower shoes, washing clothing in hot water, use of drying powders, and wearing loose-fitting clothing.
6. Develop a plan to assess effectiveness of antifungal therapy.
7. Determine if long-term prophylactic therapy is necessary to prevent recurrence.
8. Evaluate the patient for the presence of adverse drug reactions, drug allergies, and drug interactions.
9. Stress the importance of adherence with the antifungal regimen.
10. Provide the patient education pertaining to mycotic infections and antifungal therapy.
    - Causes of mycotic infections of the skin, hair, or nails
    - Different types of OTC antifungal products, such as creams, sprays, and powders
    - How to apply various OTC antifungal products
    - How long therapy should be continued
    - How to avoid spread of infection
    - How to avoid recurrent infection
    - Potential adverse effects that may occur with antifungal therapy
    - Dietary modifications that are necessary with oral agents
    - Medications that may interact with antifungal therapy, particularly with oral agents used for nail infections
    - Warning signs to report to a physician (recurrent or difficult-to-cure infections, infections with malodorous discharge or bleeding)

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81 Invasive Fungal Infections

Russell E. Lewis and P. David Rogers



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Differentiate epidemiologic differences and host risk factors for acquisition of primary and opportunistic invasive fungal pathogens.
2. Recommend appropriate empiric or targeted antifungal therapy for the treatment of invasive fungal infections.
3. Describe the components of a monitoring plan to assess effectiveness and adverse effects of pharmacotherapy for invasive fungal infections.
4. Evaluate the role of antifungal prophylaxis in the prevention of opportunistic fungal pathogens.

Key Concepts

❶ The most common route of infection for endemic fungi is via the respiratory tract, where conidia aerosolized from contaminated soil are inhaled into the lung.

❷ The diagnosis of endemic fungal infections is often prompted by a patient history of prolonged (subacute) infectious symptoms, travel or residence in an endemic area, and/or participation in activities that result in exposures to soil contaminated by endemic fungi.

❸ The approach to antifungal therapy in patients with endemic fungal infections is determined by the severity of clinical presentation, the patient's underlying immunosuppression, and potential toxicities and drug interactions associated with antifungal treatment.

❹ Secondary prophylaxis or suppressive therapy is recommended for endemic mycoses in immunocompromised patients, especially in hosts with pronounced defects in T-cell–mediated immunity (i.e., AIDS).

❺ Commensal or environmental fungi that are typically harmless can become invasive mycoses when the host immune defenses are impaired. Host immune suppression and risk for opportunistic mycoses can be broadly classified into three categories: (1) quantitative or qualitative deficits in neutrophil function, (2) deficits in cell-mediated immunity, and (3) disruption of mechanical/and or microbiologic barriers.

❻ Familiarity with the epidemiology and frequency of non-albicans *Candida* species in the institution or ICU is essential before selecting empiric antifungal therapy for invasive candidiasis.

❼ Colonization at multiple distinct body sites or with high density of *Candida* species, however, often precedes invasive infection. Preemptive antifungal therapy may be indicated in colonized high-risk populations such as neutropenic fever, transplant recipients, or following major abdominal surgery.

❽ Laboratory identification of *Candida* in clinical samples must be performed to the species level whenever possible, as *Candida* species differ considerably in their susceptibility to antifungal agents.

❾ If a patient is non-neutropenic and has never received prior azole therapy, fluconazole 800 mg/day is an appropriate first-line therapy for invasive candidiasis until identification of the *Candida* isolate. Amphotericin B deoxycholate 0.7 mg/kg per day or caspofungin 70 mg on day 1, then 50 mg/day, voriconazole, or a lipid amphotericin B formulation are recommended as empiric therapy in patients with neutropenic fever.

❿ Direct visualization of *C. neoformans* in the CSF by India ink staining is the most rapid method for diagnosing cryptococcal meningitis.

⓫ Clinical trials performed by the National Institute of Allergy and Infectious Diseases (NIAID) Mycoses Study Group showed that 2 weeks of induction antifungal therapy with combination amphotericin B (0.7 mg/kg per day) plus

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flucytosine (100 mg/kg per day) for cryptococcal meningitis, followed by consolidation therapy with fluconazole (400 mg daily) for 8 weeks was as effective as 4 weeks of combination therapy, and had fewer toxicities.

⑫ Nodular or halo-like lesions detected by high-resolution computed tomography (HRCT) scans are often the first indication of invasive pulmonary aspergillosis.

⑬ Immunocompromised patients on fluconazole with progressive sinus or pulmonary disease by radiography should be evaluated for possible mold infection.

⑭ Many experts now consider voriconazole as the initial drug of choice for invasive aspergillosis in patients without significant contraindications (e.g., drug interactions or preexisting liver dysfunction) to azole therapy.

⑮ Zygomycetes are generally resistant to voriconazole and echinocandins and their presence should be suspected in any patient with progressive mold infection while receiving voriconazole and/or echinocandin therapy.

Invasive fungal infection or **invasive mycoses** are general terms for diseases caused by invasion of living tissue by fungi. Unlike superficial mycoses (Chapter 80), invasive mycoses invade internal organs, can disseminate throughout the body, and are associated with high rates of morbidity and mortality, particularly in the immunocompromised host. Invasive fungal infections are broadly categorized as either primary or opportunistic invasive mycoses. Primary invasive fungal infections are caused by fungal spores or **conidia** in the soil that, when disturbed, can become aerosolized and inhaled leading to infection, even in an immunocompetent patient. Because these fungi are often endemic to certain soil types and hence geographically restricted, primary invasive fungal pathogens are also known as **endemic fungi**. In the United States, three species (*Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis*) account for the majority of these infections (Table 81–1). In contrast, opportunistic fungal infections occur only in the setting of compromised host immune defenses and are caused by a wider spectrum of less virulent fungal species that are generally incapable of causing infection in healthy patients (see Table 81–1). Hence, the spectrum, severity, and outcome of opportunistic fungal infections are heavily influenced by the degree, type, and severity of host immunosuppression. As a general rule, opportunistic fungal infections are difficult to diagnose, uniformly fatal if not treated early and aggressively, and associated with high rates of morbidity and mortality.

TABLE 81–1. Invasive Mycoses

Primary (Endemic) Invasive Fungi
Histoplasma capsulatum[a]
Coccidioides immitis[a]
Blastomyces dermatitidis[a]
Opportunistic Invasive Fungi
Yeast
Candida species (*C. albicans, C. glabrata, C. parapsilosis, C. tropicalis, C. krusei* and others)
Cryptococcus neoformans[a]
Trichosporon spp. and others
Mold
Hylohyphomycetes
Aspergillus fumigatus and other species[a]
Fusarium solani and *Fusarium oxysporum*
Zygomycoses (*Mucor, Absidia, Rhizopus, Cunninghamella,* and *Rhizomucor*)
Penicillium
Phaeohyphomycetes
Pseudallescheria boydii (*Scedosporium* spp.)
Bipolaris
Alternaria
Other
Pneumocystis jiroveci (formerly *P. carinii*)[a,b]

[a]Most common.
[b]Recently reclassified as a fungus.



Patient Encounter, Part 1

A 39-year-old male with chronic steroid-dependent asthma who recently relocated to Phoenix, Arizona presents with a 4-week history of increasing fever, dry cough, and pain upon deep inspiration. He also reports arthralgias and night sweats over the last 3 weeks. A chest radiograph reveals a small area of consolidation in the left lower lobe and some hilar adenopathy. Otherwise, all other routine tests and cultures appear negative.

- What are this patient's risk factors for developing an endemic fungal infection?
- What is the most likely endemic fungal pathogen based on this patient's history?
- What additional information is needed to select antifungal therapy?

ENDEMIC MYCOSES

Epidemiology

Endemic mycoses are true primary fungal pathogens capable of causing infection in otherwise healthy individuals. In immunocompromised patients, endemic fungal infections often present with a more fulminant course (in the case of primary infections) or reactivate to cause life-threatening infection. Because initial symptoms of an endemic fungal infection are often non-specific and overlap with other slowly-progressing infections (e.g., tuberculosis and infective endocarditis), a careful patient history concerning travel and activities associated with potential exposure to soil contaminated with endemic fungi is essential for the diagnosis and early treatment of infection.

Two of the most common endemic fungal infections (histoplasmosis and North American blastomycosis) are found in

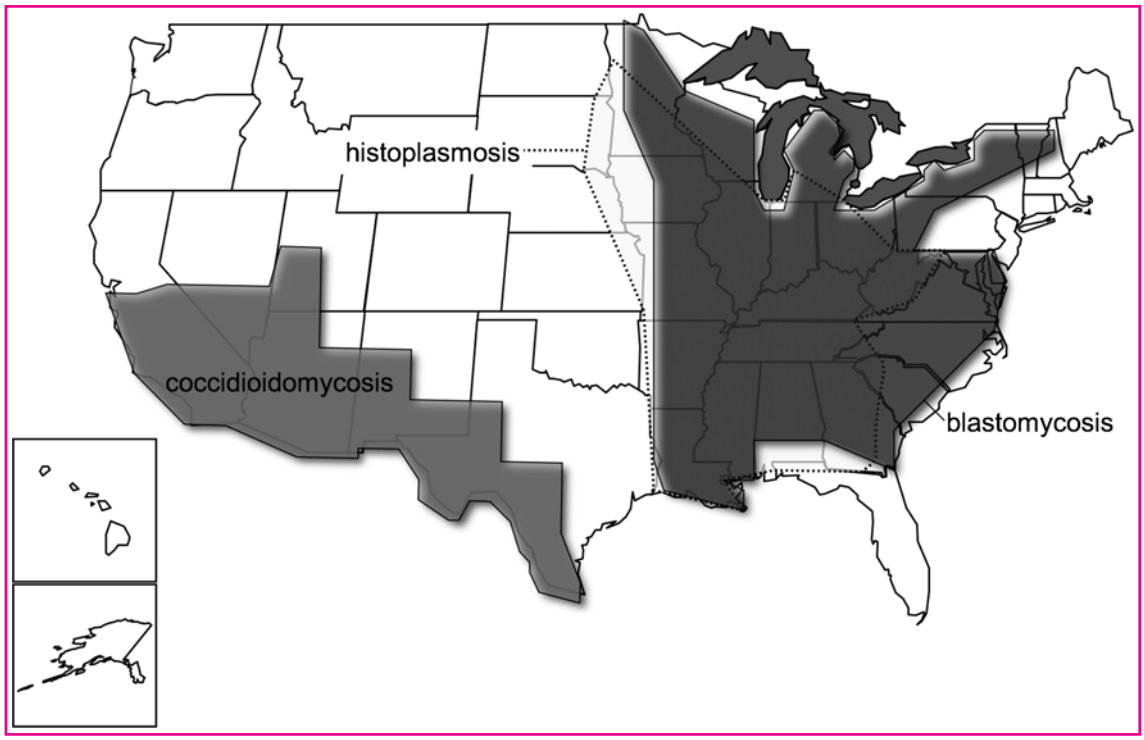


FIGURE 81–1. Geographic localization of primary (endemic) fungi in the United States.

overlapping regions in the eastern and central river basins of the United States (Fig. 81–1).[1] *Histoplasma capsulatum* var. *capsulatum*, the causative fungus of histoplasmosis, grows heavily in soil contaminated with bird or bat excreta, which serve to enhance sporulation of the fungus.[2] Activities in endemic regions that are classically associated with high exposures to *Histoplasma capsulatum* include cave exploration (spelunking), working in or demolishing chicken coops, demolition of older buildings, woodcutting in forests with large bird roosts, or spreading avian excreta as fertilizer. For blastomycosis, decaying organic matter, warm humid conditions, and close proximity to water or frequent rainfall seems to support growth of this fungus.[3] Occupational or recreational activities that disturb soil heavily contaminated with *Blastomyces dermatitidis* are the most common risk factor for development of blastomycosis. Coccidioidomycosis differs from histoplasmosis and blastomycosis, as the fungus is associated with arid to semi-arid climates, hot summers, low altitude, alkaline soil, and sparse flora. Hence the fungus is found in the southwestern regions of the United States stretching from western Texas to southern California (see Fig. 81–1).[4] Epidemics of coccidioidomycosis have been reported in California following dust storms and earthquakes, as well as cycles of intense drought and rain which favor the growth cycle of the fungus and enhance dispersion of its specialized spore forms called arthroconidia.

Pathophysiology

Endemic fungi share several key biologic and ecological characteristics that contribute to their pathogenicity in humans. All endemic fungi exhibit temperature-dependent dimorphism, meaning they can propagate as either a **yeast** (single cells that reproduce by budding into daughter cells) or **molds** (multi-cellular filamentous fungi that reproduce through production of conidia or spores). At environmental temperatures (25° to 30°C) *H. capsulatum*, *B. dermatitidis*, and *C. immitis* grow in the mold form producing 2- to 10-μm round to oval-shaped (*Histoplasma* and *Blastomyces*) or barrel-shaped (*Coccidioides*) conidia that are dispersed throughout the environment and in air currents. At physiologic temperatures, the conidia germinate into yeast (*Histoplasma* and *Blastomyces*) or in specialized cell forms called spherules (*Coccidioides*) that are resistant to killing by resident alveolar macrophages and neutrophils in the lung. Control of infection is mediated by the development of antigen-specific T-lymphocyte response to enhance macrophage fungicidal activity, and lymphocyte/macrophage-mediated formation of a granuloma to contain the fungus.[5] Not surprisingly, patients with T-cell–mediated immune deficiency (e.g., acquired immunodeficiency syndrome [AIDS] patients and transplant recipients) or suppressed cellular immunity due to drug therapy (e.g., chemotherapy, high-dose corticosteroids, or tumor necrosis-α blockers) are especially prone to severe infections.

❶ The most common route of infection for endemic fungi is the respiratory tract, where conidia aerosolized from contaminated soil are inhaled into the lung. Once in the lung, conidia are phagocytosed but not destroyed by resident macrophages and neutrophils in the alveoli and bronchioles. Within 2 to 3 days, conidia germinate into **facultative** yeast resistant to phagocytosis and killing by macrophages

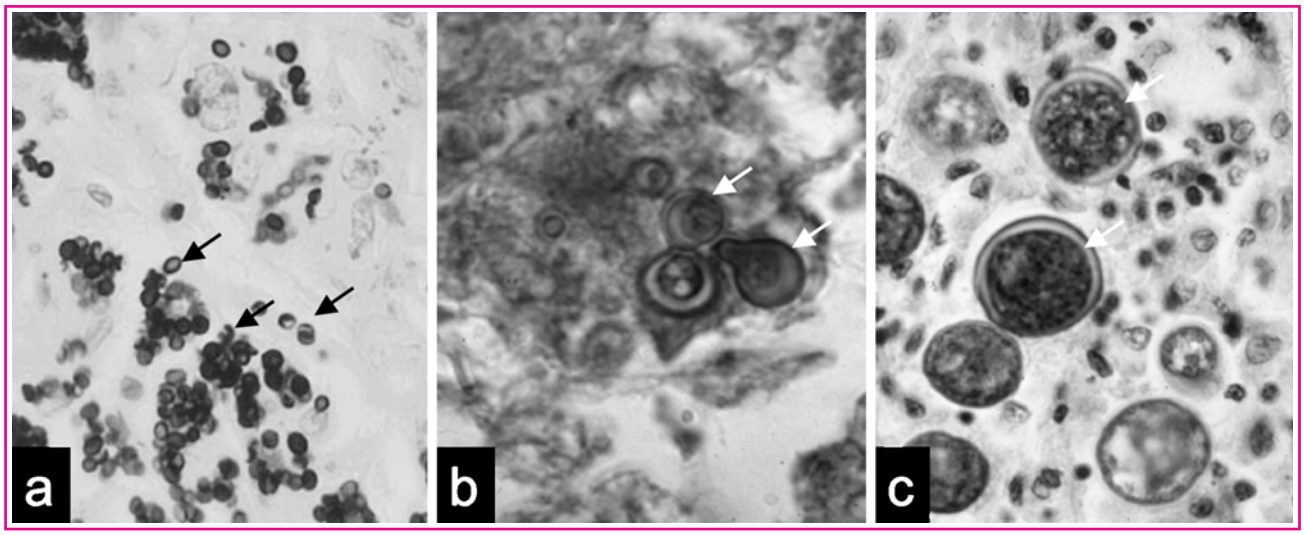


FIGURE 81–2. Histopathology of endemic mycoses in tissue. *a.* Histoplasmosis (yeast). *b.* Blastomycoses (broad-based budding yeast). *c.* Coccidioidomycoses (spherules with endospores).

and neutrophils (Fig. 81–2a and 2b). For *C. immitis* germination of the arthroconidia results in the formation of a sac-like structure called a spherule filled with endospores (Fig. 81–2c). Spherules then rupture to release large numbers of endospores, which are the propagating form of the infection. Control of infection in the lungs is typically accomplished through formation of **granulomas**. However, in patients exposed to an overwhelming inoculum, or lower inocula in the setting of suppressed T-cell–mediated immunity, dissemination outside the lung to the skin and oral mucosa (especially blastomycoses), adrenal glands, bone, spleen, thyroid, gastrointestinal tract, heart, and central nervous system is possible and uniformly fatal if left untreated.

Clinical Presentation and Diagnosis

Histoplasmosis and coccidioidomycosis are frequently asymptomatic infections in a majority of immunocompetent patients or present as a self-limiting, influenza-like illness 1 to 3 weeks after inhalation of conidia. The clinical presentation of blastomycosis varies ranging from asymptomatic infection, to acute or chronic pneumonia that develops 30 to 40 days after exposure, to full-blown disseminated disease. Symptomatic endemic fungal infections generally present as persistent and sometimes progressive pneumonia accompanied by fever, chills, cough, arthralgias, night sweats, and weight loss that is indistinguishable from other chronic infections such as pulmonary tuberculosis. ❷ Therefore, diagnosis of endemic fungal infection is often prompted by a patient history of a prolonged infectious symptoms, travel or residence in an endemic area, and/or participation in activities that result in exposures to soil contaminated by endemic fungi. Chest radiographs often reveal either diffuse or nodular infiltrates in the lung, accompanied by enlargement of the hilar and/or mediastinal lymph nodes. Fulminant pneumonia may be seen with high inoculum exposures, resulting in diffuse lung infiltrates that proceed to acute respiratory distress syndrome (ARDS) and respiratory failure. Rheumatologic symptoms such as severe arthritis, pericarditis, and erythema nodosum may be seen in 10% to 30% of patients with endemic fungi.[2,6] Dissemination outside the lung is common in patients with suppressed cellular immunity and frequently produces signs of progressing infection. Ulcerative oral and cutaneous lesions may also arise with any endemic fungal infections. Verrucose skin lesions on sun-exposed areas on the face, however, are particularly suggestive of progressing blastomycosis and are frequently mistaken for cutaneous malignancy.[6] Dissemination of the fungi to bone may result in anemia or thrombocytopenia. Hepatomegaly, splenomegaly, and adrenal insufficiency are also common with dissemination of the endemic fungi to these internal organs. Seizures, meningeal signs, and hydrocephalus are common findings with dissemination to the central nervous system and portends an especially poor prognosis in the setting of disseminated coccidioidomycosis.

Definitive diagnosis of an endemic fungal infection requires growth of the fungus from body fluids or tissue, or evidence of cellular or tissue invasion in clinical samples by histopathologic staining. However, cultures may only be positive in the setting of high inoculum exposures or disseminated disease.[7] Serologic testing has been shown to be helpful in the diagnosis and management of patients with histoplasmosis or coccidioidomycosis, but has lacked sufficient sensitivity for diagnoses of *B. dermatitidis*.[6] In general, a four-fold rise in antibody titers of *Histoplasma* or *Coccidioides*, or any titer greater than 1:16 suggests active infection. However, many clinicians still consider titers as low as 1:8 as evidence of active disease because undetectable

titers may be present in one-third of all active infections.[4] More recently, enzyme-linked immunosorbent assays (ELISAs) have been developed for detection of *Histoplasma* antigen in serum and urine, and a new radioimmunoassay directed against surface proteins of *B. dermatitidis* has shown promising sensitivity.[8] Serial serologic monitoring and antigen testing can also provide a means for assessing response to antifungal therapy and early detection of relapse in patients with histoplasmosis or coccidioidomycosis.

TREATMENT

General Approach

❸ The approach to antifungal therapy in patients with endemic fungal infections is determined by the severity of clinical presentation, the patient's underlying immunosuppression, and potential toxicities and drug interactions associated with antifungal treatment. Immunocompetent patients with mild disease following exposure to *H. capsulatum* or *C. immitis* often experience a benign course of infection and rarely require antifungal therapy. Typically these patients are followed in the outpatient setting with serial antigen testing to confirm resolving infection. Patients without clinical improvement in the first 6 weeks are typically treated with oral itraconazole or fluconazole for 6 to 12 weeks (Table 81–2).[4] Other newer azoles such as voriconazole and posaconazole appear to have good activity against endemic fungi; however, there are currently insufficient data to recommend their routine first-line use. Patients with prolonged, progressive symptoms longer than 2 weeks or titers greater than 1:8 of histoplasmosis or coccidioidomycosis antigen are candidates for immediate antifungal therapy.[1,4] Any patient with underlying immunosuppression

TABLE 81–2. Therapeutic Approach to Endemic Fungal Infections

Mycosis	Recommended Treatment Regimens	Comments
Histoplasmosis		
Mild to moderate	Observation or itraconazole 200 mg PO daily for 6–12 weeks **OR** Itraconazole 200 mg PO daily for 6–12 weeks or IV 200 mg q12hour for 1 day, then 200 mg q24hour (non-CNS disease only), **OR** Fluconazole 12 mg/kg/day PO for 6–12 weeks	Itraconazole is less effective for CNS infections Fluconazole is less effective but better tolerated than itraconazole Lipid formulation may be more effective than conventional formulations, especially for CNS disease. Once the patient is clinically stable, may be transitioned to itraconazole or fluconazole Corticosteroid therapy should be considered in hypoxic patients with acute pulmonary infection
Severe including CNS disease or immunocompromised host	Amphotericin B (AM-B) 0.7 mg/kg per day IV or liposomal AM-B 3–5 mg/kg per day for 12 weeks or until clinically stable	
Blastomycosis		
Mild to moderate	Itraconazole 200 mg PO daily × 6 months **OR** Fluconazole 6–12 mg/kg/day PO	Relapses are common in immuno-compromised host Suppressive therapy with itraconazole 200 mg/day PO or fluconazole 800 mg/day PO is recommended
Severe including CNS disease or immunocompromised host	AM-B 0.7 mg/kg per day IV until patient is clinically stable, then Itraconazole (non-CNS) or fluconazole 800 mg PO daily for 6 months	
Coccidioidomycosis		
Mild to moderate	Observation or itraconazole 200 mg PO twice daily for 6–8 months **OR** Fluconazole 6–12 mg/kg/day PO daily	Itraconazole demonstrated trend towards superiority over fluconazole in a randomized controlled trial for progressive, non-meningeal coccidioidomycosis; however, fluconazole is better tolerated than itraconazole
Diffuse pneumonia or disseminated infection	AM-B 1–1.5 mg/kg per day with dose and frequency decreased as improvement occurs **OR** Lipid AM-B formulations	Fluconazole 800–1000 mg/day is sometimes recommended after initial AM-B therapy for meningitis

CNS, central nervous system; IV, intravenous; PO, oral.



Patient Encounter, Part 2

Selecting Antifungal Therapy

The patient's serum titer for coccidioidomycosis returns as greater than 1:32. Based on the information presented, select an appropriate treatment plan for the patient's coccidioidomycosis.

- Does the patient require antifungal treatment at this time?
- If the patient is considered to have moderately severe disease, what are the recommended treatment options?

should also receive immediate antifungal therapy. The following signs and symptoms are considered to be indicators of severe disease that requires hospitalization and initial treatment with systemic amphotericin B therapy (see Table 81–2).[1,4]

- Hypoxia indicated by a partial pressure of oxygen less than 80 mm Hg
- Hypotension (systolic blood pressure less than 90 mm Hg)
- Impaired mental status
- Anemia (hemoglobin less than 10 g/dL (100 g/L or 6.2 mmol/L)
- Leukopenia (less than 1,000/cm^3)
- Elevated hepatic transaminases (greater than 5 times upper limit of normal) or bilirubin (greater than 2.5 upper limit of normal)
- Coagulopathy
- More than 10% loss in body weight
- Evidence of dissemination including cutaneous manifestations
- Meningitis

The clinical presentation of blastomycosis covers a wide spectrum ranging from asymptomatic infections, to flu-like illness resembling other upper respiratory tract illnesses, to infections resembling bacterial pneumonia with acute onset, high fever, lobar infiltrates and cough, to subacute or chronic respiratory illness with complex symptoms resembling tuberculosis or lung cancer, or fulminant lung infections with high fever, diffuse infiltrates, and an ARDS-like presentation.[6] As mentioned previously, the skin is the most common site of dissemination, typically involving sunlight exposed body areas (i.e., nose, face, and arms) and mucous membranes. The treatment of blastomycoses, therefore, is heavily dependent on the severity of clinical manifestations. Generally, patients with mild disease can be managed as outpatients with oral itraconazole or fluconazole.[6] Patients with evidence of severe pulmonary disease or dissemination require initial treatment as inpatients with amphotericin B–based regimens until they are clinically stable, whereupon they can complete a 6- to 12-month treatment course as outpatients with oral itraconazole or fluconazole.

Patient Monitoring and Side Effects

Response to antifungal therapy may be slow in patients with a prolonged history of infection or severe manifestations. However, gradual improvements in symptoms and reduction in fever are indicators of response to antifungal therapy. For histoplasmosis and coccidioidomycosis, decreasing antigen titers are also indicative of response to antifungal therapy.[1]

Antifungals used for the treatment of endemic mycoses can be associated with a number of clinically-significant drug interactions and toxicities, especially with the prolonged treatment courses that are often required in the management of endemic mycoses. Itraconazole is available as a capsule formulation and as a liquid. The liquid formulation of itraconazole has several advantages over the capsule: it has a better oral bioavailability and does not require the low gastric pH that is required for dissolution and absorption of the capsule. However, the oral solution is somewhat dilute, has an unpalatable aftertaste (an issue when taking months of therapy), and has a much higher rate of gastrointestinal side effects. Therefore the capsule formulation is often preferred provided patients are not on acid-suppression therapy (i.e., proton pump inhibitors, histamine antagonists, or antacids).

Drug interactions are a particularly important concern in patients taking long-term azole therapy, especially with itraconazole. Itraconazole is a substrate and inhibitor of the cytochrome P-450 (CYP)3A4 enzyme and P-glycoprotein. Co-administration of itraconazole with inducers of this enzyme system (e.g., rifampin, phenytoin, and phenobarbital) can dramatically increase the clearance of itraconazole (and to a lesser extent fluconazole), resulting in ineffective plasma and tissue concentrations of the drug.[9–11] In general, co-administration of itraconazole with these inducers should be avoided. In some cases, plasma trough levels can be drawn once the patient reaches steady state (greater than 7 days of therapy). Concentrations less than 0.25 mcg/mL should be considered evidence of insufficient itraconazole exposure.[12] As a potent inhibitor of CYP3A4, itraconazole can dramatically decrease the clearance of a number of important medications metabolized through this enzyme, leading to potentially dangerous drug interactions. Patients receiving anticoagulation therapy with warfarin, immunosuppressive therapy with cyclosporine or tacrolimus, those taking midazolam, HMG-CoA reductase inhibitors (statins), rifabutin, chemotherapy agents (e.g., vinca alkaloids, busulfan, and cyclophosphamide), and digoxin will require dosage adjustment and careful monitoring while receiving itraconazole therapy.[13] Although fluconazole is not as potent an inhibitor of CYP3A4 as itraconazole, drug interactions can still be severe, especially at higher fluconazole dosages (i.e., 800 mg/day).[13]

All azole antifungals carry the potential for rash, photosensitivity, and hepatotoxicity. In general, hepatotoxicity is mild and reversible, presenting as asymptomatic increases in liver transaminases. However, fulminant hepatic failure has been reported with itraconazole. Therefore, serial monitoring of liver function

is recommended in all patients on long-term azole therapy. Long-term therapy with itraconazole has also been associated with reversible adrenal suppression and cardiomyopathy. These adverse effects can be prevented or managed with close monitoring and follow-up of patients on long-term therapy.

Amphotericin B is the mainstay of treatment of patients with severe endemic fungal infections. The conventional deoxycholate formulation of the drug can be associated with substantial infusion-related adverse effects (e.g., chills, fever, nausea, rigors, and in rare cases hypotension, flushing, respiratory difficulty, and arrhythmias). Pre-medication with low doses of hydrocortisone, acetaminophen, nonsteroidal anti-inflammatory agents, and meperidine is common to reduce acute infusion-related reactions. Venous irritation associated with the drug can also lead to thrombophlebitis, hence central venous catheters are the preferred route of administration in patients receiving more than a week of therapy.

The most severe adverse effect associated with amphotericin B therapy is nephrotoxicity, which occurs through the drug's renal vascular effects (constriction of afferent arterioles in the kidney tubule) and direct toxicity to the renal tubules. Generally, nephrotoxicity with amphotericin B is reversible provided the drug is stopped. However, treatment interruptions can be problematic in patients with severe infections. Precipitous decreases in glomerular filtration occasionally are seen with the initiation of amphotericin B therapy, and can be minimized by ensuring that patients remain well hydrated during therapy, and using normal saline infusions before and after amphotericin B to counter decreases in renal perfusion pressure, a practice known as sodium loading. Tubular toxicity can be delayed by avoiding the use of other drugs with known tubular toxicity such as aminoglycosides, cyclosporine, cisplatin, or foscarnet. Generally, tubular toxicity manifests in patients with severe wasting of potassium and magnesium in the urine. Therefore, patient electrolytes must be carefully monitored and potassium and magnesium supplementation is often required. Hypokalemia and hypomagnesemia frequently precede decreases in glomerular filtration (increased serum creatinine), especially in patients who are adequately hydrated.[14] Continued tubular damage, however, eventually results in decreases in renal blood flow and glomerular filtration through tubuloglomerular feedback mechanisms that further constrict the afferent arteriole.

In the last decade, amphotericin B has been reformulated into three different lipid-based formulations (Abelcet, Ambisome, and Amphotec) that have reduced rates of nephrotoxicity compared to the conventional deoxycholate formulation (Fungizone). Two of the formulations (Abelcet and Ambisome) have also shown to varying degrees reductions in the rates of infusion-related reactions. Although these lipid formulations are generally considered to be as effective as conventional amphotericin B deoxycholate, they are not dosed equivalently to the standard formulation. Unlike conventional amphotericin B, which is administered at dosages ranging from 0.6 to 1.5 mg/kg per day, lipid formulation doses are three- to five-fold higher on a milligram-per-milligram basis, ranging from 3 to 5 mg/kg per day. Only one prospective study has directly compared the efficacy of a lipid amphotericin formulation to the conventional formulation.[15] In a small study of AIDS patients with moderate to severe histoplasmosis, liposomal amphotericin B (Ambisome) was more effective than amphotericin B, with response rates of 84% and 64%, respectively. Ambisome may also be the preferred agent in patients with central nervous system (CNS) infections, due to its high penetration into the brain compared to other lipid amphotericin B formulations.[16]

Prophylaxis

Primary prophylaxis is generally not recommended for endemic fungi, but may be considered for patients who are severely immunocompromised and living in endemic areas with high case rates (greater than 5 cases per 100 patient-years). ❹ Secondary prophylaxis or suppressive therapy is recommended for endemic mycoses in immunocompromised patients, especially in hosts with pronounced defects in T-cell immunity (i.e., AIDS patients).[4,6,17] Itraconazole 200 mg/day or fluconazole 200 to 400 mg/day are the most common prophylactic regimens used for endemic fungi. In patients with prior CNS disease, fluconazole is the preferred drug due to the limited penetration of itraconazole into the CNS.

OPPORTUNISTIC MYCOSES

❺ Commensal or environmental fungi that are typically harmless can become invasive mycoses when the host immune defenses are impaired. Host immune suppression and risk for opportunistic mycoses can be broadly classified into three categories:

- Quantitative or qualitative deficits in neutrophil function
- Deficits in cell-mediated immunity
- Disruption of mechanical/and or microbiologic barriers

Quantitative defects in neutrophils (neutropenia) resulting from neoplastic diseases, cytotoxic chemotherapy, marrow transplantation, or aplastic anemia are among the most common risk factors for opportunistic mycoses. Qualitative defects may be seen in certain disease states (e.g., advanced diabetes mellitus and chronic granulomatous disease) or with high-dose corticosteroid therapy. Deficits in T-cell–mediated immunity secondary to AIDS, high-dose corticosteroid therapy, cyclosporine or other anti-rejection drugs, chemotherapy, transplantation, bone marrow failure, and various other disorders have become increasingly common with the prolonged survival of transplant patients on chronic immunosuppressive therapy. Immune deficits arising from disruption of the integument or gastrointestinal/genitourinary barriers can also predispose patients to fungal infections. The most common types of mechanical/barrier immunosuppression are surgery,

use of central venous and urinary catheters, hyperalimentation, and mucositis secondary to cytotoxic chemotherapy. Broad spectrum antibacterial therapy can also predispose patients to fungal infections through disruption of the microbiologic flora in the gut, which allows overgrowth of opportunistic fungal pathogens such as *Candida*. Successful management of opportunistic fungal pathogens, therefore, requires the reversal or reduction of underlying deficits in the host immune system.

The most common opportunistic fungal pathogen is *Candida* species, which are commensal colonizers of the gastrointestinal tract and the genitourinary tract of women. *Candida* infections can arise in any of the three types of immune deficits listed above, but are most common in patients with disruptions in mechanical and/or microbiologic barriers. *Cryptococcus*, on the other hand, is seen predominantly in patients with cell-mediated immune deficits (AIDS and/or high-dose corticosteroid therapy). Opportunistic molds such as *Aspergillus* are acquired primarily through inhalation of spores in the environment and cause invasive infection most commonly in patients with either prolonged neutropenia or severe defects in cell-mediated immunity. Additional risk factors such as environmental exposures, prior antifungal therapy, and metabolic disorders can predispose patients to specific types of opportunistic molds including *Fusarium* or Zygomycetes.

All of the opportunistic mycoses are difficult to diagnose and often must be treated empirically before diagnosis is proven. Deciding when to initiate antifungal therapy and what opportunistic pathogens to cover is a decision governed largely by the *cumulative* immune deficits of the host. For example, a post-surgical patient with persistent fever on broad-spectrum antimicrobials who has a central venous catheter may only require empiric therapy for suspected *Candida* infections, because the deficits in host defenses (surgery, catheters, and antimicrobial therapy) are largely restricted to disruption of mechanical and/or microbiologic barriers. However, if the patient had a history of prolonged high-dose corticosteroid use (e.g., greater than 600 mg prednisone equivalent in the previous month), deficits in cell mediated immunity in combination with barrier disruption need to be considered, possibly warranting empiric coverage of opportunistic molds along with *Candida* species.



Patient Encounter, Part 1

A 43-year-old male in the surgical ICU after exploratory laparotomy following a motor vehicle accident develops fever that is unresponsive to broad-spectrum antibacterial therapy (piperacillin-tazobactam 3.75 g every 6 hours, gentamicin 120 mg every 8 hours, and vancomycin 1 g every 12 hours). The patient has a central venous catheter and a Foley catheter. Blood cultures are negative at the time, but the patient has yeast growing in the sputum and urine. Laboratory studies reveal a white blood cell count of 11,300 cells/mm^3 (11.3 × 10^9/L).

- What are this patient's risk factors for developing an invasive fungal infection?
- What current evidence suggests that this patient has an invasive fungal infection?
- If antifungal therapy is empirically started in this patient, which species need to be treated?

INVASIVE CANDIDIASIS

Epidemiology

Candida species are the most common opportunistic fungal pathogens encountered in hospitals, ranking as the third to fourth most common cause of nosocomial bloodstream infections in United States Hospitals.[18] The incidence of nosocomial candidiasis has increased steadily since the early 1980s, with the widespread use of central venous catheters, broad-spectrum antimicrobials, and other advancements in the supportive care of critically-ill patients. In the 1980s, *C. albicans* accounted for over 80% of all bloodstream yeast isolates cultured from patients. By the late 1990s, this relative frequency of *C. albicans* had decreased to 50% in national surveys of bloodstream infections without a corresponding decrease in infections caused by non-albicans species. Because of the inherent resistance (e.g., *C. krusei*) or diminished susceptibility (e.g., *C. glabrata*) of many of the non-albicans species, the introduction of fluconazole in the early 1990s is often cited as the key element driving the shift in the microbiology of invasive candidiasis. However, it is likely that other institution-specific factors (e.g., increasing use of central venous catheters and increasing intensity of cytotoxic/mucotoxic chemotherapy) have contributed equally to this trend. ❻ It is important to be familiar with the relative epidemiology and frequency of non-albicans *Candida* species in the institution or intensive care unit (ICU) before selecting empiric antifungal therapy for invasive candidiasis.

Pathogenesis and Clinical Presentation

Invasive candidiasis is not a single syndrome, but rather a spectrum of infections that differ in terms of clinical presentation and course depending on host immune deficits. All forms of invasive candidiasis, however, are potentially severe, with high (30% to 60%) rates of crude morbidity and mortality. The most common form of invasive candidiasis is seen in non-neutropenic patients with disruption of mechanical/microbiologic barriers giving rise to a bloodstream infection (fungemia) from, or seeding to, a central venous catheter. Catheter-related candidemia carries a good prognosis if appropriate antifungal therapy is instituted early with catheter removal.[19] Fungemia can be of high density, however, leading

to distal sites of infection and increased morbidity. Therefore the infection must be taken seriously, especially in patients with poor performance status (i.e., a high Acute Physiology, Age, and Chronic Health Evaluation II score) in the ICU.

Patients with acute disseminated candidiasis share many similar features as patients with catheter-related candidemia, except infection generally arises from the gut following mucotoxic chemotherapy and the patients are often profoundly ill. Hematogenous spread to non-contiguous organs is common in patients with acute disseminated candidiasis and outcome is heavily dependent upon recovery from neutropenia. Fluconazole prophylaxis has markedly decreased the incidence of acute disseminated candidiasis among high-risk patient groups such as bone marrow transplant and acute leukemia patients. However, breakthrough infections with fluconazole-resistant *C. glabrata* and *C. krusei* are still a concern.

Some forms of invasive candidiasis are dominated by deep organ infection and may never be detected by blood cultures. Chronic disseminated candidiasis or hepatosplenic candidiasis is a unique form of candidemia seen after recovery from neutropenia. Candidemia during the period of neutropenia may be initially localized to the portal circulation with dissemination to contiguous organs. After recovery of neutrophils, an inflammatory response is seen against areas of focal infection in the liver and spleen. This inflammatory response produces abdominal pain that is associated with increases in alkaline phosphatase levels and hepatocellular enzymes. Diagnosis is typically confirmed by patient history (recent neutropenia), and multiple areas of lucency in the liver and spleen on computed tomography (CT).

Focal invasive candidiasis has been reported for virtually every organ, even following apparently uncomplicated catheter-related fungemia. The most common sites of infection are the kidney, eye, and bone. *Candida* in the urine can be an indication of renal candidiasis; however, it must be distinguished from more benign colonization of the urinary tract, especially in catheterized patients. All patients with candidemia should undergo an eye exam to rule out *Candida* endophthlamitis, which can be sight-threatening if not recognized early.

Laboratory diagnosis of invasive candidiasis is established by detection of the yeast in blood cultures or another sterile site (Fig. 81–3a). Growth of *Candida* from urine, sputum, or respiratory secretions (including bronchoalveolar lavage) is not considered to be evidence of invasive infection, as these areas frequently become colonized with *Candida* species in patients receiving broad-spectrum antibiotics. Colonization at multiple distinct body sites or with high density of *Candida* species, however, may precede invasive infection. Therefore preemptive antifungal therapy may be indicated in colonized high-risk populations such as those with neutropenic fever, transplant recipients, or following major abdominal surgery.[20] Although

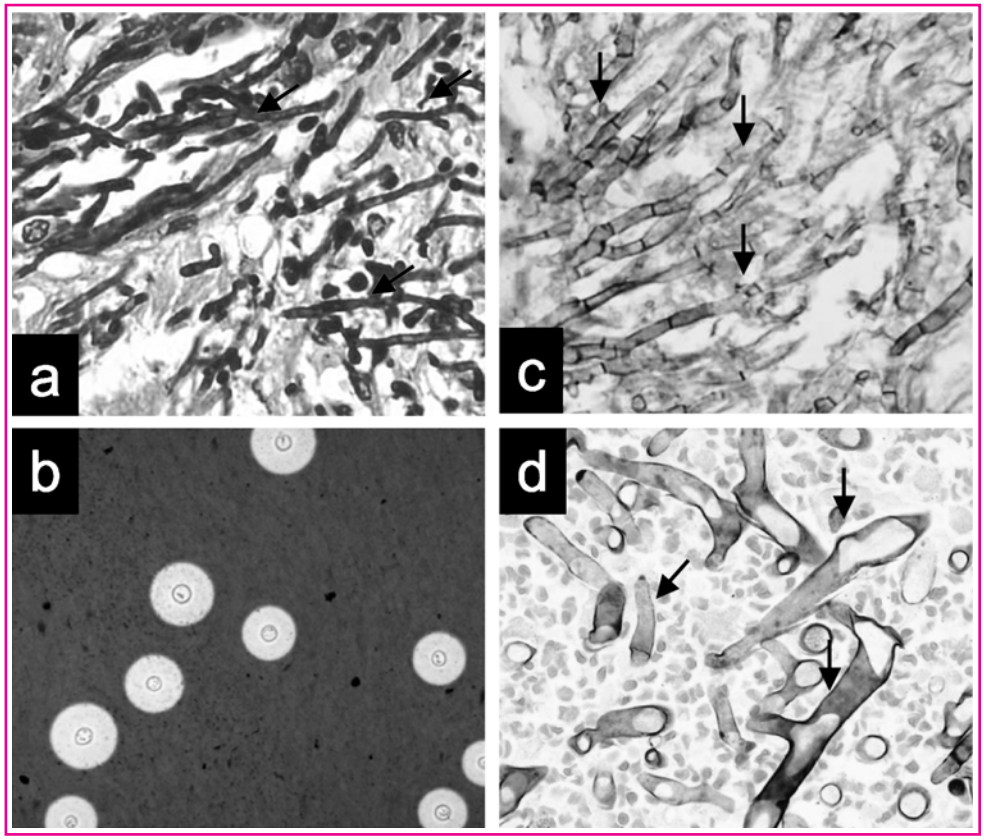


FIGURE 81–3. Opportunistic mycoses in clinical samples. *a.* Candidiasis (tissue). *b.* Cryptococcosis (India ink stain of CSF). *c.* Aspergillosis (tissue). *d.* Zygomycosis (tissue).

Candida are not particularly fastidious organisms, the sensitivity of blood cultures is relatively poor (less than 60%) and a negative culture does not rule out infection.[20] The poor sensitivity of blood cultures for detecting invasive disease has led to the study of novel serodiagnostic tests to detect antibodies, fungal metabolites, fungal cell wall antigens, or nucleic acids of *Candida* species. Of the four approaches, antigen testing based on the detection of β-glucan polymers in the cell wall of *Candida* have appeared most promising; however, none of these diagnostic tests have achieved routine clinical use.

❽ Laboratory identification of *Candida* in clinical samples must be performed to the species level whenever possible, as *Candida* species differ considerably in their susceptibility to antifungal agents.[20] Rapid discrimination of *C. albicans* from most common non-albicans *Candida* species can be accomplished by the germ-tube test, which presumptively identifies *C. albicans* by the early formation (less than 4 hours) of a hyphae-like structure when the yeast in incubated in serum at 98.6°F (37°C). Definitive species identification, however, may require an additional 48 to 72 hours after the organism is isolated on agar. *C. albicans* remains the most common cause of invasive candidiasis, is the most virulent of *Candida* species, but is the most susceptible to commonly used antifungals including fluconazole. Like *C. albicans*, *C. tropicalis* is a relatively virulent species and has tropism for causing deep tissue infections, such as myositis. *C. tropicalis* is generally sensitive to antifungals including fluconazole. *C. parapsilosis* is a less virulent species seen frequently in neonates and in adults with central venous catheters. Although *C. parapsilosis* is not as invasive, many isolates form thick biofilms that make the organism difficult to eradicate from prosthetic materials. *C. parapsilosis* is generally susceptible to most antifungals including fluconazole.[21] However, higher dosages of echinocandins (e.g., 70 to 100 mg/day of caspofungin) have been suggested due to the decreased potency of the echinocandin class against this species. *C. krusei* is a less-common species associated with breakthrough infections in heavily immunocompromised patients and should always be considered resistant to fluconazole. Interestingly, most fluconazole-resistant isolates of *C. krusei* retain susceptibility to itraconazole and voriconazole, based on laboratory analysis.[22]

C. glabrata has become a common cause of both de novo candidemia in heavily immunocompromised hosts and breakthrough infection in patients on fluconazole prophylaxis. Although *C. glabrata* is less virulent than other *Candida* species, infections with this organism are typically seen in patients with poor performance status, therefore mortality remains high. The marginal susceptibility of *C. glabrata* to fluconazole dictates that other agents such as amphotericin B or the echinocandins be considered as first-line therapy until susceptibility to fluconazole can be documented. The effectiveness of voriconazole or posaconazole for fully fluconazole-resistant *C. glabrata fungemia* is not well-established, although cross-resistance has been documented in laboratory studies.[23]

Treatment

At the time of writing, three antifungals (amphotericin B, fluconazole, and caspofungin) have been studied in prospective, randomized comparative clinical trials for the treatment of invasive candidiasis.[24–26] Two other echinocandins (micafungin and anidulafungin) are nearing completion of prospective candidemia studies and are anticipated to have similar efficacy to caspofungin, and voriconazole was recently compared to amphotericin B in patients with candidemia.[27] Although other antifungal agents that can be administered intravenously (lipid amphotericin B formulations and itraconazole) are possibly as effective as amphotericin B, fluconazole, and caspofungin for invasive candidiasis, evidence supporting their use is derived principally from open-label observational studies, and empiric therapy trials of febrile neutropenia. As a result, their first-line use is not prominently recommended in evidence-based guidelines for proven infection.[20] No prospective randomized, controlled clinical trials have been published comparing antifungal therapies for proven acute disseminated candidiasis in neutropenic patients, chronic disseminated candidiasis, or other forms of deep-organ candidiasis.

A majority of patients are treated empirically for invasive candidiasis before conclusive evidence of infection is available to direct therapy. Empiric therapy for invasive candidiasis should be considered in any patient with persistent, unexplained fever and host deficits that predispose patients to candidemia, including broad-spectrum antibacterial therapy, presence of a central venous catheter, patients with severe organ dysfunction or on dialysis, patients with neutropenia or qualitative deficiencies in host immunity (e.g., due to high-dose corticosteroid therapy), or colonization with *Candida* at one or more body sites. ❾ If a patient is non-neutropenic and has never received prior azole therapy, fluconazole 800 mg/day is an appropriate first-line therapy for invasive candidiasis until speciation of the *Candida* isolate is confirmed (Table 81–3). Amphotericin B deoxycholate 0.7 mg/kg per day or caspofungin 70 mg on day 1, then 50 mg/day; voriconazole; or a lipid amphotericin B formulation are recommended as empiric therapy in patients with neutropenic fever. Other newer echinocandins (micafungin and anidulafungin) are effective alternatives to caspofungin. If the neutropenia is of shorter duration and the patient is at lower risk for mold infections (e.g., solid tumor patients with less than 2 weeks of neutropenia), higher-dose fluconazole (i.e., 800 mg/day or 12 mg/kg) could be considered. Lipid amphotericin B formulations, an echinocandin, or voriconazole are often the preferred agents in higher-risk patients with neutropenic fever to expand coverage against molds.[28,20] If the yeast is identified as *C. glabrata*, published treatment guidelines recommend the use of either caspofungin or possibly amphotericin B deoxycholate. Voriconazole is not recommended until further clinical data support its use for *C. glabrata*, as laboratory studies have suggested potential cross-resistance with fluconazole-resistant isolates of this species. High-dose fluconazole can also be considered for *C. glabrata*

TABLE 81–3. Therapeutic Approach to Opportunistic Fungal Infections

Mycoses	Recommended Treatment Regimens	Comments
Candidiasis		
Catheter-related and acute hematogenous	Amphotericin B 0.7 mg/kg per day IV **OR** Fluconazole 6–12 mg/kg/day IV q24hour **OR** Caspofungin[a] 70 mg IV on day 1, then 50 mg q24hour **OR** Amphotericin B + fluconazole *Second line:* Lipid amphotericin B formulation 3–5 mg/kg per day[b] **OR** Amphotericin B 0.5–7 mg/kg per day + flucytosine 100 mg/kg per day PO divided q6hour **OR** Voriconazole 6 mg/kg q12hour for 1 day, then 3 mg/kg q12hour **OR** Itraconazole 200 mg q12hour for 2 days, then 200 mg IV q24hour	Treat for 14 days after the last positive blood culture and resolution of signs and symptoms catheter should be removed whenever possible Patients can be switched to oral fluconazole when clinically stable if isolate is susceptible Caspofungin and amphotericin B are preferred agents for fluconazole-resistant species Voriconazole appears to be effective against fluconazole-resistant *C. krusei* Echinocandins likely equivalent
Empirical therapy in neutropenic patient	Fluconazole 6–12 mg/kg/day (low risk) **OR** Amphotericin B 0.7 mg/kg per day IV **OR** Itraconazole 200 mg q12hour for 2 days, then 200 mg IV q24hour **OR** Liposomal amphotericin B 3 mg/kg q24hour	Antifungals with coverage of *Aspergillus* should be used in higher-risk patients or prolonged neutropenia (i.e., longer than 2 weeks)
Urinary candidiasis	Fluconazole 200 mg IV or PO for 7–14 days **OR** Amphotericin B 0.3 mg/kg per day IV for 1–7 days	Asymptomatic candiduria does not required therapy However, treatment is recommended in neutropenic, low-birth-weight infants, and patients undergoing urologic manipulations or those with renal allografts Amphotericin B bladder irrigation no longer recommended
Cryptococcosis		
Pulmonary-isolated Severe pulmonary and meningitis	Fluconazole 6 mg/kg/day IV or PO for 6–12 mo *Induction:* Amphotericin B 0.7–1 mg/kg per day + flucytosine 100 mg/kg per day PO divided q6hour for 2 weeks *Consolidation:* Fluconazole 6–12 mg/kg/day for 10 weeks *Second line:* Fluconazole + flucytosine for 2 weeks then fluconazole for 10 weeks **OR** Amphotericin + fluconazole for 2 weeks then fluconazole for 10 weeks **OR** Liposomal amphotericin B 5 mg/kg per day × 2 weeks then fluconazole for 10 weeks	Regimens reported to produce faster sterilization of CSF compared to amphotericin B deoxycholate alone during the first 2 weeks: Amphotericin B + 5-flucytosine Amphotericin B + Fluconazole Liposomal amphotericin B Echinocandins have no activity against cryptococci
Aspergillosis	Voriconazole 6mg/kg q12hour for 1 day, then 4 mg/kg q12hour **OR** Lipid formulations of amphotericin B **OR** Caspofungin 70 mg IV for 1 dose, then 50 mg IV q12hour **OR** Posaconazole 200 mg PO qid × 14 days, then 200 mg PO bid **OR** Combination therapy	Voriconazole can be administered as oral therapy in patients taking oral medications Voriconazole can cause reversible visual disturbances and occasionally hallucinations Because of the high-dosages and prolonged treatment courses, lipid formulations are preferred for amphotericin B–based therapy

(*Continued*)

TABLE 81–3. Therapeutic Approach to Opportunistic Fungal Infections (*Continued*)

Mycoses	Recommended Treatment Regimens	Comments
		Preclinical studies suggest mold-active azoles plus echinocandins have enhanced activity against *Aspergillus* *A. terreus* should be considered resistant to amphotericin B Activity of amphotericin B and voriconazole is decreased versus *Aspergillus* species; higher doses or combination therapy may be indicated in more refractory cases
Fusariosis	Lipid formulations of amphotericin B **OR** Voriconazole 6 mg/kg q12hour for 1 day, then 4 mg/kg q12hour **OR** Posaconazole 200 mg PO qid for 14 days, then 200 mg PO q12hour **OR** Combination therapy	
Zygomycoses	High-dose lipid amphotericin B (e.g., 7.5–10 mg/kg per day) **OR** Posaconazole 200 mg PO qid for 14 days, then 200 mg PO q12hour **OR** Combination therapy	Prompt diagnosis and surgical débridement are essential for successful outcome; high dosages of lipid amphotericin B are required; posaconazole is the only azole with activity against zygomycoses

[a]Or equivalent echinocandin (micafungin 100–150 mg/day, anidulafungin 200 mg day 1, then 100 mg/day)
[b]Ambisome 3–5 mg/kg per day; Abelcet 5 mg/kg per day; Amphotec 4 mg/kg per day.
CSF, cerebrospinal fluid; IV, intravenous; PO, oral.

infections if the isolate is documented to be susceptible or susceptible-dose-dependent to fluconazole.[20] *C. krusei* infections can be treated with an echinocandin, amphotericin B or voriconazole. Patients who respond to therapy, are medically stable, not neutropenic, and are taking oral medications can be transitioned to oral fluconazole provided isolate susceptibility is documented by minimum inhibitory concentration testing. For uncomplicated catheter-related candidemia (no evidence of organ involvement), therapy should be continued for at least 2 weeks from the last positive blood culture.[20] In neutropenic patients, therapy should be continued until resolution of neutropenia.[20] All central venous catheters should be removed to decrease the duration of fungemia and risk of recurrent infections.[20]

Treatment recommendations for other forms of invasive candidiasis are based primarily on anecdotal evidence and expert opinion. Deep organ candidiasis requires prolonged therapy to achieve a cure; therefore importance is placed on the use of convenient and non-toxic long-term treatment regimens. Fluconazole (400 mg/day or 6 mg/kg per day) is the preferred regimen in clinically stable patients. Amphotericin B, lipid amphotericin B formulations, and possibly caspofungin can be considered for refractory cases or clinically unstable patients. Infections of the eye, bone, pancreas, or gallbladder are typically treated with either amphotericin B or fluconazole; however, there are few data to support the use of echinocandins. Urinary candidiasis is an ill-defined group of syndromes that can range from benign colonization (candiduria) to invasive disease of the renal parenchyma. Asymptomatic non-neutropenic patients with candiduria do not require antifungal therapy, as no study has demonstrated the value of transiently clearing *Candida* from the urine. Patients should



Patient Encounter, Part 2

Selecting Antifungal Therapy

The patient is started on fluconazole 400 mg/day, but 3 days later has persistent fever and develops hypotension and decreased urine output. Blood cultures reveal a germ tube–negative yeast growing in the blood. Laboratory studies revealed a white blood cell count of 12,300/mm^3 (12×10^9/L), aspartate aminotransferase 68 IU/L (1.13 μKat/L), alanine aminotransferase 75 IU/L (1.25 μKat/L), alkaline phosphatase 168 IU/L (2.8 μKat/L), and normal bilirubin. Serum creatinine is 1.8 mg/dL (159 μmol/L).

- What factors suggest empiric antifungal therapy should be changed in this patient?
- What are the most likely fungal species growing from the blood?
- What other procedures should be recommended in this patient to improve response to antifungal therapy?

receive 7 to 14 days of antifungal therapy for urinary candidiasis if they are: (1) symptomatic, (2) have clinical or laboratory evidence of infection, (3) are neutropenic, (4) are low-birth-weight infants, (5) will undergo urologic manipulations, or (6) have renal allografts. Removal of urinary tract instruments, including Foley catheters and stents, is recommended whenever possible. The preferred therapy is fluconazole 200 mg daily, although intravenous amphotericin B deoxycholate 0.3 to 1 mg/kg per day is also effective. Other antifungal agents do not achieve appreciable concentrations in the urine and therefore should not be considered for urinary candidiasis. Irrigation with amphotericin B is not effective for infections above the bladder and should not be used in higher-risk patients with the possible exception of as a diagnostic tool for confirming a localized infection of the bladder.

Mucocutaneous candidiasis is generally not life-threatening nor invasive and can be treated with topical azoles (clotrimazole troches), oral azoles (fluconazole, ketoconazole, or itraconazole), or oral polyenes (such as nystatin or oral amphotericin B). Orally administered and absorbed azoles (ketoconazole, fluconazole, or itraconazole solution), amphotericin B suspension, intravenous caspofungin, or intravenous amphotericin B are recommended for refractory or recurrent infections.[20]

Although more invasive, esophageal candidiasis does not typically evolve into a life-threatening infection. However, topical therapy is ineffective. Azoles (fluconazole, itraconazole solution, or voriconazole), echinocandins, or intravenous amphotericin B (in cases of unresponsive infections) are effective treatment options. Parenteral therapy should be used in patients who are unable to take oral medications.[20]

Patient Monitoring and Side Effects

Response to antifungal therapy in invasive candidiasis is often more rapid than for endemic fungal infections. Resolution of fever and sterilization of blood cultures are indications of response to antifungal therapy. Toxicity associated with antifungal therapy is similar in these patients as described earlier with the caveat that some toxicities may be more pronounced in critically-ill patients with invasive candidiasis. Nephrotoxicity and electrolyte disturbances, with amphotericin B in particular, are problematic and may not be avoidable even with lipid amphotericin B formulations. Fluconazole and echinocandins are generally safer options, and are generally well tolerated. Decisions to use one class of agents over the other is principally driven by concerns of non-*albicans* species, patient tolerability, or history of prior fluconazole exposure (risk factor for non-*albicans* species.).

Prophylaxis

Fluconazole (400 mg/day) has been extensively studied as a prophylactic regimen to prevent invasive candidiasis in patients with prolonged (greater than 2 weeks) neutropenia.[29–32] Placebo-controlled, prospective randomized trials performed in the 1990s demonstrated that fluconazole was effective in reducing the frequency, morbidity, and in some trials mortality, due to invasive candidiasis when administered until marrow recovery. However, the major limitation with fluconazole is its lack of mold coverage needed for high-risk patients with persistent neutropenia. More recent studies have examined the use of itraconazole or the echinocandin micafungin as prophylaxis in hematopoietic cell transplant recipients until engraftment to provide protection against both *Candida* and *Aspergillus* species.[33,34] Although both agents were effective, neither therapy was ideal because of either poor tolerability (itraconazole) or lack of an oral formulation (micafungin). Posaconazole has also shown promise as a prophylactic agent for both yeast and molds in high-risk cancer patients.

Antifungal prophylaxis in the non-neutropenic, non-cancer population is focused on the prevention of invasive candidiasis, and should be similarly targeted towards certain high-risk transplant populations (e.g., liver, pancreatic, or small-bowel transplantation) or ICU patients (i.e., neonatal intensive care) with rates of invasive candidiasis exceeding 10% despite aggressive infection-control procedures. Fluconazole prophylaxis (400 mg/day) has been shown to reduce the rate of *Candida* peritonitis in patients with refractory gastrointestinal perforation, and trended towards decreased rates of invasive candidiasis in select adult patients admitted to a surgical ICU for more than 3 days.[35] Fluconazole has also been shown to be effective in reducing the rate of invasive candidiasis in neonates.[36] It is hoped that ongoing studies will define the risks versus benefits of routine antifungal prophylaxis in the general ICU setting.

CRYPTOCOCCOSIS

Epidemiology

Cryptococcus neoformans is an encapsulated yeast that can infect apparently normal hosts, but is more frequently associated with severe infections in immunocompromised patients. *C. neoformans* is divided into two varieties based on serotype: *C. neoformans* var. *neoformans* (Serotypes a and d) and *C. neoformans* var. *gatti* (serotypes b and c). *C. neoformans* var. *gatti* is found predominantly in tropical and sub-tropical climates associated with eucalyptus trees, whereas *C. neoformans* var. *neoformans* is found worldwide and is associated with pigeon droppings and other avian excreta. Before the AIDS pandemic, cryptococcosis was a relatively uncommon disease, but became a leading cause of meningitis among HIV-infected patients. Although the incidence of this infection has declined somewhat with the widespread use of highly active antiretroviral therapy (HAART), *C. neoformans* remains an important pathogen in immunocompromised patients, including cancer

patients who often present with the pulmonary form of the infection.

Pathogenesis and Clinical Presentation

C. neoformans is acquired primarily through inhalation of the desiccated yeast particles found in the environment. Inhaled cells reach distal alveolar spaces where they gradually rehydrate and form their characteristic polysaccharide capsules that enable resistance to phagocytosis. Defects in cellular immunity allow reconstitution of the protective capsule and multiplication of yeast in the lungs. Although alveolar macrophages phagocytose the yeast, containment and killing requires a coordinated response between innate and adaptive humoral (complement and anticryptococcal antibodies) and T-cell–mediated host responses.[5] Deficiencies in cell-mediated immunity allow the yeast to survive as a facultative intracellular pathogen in macrophages as they migrate from the lung to draining lymph nodes, leading to dissemination via the bloodstream to the meninges.

Unlike most opportunistic fungi, true virulence factors have been identified for *C. neoformans*. The capsules, as well as the soluble polysaccharides released from the yeast cells during infection, impair phagocytosis and binding of anticryptococcal antibodies. Primary cryptococcal infection begins in the lung, presenting as a mildly symptomatic or asymptomatic infection that resolves spontaneously or results in an encapsulated, usually non-calcified lung nodule. It is not uncommon for these isolated nodules to be detected on chest x-rays during routine work-up. Diagnosis of primary cryptococcosis is only made if the nodule is aspirated or removed because of concerns of primary lung cancer.

In the immunocompromised host, infection of the lung may present with more diffuse, bilateral, interstitial disease that mimics the presentation of *Pneumocystis jiroveci (carinii)* pneumonia (PCP). Dissemination to other organs, particularly the CNS, eye, and possibly the skin, is more likely to occur in patients with severe deficits in cell-mediated immunity. Fever, cough, dyspnea, and pleural pain are common at presentation with accompanying hypoxemia that can rapidly evolve to acute respiratory failure. Because of the overlapping features of diffuse pulmonary cryptococcosis with other opportunistic pathogens, early diagnosis requires bronchoalveolar lavage or transbronchial biopsy, which can effectively diagnose 80% to 100% of cases.[37] The clinical course of diffuse cryptococcal pneumonia can be as severe as PCP, with mortality rates approaching 100% in untreated patients by 48 hours.

C. neoformans is strongly neurotropic and readily disseminates from the lung to the CNS, specifically the leptomeninges, and occasionally the parenchyma of the brain. The clinical characteristics of cryptococcal meningitis differ somewhat, however, between patients with and without underlying AIDS. In patients without AIDS, disease presentation is more insidious and symptoms such as dizziness, irritability, decreased comprehension, and unstable gait may present many weeks to months before the diagnosis is made.[37] Patients with AIDS generally present much later in the course of disease with severe meningoencephalitis.[37] The most common signs and symptoms on presentation are fever, headache, meningismus, photophobia, mental status changes, and seizures. Computed tomography or more sensitive magnetic resonance imaging may reveal cerebral edema, multiple areas of enhanced nodules, or a single mass lesion (cryptococcoma). Examination of the cerebrospinal fluid often reveals increased opening pressure upon lumbar puncture, but glucose, protein, and leukocyte levels can be normal.[37]

Laboratory Diagnosis

Clinical diagnosis is confirmed by cultures from the blood, CSF, or other clinically relevant fluids or tissue. ⑩ Direct visualization of *C. neoformans* in the CSF by India ink staining is the most rapid method for diagnosing cryptococcal meningitis.[37] Detection of cryptococcal antigen in either serum or CSF has greater than 95% sensitivity and specificity in the diagnosis of true invasive cryptococcal infection and appears to correlate with fungal burden.[37] A positive serum antigen test of greater than 1:4 strongly suggests cryptococcal infection, and greater than or equal to 1:8 is indicative of active disease. Antigen titers in serum are positive in 99% of patients with cryptococcal meningitis, and typically exceed titers of 1:2,048 in patients with AIDS.[37] However, the time course of cryptococcal antigen elimination is unknown and a positive test result can persist for many years. Changes in the CSF cryptococcal antigen titers have limited value in the monitoring of drug therapy for cryptococcal meningitis, although it is expected that a decrease should be seen after 2 or more weeks of antifungal therapy.[37]

Treatment

Cryptococcal meningitis is fatal if left untreated. Because pneumonia frequently precedes dissemination of disease and subsequent meningitis, all patients with culture-, histopathology-, or serology-proven disease should receive antifungal therapy. In patients with isolated pulmonary cryptococcosis, fluconazole is generally considered to be the therapy of choice (see Table 81–2).[37] Alternatively, itraconazole or combination therapy (fluconazole plus flucytosine) has also been used with some success in patients.

Disseminated or CNS cryptococcosis requires a more aggressive treatment approach, particularly in the immunocompromised host. Pretreatment predictors of poor outcome with antifungal therapy include:

- Progressive underlying disease or immunodysfunction
- Abnormal mental status at the time of presentation
- Increased opening pressure on lumbar puncture (greater than 260 mm H_2O)
- High fungal burden as reflected by a CSF antigen titer [in AIDS patients] of greater than 1:2048

Prospective randomized trials completed prior to the recognition of AIDS demonstrated high response rates (approximately 80%) with the combined use of amphotericin B and flucytosine for 4 to 6 weeks. Although sterilization of the CSF could be achieved in most patients within 2 weeks with this regimen, a substantial number of patients (30% to 40%) developed dose-limiting toxicities and relapse was seen in roughly 50% of patients. Therefore a new treatment approach was devised that consisted of distinct treatment phases to minimize toxicity and reduce the risk of relapse. ⓫ Clinical trials performed by the National Institute of Allergy and Infectious Diseases (NIAID) Mycoses Study Group after the recognition of AIDS showed that 2 weeks of induction antifungal therapy with combination amphotericin B (0.7 mg/kg per day) plus flucytosine (100 mg/kg per day) for cryptococcal meningitis, followed by consolidation therapy with fluconazole (400 mg daily) for 8 weeks was as effective as 4 weeks of combination therapy, with fewer toxicities (see Table 81–2). More recent studies have suggested fluconazole plus amphotericin may be an acceptable option in patients who cannot tolerate therapy with flucytosine (see Table 81–2).

Prophylaxis

Fluconazole (200 mg per day) is recommended as maintenance therapy for life in patients with persistent underlying immune dysfunction to prevent recurrent cryptococcal meningitis. With the introduction of HAART, the United States Public Health Service guidelines have recently changed secondary prophylaxis recommendations for cryptococcosis based on data that demonstrated it is safe to discontinue maintenance therapy in AIDS patients who have had a sustained immunologic response on effective antiretroviral therapy.[38] Occasionally, initiation of HAART can result in the reactivation of a sub-clinical, immunologic manifestation of cryptococcal infection (or other opportunistic infections). Manifestations of this so-called *immune reconstitution syndrome* may include exacerbations of meningitis or necrotizing pneumonia. Antifungal therapy plus a nonsteroidal anti-inflammatory agent or prednisone have been used successfully in patients with cryptococcal-associated immune reconstitution syndrome. However, the optimal management of this recently defined clinical entity remains unknown.

INVASIVE ASPERGILLOSIS

Epidemiology

Invasive molds, particularly *Aspergillus,* have become an increasingly important complication of cancer therapy and organ transplantation. Patients with acute leukemia and recipients of allogeneic hematopoietic cell transplants are at especially high risk for invasive aspergillosis due to prolonged neutropenia and deficiencies in cell-mediated immunity associated with graft-versus-host disease and its treatment. More than 180 species within the genus *Aspergillus* have been described, but only four species are commonly associated with invasive infection: *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus terreus*, and *Aspergillus niger.* Of these four species, *A. fumigatus* accounts for the majority of human pulmonary fungal infections. However, identification of *Aspergillus* mold in culture to the species level is still essential, because the incidence of amphotericin B–resistant *Aspergillus terreus* and *Aspergillus flavus* have increased over the last 5 years among high-risk patients. Early and accurate diagnosis of invasive aspergillosis (IA) remains the most important barrier to the effective management of this infection, which is associated with crude mortality rates ranging from 60% to 100%.[39]

Pathogenesis and Clinical Presentation

The pathogenesis of IA is defined largely by the underlying immune dysfunction of the host. The most common route of acquisition for *Aspergillus* is through the respiratory tract. Conidia dispersed in air currents are continuously inhaled through the sinuses and mouth and penetrate down to distal alveolar spaces (see Fig. 81–3c). Most conidia are rapidly phagocytosed and removed by resident macrophages in the upper and lower respiratory tract.[5] However, macrophage function may be suppressed following transplantation, cytotoxic chemotherapy, or in patients who have received high-dose corticosteroid therapy. Conidia that escaped phagocytosis begin to germinate into hyphal forms that are too large for ingestion by macrophages. Hyphal forms of *Aspergillus* then invade blood vessels or contiguous tissues or bone (in sinuses) resulting in hemorrhage and/or infarction, and coagulative necrosis. Once in the bloodstream, viable hyphal fragments can break off and disseminate to distal organs including the brain. Control of the infection at this stage requires development of an adaptive Th-1 type response to enhance the fungicidal activity of professional effector cells (i.e., neutrophils) against hyphal elements.[5] Patients with dysregulated, suppressed T-cell–mediated immunity, or prolonged neutropenia are unable to control the infection and are at high risk for dissemination of the infection. Without antifungal therapy, invasive aspergillosis is uniformly fatal.

Signs and symptoms of invasive aspergillosis are predictably muted in the immunocompromised host. Fever is common but non-specific for infection and may be accompanied by pleuritic chest pain, cough, hemoptysis, and/or friction rub.[40] Neurologic signs including seizures, hemiparesis, and stupor may be present in patients with dissemination to the brain. Cutaneous plaques or papules characterized by a central necrotic ulcer or eschar occur in up to 10% of patients with disseminated disease; however, concomitant blood cultures are often negative. Chest radiographs cannot detect early forms of disease and may remain negative in up to 10% of patients within 1 week of death.[41] ⓬ Nodular lesions detected



Patient Encounter, Part 1

Invasive Mold Infection

A 40-year-old female with acute myelogenous leukemia at day 115 post matched-allogeneic donor hematopoietic stem cell transplantation presents to the clinic with increasing complaints of nausea, stomach cramping, and rash on the hands spreading up her arms. She also complains of pain upon deep inspiration. By laboratory examination, she is noted to have an alanine aminotransferase of 85 IU/L (1.42 μKat/L), aspartate aminotransferase 75 IU/L (1.25 μKat/L) and total bilirubin of 2.1 mg/dL (36 μmol/L). Her current medications include tacrolimus 5 mg twice daily (most recent level: 8 ng/mL), levofloxacin 500 mg daily, fluconazole 200 mg/day, valacyclovir 500 mg twice daily, metoprolol 25 mg twice daily, and benzonatate (tessalon) pearls. She is admitted to the hospital for suspected graft-versus-host disease exacerbation. Computed tomography scan of the chest revels three to four dense pleural base nodules in both lung fields. The primary service wishes to start voriconazole.

- What are the patient's risk factors for developing an invasive mold infection?
- Is voriconazole an acceptable option in this patient? Are there any drug interaction concerns?

by high-resolution computed tomography (HRCT) scans are often the first indication of invasive pulmonary aspergillosis along with fever, and reveal small wedge-shaped or nodular lesions, typically surrounded by intermediate attenuation called the "halo sign."[41–43] These early lesions on CT scans represent hemorrhage and edema surrounding an infarcted blood vessel. Despite "effective" antifungal therapy, lesions on CT scan may continue to increase in size in neutropenic patients until neutrophils recover, at which time they begin to cavitate, forming the "air-crescent sign" on chest radiographs, indicative of resolving infection. ⓭ Immunocompromised patients on fluconazole with progressive sinus or pulmonary disease by radiography should be evaluated for possible mold infection.[40,43,44]

Laboratory Diagnosis

Like other invasive mycoses, definitive diagnosis of aspergillosis requires histopathologic evidence of hyphal invasion in tissue (Fig. 81–4). However, procedures needed to establish a definitive diagnosis by sampling of suspicious lesions (e.g., fine-needle aspiration or thoracoscopic lung biopsy) are not feasible in a large proportion of patients with underlying thrombocytopenia secondary to hematologic malignancies or chemotherapy. Even if hyphae are observed in tissue, histopathology alone cannot

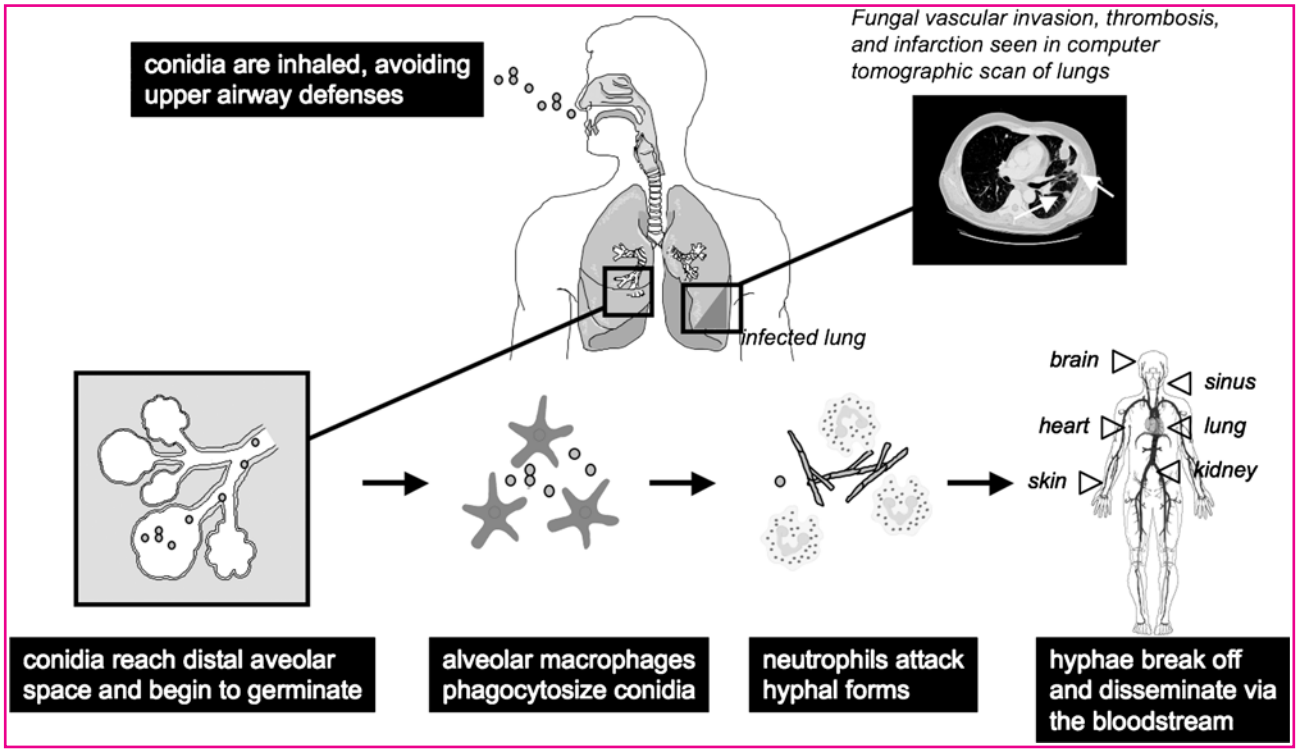


FIGURE 81–4. Pathogenesis of invasive aspergillosis.

distinguish *Aspergillus* from other angioinvasive septate molds such as *Fusarium*, which have different patterns of antifungal susceptibility.[40] Therefore, respiratory and/or wound cultures (if cutaneous or sinus/hard palate lesions are present) are important factors in the modification of empiric antifungal therapy.

Respiratory cultures including sputum, bronchial washings, or bronchoalveolar lavage have a low sensitivity for diagnosis of invasive aspergillosis but a high positive predictive value in immunocompromised patients.[45] Therefore, a negative bronchoalveolar lavage culture does not rule out invasive pulmonary aspergillosis, but a positive culture in a high-risk patient (e.g., allogeneic hematopoietic cell transplant patients) indicates pulmonary aspergillosis in at least 60% of such patients. Blood cultures have little diagnostic value for invasive aspergillosis, but may reflect true disease with *A. terreus.* Patients with limited lung involvement or on prophylactic or empiric antifungal therapy may continue to be culture-negative for *Aspergillus* species despite the appearance of progressing disease. Therefore, clinical specialists should never consider negative cultures as an indication for stopping antifungal therapy in patients with suspected or proven aspergillosis.

Considerable effort has been focused in the last decade to develop non–culture based laboratory methods (antigen detection, polymerase chain reaction [PCR], and metabolite detection) for the diagnosis of invasive aspergillosis. The hope is that these surrogate tests could detect early evidence of *Aspergillus* infection before significant target organ damage eventually detected by CT scans occurs. Recently, the Food and Drug Administration has approved an ELISA-based assay for the detection of a polysaccharide component of the *Aspergillus* cell wall called galactomannan. Although several large prospective studies have found that the sensitivity and specificity of the assay exceeded 90% in neutropenic patients with hematologic malignancies, the median time span between galactomannan detection and clinical signs and symptoms of IA averages less than 6 days.[46,41] Other factors such as patient immune status (neutropenia versus graft-versus-host disease), antifungal therapy, and diet may affect the interpretation of the galactomannan test.[47,48] For example, false-positive results have been reported in pediatric patients, patients receiving piperacillin-tazobactam for neutropenic fever, and following the ingestion of certain cereals, pastas, nutritional supplements, or soy sauce.[48] Hence, there are numerous opportunities for false-positive tests. Although some animal studies and clinical data suggest that rising galactomannan levels are a harbinger of breakthrough infection, there are still limited data supporting the use of this test to guide and monitor antifungal therapy. At this time it appears that the galactomannan test (and other non–culture based strategies) will be serve as complementary methods to confirm results from microbiologic, histopathologic, and radiographic investigations directed towards diagnosing invasive aspergillosis.

Treatment

To date, only two comparative randomized controlled clinical trials have evaluated antifungal therapies for the treatment of invasive aspergillosis and only one study was sufficiently powered to measure differences in response to antifungal therapy.[49] In that study, unblinded investigators compared patients initially randomized to the newer triazole, voriconazole, to patients initially treated with amphotericin B deoxycholate.[49] The study design was unique in that it allowed a change from the randomized drug to any other licensed antifungal therapy, without requiring that the patient be classified as a treatment failure on randomized therapy. Nearly 80% of patients randomized to receive amphotericin B deoxycholate were switched to other licensed antifungal therapies (mean duration 10 days) versus 36% of patients in the voriconazole arm (mean duration 77 days). The poor tolerability of amphotericin B deoxycholate was not surprising given the relatively higher dosages (1 mg/kg per day intravenously) and prolonged treatment courses required in the treatment of invasive aspergillosis. At the end of the study (12 weeks), a higher proportion of patients in the voriconazole arm remained alive (70.8%) compared to amphotericin B deoxycholate–treated patients (57.9%). ⓮ On the basis of these results, many experts now consider voriconazole as the initial drug of choice for invasive aspergillosis in patients without significant contraindications (e.g., drug interactions or preexisting liver dysfunction) to azole therapy (see Table 81–2). Voriconazole also appears to have some efficacy in CNS aspergillosis, a form of invasive aspergillosis with historical mortality rates approaching 100%. Itraconazole has activity against *Aspergillus* and is frequently used as prophylaxis, but is not considered a particularly effective treatment option for invasive disease.[50,51]

Lipid formulations of amphotericin B, caspofungin, or other echinocandins, and the investigational triazole posaconazole, can be considered as possible alternatives to voriconazole therapy and may be preferred agents in patients with breakthrough infection on azole antifungals (including itraconazole or fluconazole). Several recent open-label case series have suggested that combination therapy, with an echinocandin and mold-active traizole such as voriconazole, may be more effective than voriconazole alone for invasive aspergillosis that has failed amphotericin B–based therapy.[52,53] Once antifungal therapy has begun, the duration and intensity of antifungal therapy is directed by host-specific factors including clinical response, underlying immunosuppression, tolerability, and plans for future chemotherapy/immunosuppression. In the heavily immunocompromised patient, complete eradication of the fungus is unlikely and suppressive therapy may be required until well after recovery of cellular immune function. Reactivation from residual infracts or devitalized tissue in the sinus or lung harboring aspergillosis is a concern if the patient will receive further immunosuppressive therapy. Therefore, surgical débridement of the sinus or excision of large lung lesions is often pursued. Relapsing or breakthrough *Aspergillus*



Patient Encounter, Part 2

Voriconazole is started in the patient along with 1 mg/kg per day of methylprednisolone to control the graft-versus-host disease. Her tacrolimus dose was also decreased by 70% with the addition of voriconazole and a recent tacrolimus blood level of 10 ng/mL. Unfortunately, the patient remains febrile with worsening respiratory pain. A repeat CT scan of the lung demonstrates new nodules, and pleural effusion in the right lung.

- What are the possible reasons this patient appears to be progressing on voriconazole therapy?
- What other molds may be implicated as a cause of infection that may not respond to voriconazole in this patient?
- What treatment options can be considered in this patient?

infections respond less favorably to antifungal therapy than de novo IA and may require more aggressive measures (combination therapy, immunotherapy, or surgery) to stabilize the infection.

Prophylaxis

Although recently published guidelines for preventing opportunistic infections in hematopoietic cell transplant recipients do not provide concrete recommendations for antifungal prophylaxis against *Aspergillus*, prophylaxis should be considered in certain high-risk subgroups with rates of invasive aspergillosis exceeding 10%. These groups include: (1) patients with prolonged pre-engraftment periods (e.g., cord-blood transplant recipients), (2) patients with a history of invasive aspergillosis prior to transplantation, (3) patients receiving transplants with a high risk of graft-versus-host disease (e.g., haploidentical allogeneic transplant) or infection (e.g., T-cell–depleted transplant), any patient with graft-versus-host disease on high-dose corticosteroid therapy (greater than 1 mg/kg prednisone equivalent) with or without anti-thymocyte globulin or tumor necrosis factor blockade (i.e., infliximab), and (4) any patient transplanted with active cytomegalovirus disease, which is associated with an increased risk of subsequent mold infections due to the immunosuppressive effect of the virus.

Patient Monitoring and Side Effects

Response to antifungal therapy in invasive molds is slow and difficult to judge by clinical signs alone. Resolution of fever, and eventual clearing of CT scans (in the case of lung infections) are indications of response to antifungal therapy. Toxicity associated with antifungal therapy is similar in these patients as in those described earlier. Patients often require prolonged therapy, particularly if they remain immunosuppressed. In many cases, antifungal therapy may be continued indefinitely until complete resolution of underlying immunosuppression.

OTHER MOLDS

Although *Aspergillus* is the most common mold infection in immunocompromised patients, virtually any mold can cause invasive infection in the right immunocompromised host. However, studies describing the epidemiology, management, and outcome of these less-common opportunistic molds are available only from case reports or case series. For this reason, current treatment guidelines for fungal infections do not address the management of these less-common mycoses. Yet, as survival has improved in patients with *Candida* and *Aspergillus* infections, less common opportunistic molds, particularly the agents of zygomycosis and fusariosis are becoming important causes of breakthrough infections on antifungal prophylaxis and therapy. Therefore, the epidemiology, clinical presentation, and treatment of these infections will be briefly reviewed.

Fusariosis

Fusarium species are the second to third most common pathogenic mold among immunocompromised patients, particularly those with hematologic malignancies. Risk factors for disseminated fusariosis are similar to those of invasive aspergillosis and include neutropenia, lymphopenia, graft-versus-host disease, and high-dose corticosteroid therapy. Although the clinical presentation of fusariosis is often indistinguishable from that of invasive aspergillosis, skin lesions and fungemia are significantly more common with *Fusarium* infections.[54] Skin lesions typically precede fungemia, which can be detected by blood culture in up to 40% of patients. Histopathology reveals acute-branching septate hyphae similar to those found in aspergillosis. Invasive fusariosis carries a mortality rate of up to 80% depending on the underlying host immune status. Patients with persistent neutropenia are at especially high risk for poor outcome. Anecdotal success has been reported with the use of high-dose (greater than 7.5 mg/kg per day) lipid amphotericin B, voriconazole, and posaconazole.[54] Transfusions of granulocytes stimulated with cytokines have also been attempted in patients with persistent neutropenia to control refractory infections.

ZYGOMYCOSIS

Zygomycosis is an uncommon infection caused by the fungi of the order Mucorales, class Zygomycetes, with the most commonly representative organisms being *Mucor, Rhizopus,*

Absidia, Cunninghamella, and *Rhizomucor*.[55] Zygomycosis is classically associated with progressive invasive rhinocerebral infections in patients with diabetes mellitus and/or diabetic ketoacidosis that extends to the periorbital region and face and invades the brain.[56] However, invasive zygomycosis is increasingly encountered in cancer patients, particularly transplant or leukemic patients who have received high doses of steroids, or patients with prolonged, profound neutropenia. Unlike the classic rhinocerebral form of invasive zygomycosis seen in diabetic patients, pulmonary infections appear to be more common in the cancer population. ⓯ Zygomycetes are generally resistant to voriconazole and echinocandins and their presence should be suspected in any patient with progressive mold infection while receiving voriconazole and/or echinocandin therapy.[56,57] Because of the rapid progression of disease, early diagnosis and aggressive therapy are essential for favorable outcome. Lipid amphotericin B, radical surgical débridement, cytokine-stimulated granulocyte transfusions, and even hyperbaric oxygen therapy have been reported to reduce the morbidity and high mortality of this devastating infection. Posaconazole is the only triazole antifungal with activity against Zygomycetes and has been reported to be effective against sinopulmonary forms of infection.[57]

CONCLUSION

Modern medical practices and advances in transplantation and cancer therapy have elevated primary and opportunistic mycoses to relatively common causes of infectious disease–related morbidity and mortality in humans. Although invasive mycoses are often more difficult to diagnose and treat compared to common bacterial pathogens, the continued introduction of effective and better-tolerated treatment alternatives to amphotericin B–based therapy has allowed greater flexibility and more treatment options for these challenging infections. The development of early, accurate, and effective non–culture based diagnostic tests remains the key obstacle to improving pharmacotherapeutic trial designs and outcomes of invasive mycoses in immunocompromised patients.

ABBREVIATIONS

AIDS: acquired immunodeficiency syndrome
ARDS: acute respiratory distress syndrome
CNS: central nervous system
CSF: cerebrospinal fluid
CT: computed tomography
CYP: cytochrome P-450 isoenzyme
ELISA: enzyme-linked immunosorbent assay
HAART: highly active antiretroviral therapy
HRCT: high-resolution computed tomography
IA: invasive aspergillosis
ICU: intensive care unit
IV: intravenous
NIAID: National Institute of Allergy and Infectious Diseases
PCR: polymerase chain reaction
PCP: *Pneumocystis jiroveci (carinii)* pneumonia
PO: oral

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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82 Antimicrobial Prophylaxis in Surgery

Jeremy A. Schafer and John C. Rotschafer



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Discuss the epidemiology and impact of surgical wound infections on patient outcomes and health care costs.
2. Name and differentiate the four different types of surgical procedures.
3. Recognize at least three risk factors for post-operative wound infections.
4. Identify likely pathogens associated with different surgical operations.
5. Compare and contrast antimicrobials used for surgical prophylaxis and identify potential advantages and disadvantages for each antibiotic.
6. Discuss the importance of timing, duration, and redosing in relation to antimicrobial prophylaxis in surgery.
7. Discuss the possible impact of antibiotic-impregnated bone cement and how this affects the use of antimicrobial prophylaxis in surgery.
8. Be able to recommend appropriate prophylactic antimicrobial(s) given a surgical operation.
9. Discuss the importance of β-lactam allergy screening and how this could impact resistance and health care costs.
10. Identify non-antimicrobial methods that can reduce the risk of post-operative infection.

Key Concepts

❶ Surgical site infections (SSIs) are a significant cause of morbidity and mortality.
❷ The distinction between prophylaxis and treatment influences the choice of antimicrobial and duration of therapy.
❸ Surgical operations are classified as clean, clean-contaminated, contaminated, or dirty.
❹ Choosing the appropriate prophylactic antimicrobial relies on anticipating which organisms are likely to be encountered during the operation.
❺ A thorough drug allergy history should be taken to discern true allergy (anaphylaxis) from adverse event (stomach upset).
❻ Further study is needed before antibiotic-impregnated bone cements can be recommended as an alternative to preoperative prophylaxis with traditional antimicrobials.
❼ Correct timing of antibiotic administration is imperative to preventing SSI.
❽ The goal of antimicrobial dosing for surgical prophylaxis is to maintain antibiotic concentrations above the minimum inhibitory concentration (MIC) of suspected organisms for the duration of the operation.
❾ Studies have not shown benefit for additional doses of antibiotic and the duration of antimicrobial prophylaxis should not exceed 24 hours.
❿ According to Centers for Disease Control criteria, SSI may appear up to 30 days after an operation and up to 1 year if a prosthesis is implanted.

❶ ***Surgical site infections*** *(SSIs) are a significant cause of morbidity and mortality*. Approximately 2% to 5% of patients undergoing clean **extra-abdominal** operations and 20% undergoing **intra-abdominal** operations will develop an SSI.[1] SSIs have become the second most common cause of nosocomial infection and these data are likely underestimated.[1] More than 70% of surgical procedures are now performed on an outpatient basis, leaving significant potential for underreporting.[2]

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SSIs negatively affect patient outcomes and increase health care costs. Patients who develop SSIs are five times more likely to be readmitted to the hospital and have twice the mortality of patients who do not develop an SSI.[1] A patient infected with an SSI is also 60% more likely to be admitted to an intensive care unit.[1] Clinical studies have shown that SSIs increase lengths of hospital stay and costs.[1,3,4] The type of SSI can also affect outcome. Deep SSIs, involving organs or spaces, result in longer durations of hospital stay and higher costs compared to SSIs that are limited to the incision.[5]

SSIs are defined and reported according to Centers for Disease Control and Prevention (CDC) criteria.[5] SSIs are classified as either incisional or organ/space. Incisional SSIs are further divided into superficial incisional SSI (skin or subcutaneous tissue) and deep incisional SSI (deeper soft tissues of the incision). Organ/space SSIs involve any anatomic site other than the incised areas. For example, a patient who develops meningitis after removal of a brain tumor could be classified as having an organ/space SSI. An infection is considered an SSI if any of the above criteria is met and the infection occurs within 30 days of the operation. If a prosthetic is implanted, the timeline extends out to 1 year.

EPIDEMIOLOGY AND ETIOLOGY

Numerous **risk factors** for SSI have been identified in the literature.[5–7] These factors can be divided into two categories: patient and operative characteristics. Patient risk factors for SSI include: age, comorbid disease states (especially chronic lung disease and diabetes), malnutrition, immunosuppression, nicotine or steroid use, and colonization of the nares with *Staphylococcus aureus*. Many patients developing post-operative wound infections bring the organism with them into the hospital. Modifying risk factors may decrease the threat of SSI. Studies have shown that the use of intranasal mupirocin can decrease the incidence of SSI due to methicillin-sensitive *Staphylococcus aureus* (MSSA) or methicillin-resistant *Staphylococcus aureus* (MRSA).[8–10] Malnutrition can be corrected using enteral or parenteral feedings. Additional non-antimicrobial strategies to reduce SSI will be discussed later.

Operative characteristics are based on the actions of both the patient and the operating staff. Shaving of the surgical site prior to operating can produce microscopic lacerations and increase the chance of SSI.[5] Maintaining aseptic technique and proper sterilization of medical equipment is effective in preventing SSI. Surgical staff should wash hands thoroughly. Post-operative bacterial inoculums of clean surgeries are generally small. However, subsequent patient contact with contaminated areas (nares or rectum) and then the surgical site can lead to SSI. Finally, the appropriate use of **antimicrobial prophylaxis** can have a significant impact on decreasing SSIs.

PATHOPHYSIOLOGY

Prophylaxis versus Treatment

Properly identifying the state of an infection is important when using antimicrobial prophylaxis in surgery. Antibiotic prophylaxis begins with the premise that no infection exists but that during surgery there can be a low level inoculum of bacteria introduced into the body. However, if sufficient antibiotic concentrations are present, the situation can be controlled without infection developing. This is the case when surgery is done under controlled conditions, there are no major breaks in technique or spillage of gastrointestinal (GI) contents, and perforation or damage to the surgical site is absent. An example would be an elective hysterectomy done with optimal surgical technique.

If an infection is already present, or presumed to be present, then antimicrobial use is for treatment, not prophylaxis, and the goal is to eliminate the infection. This is the case when there is spillage of GI contents, gross damage or perforation is already present, or the tissue being operated on is actively infected (pus is present and cultures are positive). An example would be a patient undergoing surgery for a ruptured appendix with diffuse peritonitis.

❷ *The distinction between prophylaxis and treatment influences the choice of antimicrobial and duration of therapy.* Appropriate antimicrobial selection, dosing, and duration of therapy differ significantly between these two situations. A regimen for antimicrobial prophylaxis ideally involves one agent and lasts less than 24 hours. Treatment regimens can involve multiple antimicrobials with durations lasting weeks to months depending on desired antimicrobial coverage and the surgical site.

Types of Surgical Operations

❸ *Surgical operations are classified as clean, clean-contaminated, contaminated, or dirty.* Antimicrobial prophylaxis is appropriate for clean, clean-contaminated, and contaminated operations. Dirty operations take place in situations of existing infection and antimicrobials are used for treatment, not prophylaxis (Table 82–1).

Microbiology

❹ *Choosing the appropriate prophylactic antimicrobial relies on anticipating which organisms will be encountered during the operation.* SSIs associated with extra-abdominal operations are the result of skin flora organisms in nearly all cases. These organisms include gram-positive cocci, with *S. aureus* and *S. epidermidis* being among the most frequently isolated SSI pathogens according to the National Nosocomial Infections Surveillance System (NNIS)[5] (Table 82–2). *Streptococcus* spp. and other gram-positive aerobes may also be implicated.

TABLE 82–1. National Red Cross Wound Classification, Risk of Surgical Site Infection (SSI), and Antibiotic Indication[6,24]

Classification	Description	SSI Risk	Antibiotic Prophylaxis
Clean	No acute inflammation or transection of GI, oropharyngeal, GU, biliary, or respiratory tracts; elective case, no technique break	Low	Indicated
Clean-contaminated	Controlled opening of aforementioned tracts with minimal spillage or minor technique break; clean procedures performed emergently or with major technique breaks	Medium	Indicated
Contaminated	Acute, non-purulent inflammation present; major spillage or technique break during clean-contaminated procedures	High	Indicated
Dirty	Obvious preexisting infection present (abscess, pus, or necrotic tissue present)	—	Not indicated; antibiotics used for treatment

GI, gastrointestinal; GU, genitourinary.

Intra-abdominal operations involve a diverse flora with the potential for polymicrobial SSIs. *Escherichia coli* make up a large portion of bowel flora and are frequently isolated as pathogens according to the NNIS.[5] Other enteric gram-negative bacteria, as well as anaerobes (especially *Bacteroides* spp.), may be encountered during intra-abdominal operations.

Candida albicans is being implicated as the cause of a growing number of SSIs. According to the NNIS, from 1991 to 1995, the incidence of fungal SSIs rose from 0.1 to 0.3 per 1000 discharges.[5] Increased use of broad spectrum antibiotics and rising prevalence of immunocompromised and human immunodeficiency virus–infected individuals are factors in fungal SSIs. Despite this increase, antifungal prophylaxis for surgery is not currently recommended.

TABLE 82–2. Major Pathogens in Surgical Wound Infections

Pathogen	Percent of Infections[a]
Staphylococcus aureus	20
Coagulase-negative staphylococci	14
Enterococci	12
Escherichia coli	8
Pseudomonas aeruginosa	8
Enterobacter spp.	7
Proteus mirabilis	3
Klebsiella pneumoniae	3
Other *Streptococcus* spp.	3
Candida albicans	3
Group D streptococci	2
Other gram-positive aerobes	2
Bacteroides fragilis	2

[a]Data reported by the NNIS from 1990 to 1996, adapted from National Academy of the Sciences National Research Council. Postoperative wound infections: The influence of ultraviolet irradiation of the operating room and of various other factors. Ann Surg 1984; 160:32–135.
(From Kanji S, Devlin JW. Antimicrobial prophylaxis in surgery. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 2219, with permission.)

Choosing an Antibiotic

An antimicrobial used in surgical prophylaxis should meet certain criteria. Selecting an antibiotic with a spectrum that covers expected pathogens is crucial. The antibiotic should be inexpensive, available in a parenteral formulation, and easy to use. Adverse event potential should be minimal. Choosing an agent with a longer half-life reduces the likely need to redose unless the surgical procedure is prolonged.

Operations can be separated into two basic categories: extra-abdominal and intra-abdominal. SSIs resulting from extra-abdominal operations are frequently caused by gram-positive aerobes. Thus, an antimicrobial with strong gram-positive coverage is useful. Cefazolin benefits from a benign adverse-event profile, simple dosing, and low cost. These aspects have made cefazolin the mainstay for surgical prophylaxis of extra-abdominal procedures. For patients with a **χ-lactam allergy,** clindamycin or vancomycin can be used as an alternative.

Intra-abdominal operations necessitate broad-spectrum coverage of gram-negative organisms and anaerobes. Anti-anaerobic cephalosporins, cefoxitin and cefotetan, are useful but suffer from limited availability. Fluoroquinolones or aminoglycosides, paired with clindamycin or metronidazole, should provide adequate coverage for intra-abdominal operations.

The Hospital Infection Control Practices Advisory Committee allows for the use of vancomycin for surgical prophylaxis when MRSA rates at an institution are "high."[1] Unfortunately, a "high" rate of MRSA has not been standardized, but with most hospitals reporting MRSA rates greater than 50%, the definition is irrelevant. The increasing prevalence of community-acquired methicillin-resistant *Staphylococcus aureus* in patients admitted to the hospital is a concern, although this pathogen is often sensitive to clindamycin. Vancomycin use may not translate into a lower incidence of SSI. Finkelstein and associates found that the incidence of SSI between patients on cefazolin or vancomycin did not differ despite a high MRSA rate at the study institution. However,

patients who received cefazolin were more likely to develop an SSI due to MRSA.[11]

Newer antimicrobials have not demonstrated superiority in the prevention of SSI and should be reserved for treatment only. Carbapenems, antipseudomonal penicillins, and third- or fourth-generation cephalosporins are not appropriate antibiotics for surgical prophylaxis. Overuse of these antibiotics may contribute to collateral damage and the development of bacterial resistance.

Beta-Lactam Allergy

Penicillin allergy is one of the most common reported drug allergies. Concerns over cross-reactivity may limit the use of β-lactams for surgical prophylaxis. ❺ *A thorough drug allergy history should be taken to discern true allergy (e.g., anaphylaxis) from adverse event (e.g., stomach upset).* Allergy testing may be helpful in confirming a patient's penicillin allergy and could spare vancomycin. Cross-sensitivity between penicillin allergy and cephalosporins is low. Pichichero and colleagues stated that the increased risk of cephalosporin allergy in patients with a history of penicillin allergy may be as low as 0.4% when taking first-generation cephalosporins and nearly zero for second- and third-generation agents.[12] Apter and co-workers also found the risk of cross-reactivity to be very low.[13] However, in the case of severe penicillin allergy (anaphylaxis), cephalosporins should be avoided.

Alternative Methods to Decrease SSI

Several non-antimicrobial methods have been studied for reducing the risk of SSI.[14] Kurz and associates found that providing supplemental warming to patients (36.6°C or 98°F) during the intraoperative period reduced infection rates compared to control patients (34.7°C or 94.5°F).[15] Van den Berghe and co-workers studied the impact of intensive glucose control [80 to 110 mg/dL (4.44 to 6.1 mmol/L)] versus conventional control [glucose less than 210 mg/dL (less than 11.7 mmol/L)] and found an advantage for intensive glucose control in reducing infections in critically ill patients.[16] Finally, Greif and colleagues found that patients randomized to 80% inspired oxygen had lower SSI rates compared to patients on 30% oxygen after colorectal resection.[17] Despite these findings, there are insufficient data to make definitive recommendations on the use of these therapies.

Antibiotic-impregnated bone cement is being used as an adjunct or alternative to traditional antimicrobial prophylaxis. A study by Chiu and associates found cefuroxime-impregnated cement lowered the risk of deep infection after primary total knee arthoplasty.[18] Other studies have been inconclusive regarding superiority of antibiotic-impregnated bone cement versus conventional therapies.[19] Confounding this issue is the lack of standards regarding antibiotic-impregnated cements. An array of drugs, from aminoglycosides to macrolides, are used in the preparations. Some cements are produced commercially whereas others are made in the operating room. The long-term durability of impregnated cements is also unknown, as the addition of antibiotics may reduce the tensile strength of bone cement. ❻ *Further study is needed before antibiotic-impregnated bone cements can be recommended as an alternative to preoperative prophylaxis with traditional antimicrobials.*

Principles of Antimicrobial Prophylaxis

Route of Administration

Intravenous antibiotic administration is the most common delivery method for surgical prophylaxis. Intravenous administration ensures complete bioavailability while minimizing the impact of patient-specific variables. Oral administration is also used in some bowel operations. Non-absorbable compounds like erythromycin base and neomycin are given up to 24 hours prior to surgery to cleanse the bowel. Note that oral agents are used adjunctively and do not replace IV agents.

Timing of First Dose

❼ *Correct timing of antibiotic administration is imperative to preventing SSI.* The National Surgical Infection Prevention Project recommends infusing antimicrobials for surgical prophylaxis within 60 minutes of the first incision. Exceptions to this rule are fluoroquinolones and vancomycin, which can be infused 120 minutes prior to avoid infusion-related reactions.[1] No consensus has been reached on whether the infusion should be complete prior to the first incision. However, if a proximal tourniquet is used, antibiotic administration should be complete prior to inflation.

Studies have found that administration of the antimicrobial should begin as close to the first incision as possible. This is important for antibiotics with short half-lives so that therapeutic concentrations are maintained during the operation and reduce the need for redosing. Beginning the infusion after the first incision is of little value in preventing SSI. Stone and associates found that administration of the antimicrobial after the first incision had SSI rates similar to patients who did not receive prophylaxis.[20]

Dosing and Redosing

❽ *The goal of antimicrobial dosing for surgical prophylaxis is to maintain antibiotic concentrations above the MIC of suspected organisms for the duration of the operation.* Dosing recommendations can vary between institutions and guidelines. Clinical judgment should be exercised regarding dose modifications for renal function, age, and especially weight. Obese patients often require higher doses than do non-obese patients.[1] Forse and associates showed that morbidly obese patients (body mass index greater than 40) who received 2 g of cefazolin had a lower incidence of SSI compared to patients receiving 1 g.[21]

Guidelines suggest that if an operation exceeds two half-lives of the selected antimicrobial, then another dose should be administered.[1] Repeat dosing has been shown to lower rates of SSI. For example, cefazolin has a half-life of about 2 hours, thus

another dose should be given if the operation exceeds 4 hours. The clinician should have extra doses of antibiotic ready in case an operation lasts longer than planned.

Duration

The National Surgical Infection Prevention Project and published evidence suggest that the continuation of antimicrobial prophylaxis beyond wound closure is unnecessary.[1] ❾ *Studies have not shown benefit for additional doses of antibiotic and the duration of antimicrobial prophylaxis should not exceed 24 hours.* Longer durations of antibiotic prophylaxis are advocated by some guidelines and will be discussed later.

TREATMENT

Antimicrobial Prophylaxis in Specific Surgical Procedures

Gynecologic and Obstetric

Enteric gram-negative bacilli, anaerobes, group B streptococci, and enterococci are all possible pathogens that may be encountered in gynecologic or obstetric surgeries. For patients undergoing hysterectomy, cefoxitin or cefotetan are appropriate therapies (Table 82–3). Unfortunately, the availability of these drugs is an issue. Cefazolin or ampicillin/sulbactam may be used. In the case of β-lactam allergy, the following regimens are appropriate: clindamycin combined with gentamicin, aztreonam, or ciprofloxacin; metronidazole combined with gentamicin or ciprofloxacin, or clindamycin monotherapy. Metronidazole monotherapy is also indicated but has been shown to be less effective than other regimens.[1]

Cesarean sections are stratified into low- and high-risk groups. Patients who undergo emergency operations or have cesarean sections after the rupture of membranes and/or onset of labor are considered high risk. Prophylactic antimicrobials are most beneficial for high-risk patients but are used in both groups. Antimicrobial regimens similar to those for hysterectomy are appropriate. Antimicrobials should not be administered until after the first incision and the umbilical cord has been clamped. This practice prevents potentially harmful antibiotic concentrations from reaching the newborn.

TABLE 82–3. Recommended Regimens for Antimicrobial Prophylaxis of Specific Surgical Procedures[a]

Type of Operation	Recommended Prophylaxis Regimen	Alternative Regimen
Vascular	Cefazolin 1–2 g IV or cefuroxime 1.5 g IV	Clindamycin 600–900 mg IV or vancomycin 1 g IV
Neurosurgery	Cefazolin 1–2 g IV	Vancomycin 1 g IV
Head and neck	Cefazolin 1–2 g IV	Clindamycin 600–900 mg IV
Urologic	Cefazolin 1–2 g IV	Ciprofloxacin 400 mg IV
Cesarean section	Cefazolin 1–2 g IV, ampicillin/sulbactam 3 g IV	See hysterectomy
Hysterectomy	Cefazolin 1–2 g IV or cefoxitin 1–2 g IV Ampicillin/sulbactam 3 g IV	Antianaerobic agent (metronidazole 0.5–1 g IV or clindamycin 600–900 mg IV) combined with gentamicin 1.5 mg/kg IV, aztreonam 1–2 g IV, or ciprofloxacin 400 mg IV
Gastroduodenal (high-risk only: obstruction, acid suppression, morbid obesity, hemorrhage, malignancy)	Cefazolin 1–2 g IV	Ciprofloxacin 400 mg IV
Biliary tract (high-risk only: age greater than 70, acute cholecystitis, obstructive jaundice, duct stones, non-functioning gallbladder)	Cefazolin 1–2 g IV or cefoxitin 1–2 g IV	Ciprofloxacin 400 mg IV
Colorectal	[b]Oral: neomycin 1 g plus erythromycin base 1 g (give 19, 18, and 9 hours prior to procedure) IV: cefoxitin 1–2 g	Cefazolin 1–2 g IV plus metronidazole 0.5–1 g IV or hysterectomy regimens
Appendectomy	Cefoxitin 1–2 g IV	Metronidazole 0.5–1 g IV plus gentamicin 1.5 mg/kg IV
Orthopedic	Cefazolin 1–2 g IV	Vancomycin 1 g IV or clindamycin 600–900 mg IV
Cardiothoracic	Cefazolin 1–2 g IV or cefuroxime 1.5 g IV	Vancomycin 1 g IV or clindamycin 600–900 mg IV
Dental prophylaxis	Amoxicillin 2 g PO 1 hour prior to procedure	Clindamycin 600 mg PO 1 hour prior to procedure

IV, intravenous; PO, oral.
[a]Dosing recommendations are based on common clinical doses; dosing for individual patients and institutions may vary.
[b]Oral regimens should be used in conjunction with IV prophylaxis.
Adapted from references 1, 14, 24.



Patient Encounter 1, Part 1

AD is a 60-year-old woman with a history of poorly controlled diabetes mellitus and MSSA nasal colonization. She weighs 54 kg and is 156 cm tall. She presents today for a hysterectomy. She has no allergies to any medications. The surgeon approaches you for recommendations on prophylactic antibiotic use.

PE

VS: Blood pressure 128/76 mm Hg, pulse 76 beats per minute, respiratory rate 15/minute, temperature 36.4ºC (97.5°F)

Labs

White blood cell count: 5000 cells/mm^3, serum creatinine 80 µmol/L (0.9 mg/dL), glucose 5.3 mmol/L (100 mg/dL)

- What drug would you choose for this operation and why?
- What organisms are likely to be encountered in this operation?
- The surgeon asks about using metronidazole as a solo agent; what is your opinion on this?
- The surgeon agrees with your decision and wants to begin infusing the antibiotic 1 hour *after* the first incision. Comment on this.
- What other interventions besides antibiotic use could prove useful in lowering AD's risk of SSI?

Orthopedic Surgery

Orthopedic surgery is generally a clean operation done under controlled conditions. Likely pathogens include gram-positive cocci, mostly staphylococci. In the case of total joint (knee and hip) arthroplasty, cefazolin is the antimicrobial of choice. Patients with a β-lactam allergy should receive either clindamycin or vancomycin. Antimicrobial prophylaxis should not exceed 24 hours and does not need to be continued until all drains and catheters have been removed. Antibiotic-impregnated bone cement can be useful in lowering infection rates in orthopedic surgery but has not been approved for prophylaxis.

Cardiothoracic and Vascular Surgery

Cefazolin or cefuroxime are appropriate for prophylaxis in cardiothoracic and vascular surgeries. In the case of β-lactam allergy, vancomycin or clindamycin are advised. Debate exists on the duration of antimicrobial prophylaxis. The National Surgical Infection Prevention Project cites data that extending prophylaxis beyond 24 hours does not decrease SSI rates and may increase bacterial resistance.[1] American Society of Health-System Pharmacists guidelines from 1999 allow for the continuation of prophylaxis for up to 72 hours.[22] Duration of therapy should be based on patient factors and risk of development of an SSI. SSIs are rare after cardiothoracic operations, but the potentially devastating consequences lead some clinicians to support longer periods of prophylaxis.



Patient Encounter 2

GL is a 56-year-old male who presents to the emergency department with crushing chest pain described as a "10/10" and shortness of breath. He weighs 82 kg (180 lbs) and is 175 cm tall. An electrocardiogram reveals an elevated ST segment and lab data is significant for elevated troponins. GL is diagnosed with acute myocardial infarction. After GL is stabilized, the decision is made to place multiple stents. The surgeon consults with you on recommendations for antibiotic prophylaxis. Significant history for GL: allergy to amoxicillin (anaphylaxis), smokes 2 packs of cigarettes per day, and he lives with his wife and two children.

PE

VS: Blood pressure 162/95 mm Hg, pulse 120 beats per minute, respiratory rate 28/minute, temperature 35.8ºC (96.4°F)

Labs

serum creatinine 80 µmol/L (0.9 mg/dL), troponins 1.67 µmol/L (0.8 µg/L)

- The surgeon wants to use vancomycin for this case; what is your opinion on this?
- The surgeon decides to use vancomycin at a dose of 1 gram over 30 minutes. During the infusion, GL experiences a rash and a call is made for an epinephrine pen. What is happening to GL and how would you alter the therapy?
- What is the risk of overuse of vancomycin in hospitals and what pathogens are becoming problematic?
- Forty-eight hours after the end of GL's surgery he is still on vancomycin. The surgeon argues that prophylaxis should be continued for 72 hours and cites guidelines. What guidelines are the surgeon citing and what is your opinion on this decision?

Colorectal Surgery

Antimicrobial prophylaxis for colorectal operations must cover a broad range of gram-positive, gram-negative, and anaerobic organisms. Strategies include oral antimicrobial bowel preparations, parenteral antimicrobials, or both. Oral prophylaxis combinations of neomycin and erythromycin or neomycin and metronidazole are common. Oral antimicrobials should be administered at 19, 18, and 9 hours prior to surgery. A delay in surgery may require a redose, depending on the length of postponement. For parenteral prophylaxis, cefoxitin or cefotetan is appropriate. Cefazolin combined with metronidazole or ampicillin/sulbactam is an effective alternative if antianaerobic cephalosporins are not available. For patients with β-lactam allergies, use clindamycin combined with gentamicin, aztreonam, or ciprofloxacin; metronidazole combined with gentamicin or ciprofloxacin is also appropriate.

Appendectomy is one of the most common intra-abdominal operations. Antimicrobial prophylaxis used for appendectomy is similar to that used for colorectal regimens. In the case

of ruptured appendix, antimicrobials are used for treatment, not prophylaxis.

Dental Procedures

The goal of antimicrobial prophylaxis in dental procedures is to prevent endocarditis. According to American Heart Association guidelines, at-risk individuals should receive 2 g of amoxicillin 1 hour prior to the procedure.[23] Patients with a β-lactam allergy may receive clindamycin 600 mg 1 hour prior to the procedure. Interested readers should refer to the American Heart Association guidelines for a complete discussion on risk stratification and recommendations.

OUTCOME EVALUATION

The clinician should consistently follow-up post-operative patients and screen for any sign of SSI. ⑩ *According to CDC criteria, SSI may appear up to 30 days after an operation and up to 1 year if a prosthesis is implanted.*[5] This period often extends beyond hospitalization so patients should be educated on warning signs of SSI and be encouraged to contact a clinician immediately if necessary. The presence of fever or leukocytosis in the immediate post-operative period does not constitute SSI and should resolve with proper patient care. Distal infections, such as pneumonia, are not considered SSIs even if these infections occur in the 30-day period. The appearance of the surgical site should be checked regularly and any changes documented (e.g., erythema, drainage, or pus). The presence of pus or other signs suggestive of SSI must be treated accordingly. Any wound requiring incision and drainage is considered an SSI regardless of appearance. Prompt cultures should be collected and appropriate antimicrobial therapy initiated to reduce any chance of morbidity and mortality.



Patient Encounter 1, Part 2

AD has been admitted to the ward after completion of her hysterectomy. A physical examination is performed and laboratory data are collected in the immediate post-operative period. AD complains of tenderness around the incision site but no erythema is noted.

PE

VS: Blood pressure 132/80 mm Hg, pulse 82 beats per minute, respiratory rate 20/minute, temperature 37.8ºC (100.0°F)

Labs

White blood cell count 11,000 cells/mm^3, serum creatinine 88.4 μmol/L (1 mg/dL), glucose 5.55 mmol/L (100 mg/dL)

- Based on the available data, does AD have an SSI?
- What interventions may increase AD's comfort?
- How should AD be screened for SSI?
- How long should AD be followed in order to identify a possible SSI?



Patient Care and Monitoring

- Conduct a thorough medication history including prescription and non-prescription medications as well as herbals and vitamins.
- Verify the patient's allergy history and the type of reaction experienced. Attempt to discern between true allergy and adverse event. β-Lactam–allergic patients may receive clindamycin, vancomycin, or other antimicrobials. Cross-reactivity between penicillin allergy and cephalosporins is low but cephalosporins should be avoided in patients with a history of anaphylaxis to penicillins.
- Document the type of operation the patient is undergoing. Verify the surgical procedure with the patient.
- Prophylactic antimicrobials should be started within an hour of the first incision to optimize patient outcomes. Exceptions to this include vancomycin and fluoroquinolones.
- The patient should be monitored for signs of an allergic reaction during the operation. These include rash, hives, difficulty breathing, or substantial drops in blood pressure.
- Major breaks in surgical technique may cause the classification of the operation to change and require adjustments in antimicrobial prophylaxis.
- The patient should be monitored for signs and symptoms of infection post-operatively. These could include pus, erythema, and fever. If signs consistent with SSI appear, cultures should be taken and additional antimicrobial therapy should be considered.
- Patients being discharged should be counseled on recognizing signs and symptoms of SSI. An SSI can appear up to 30 days after an operation is completed.

ABBREVIATIONS

CDC:	Centers for Disease Control and Prevention
GI:	gastrointestinal
GU:	genitourinary
IV:	intravenous
MIC:	minimum inhibitory concentration
MRSA:	methicillin-resistant *Staphylococcus aureus*
MSSA:	methicillin-sensitive *Staphylococcus aureus*
NNIS:	National Nosocomial Infections Surveillance System
SSI:	surgical site infection

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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83 Vaccines and Toxoids

Marianne Billeter



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Define vaccination and immunization.
2. Classify each of the routine vaccines as an inactivated, polysaccharide, conjugate, toxoid, or subunit vaccine.
3. Describe the effect of each routine vaccine on preventing infection.
4. Recommend an immunization schedule for a child, including immunocompromised children.
5. Recommend an immunization schedule for an adult based on comorbid conditions and lifestyle issues.
6. Evaluate an adverse reaction and its probable association with a vaccine.

Key Concepts

❶ Vaccines provide active immunity against viral and bacterial pathogens.
❷ Polysaccharide vaccines are poorly immunogenic in children younger than 2 years of age.
❸ Combination vaccines decrease the number of injections and increase the likelihood of completing the immunization schedule.
❹ Health care professionals should report vaccine-adverse events.
❺ Live virus vaccines should not be given to an immunocompromised host.
❻ Vaccines are cost-effective in preventing disease.

The development and widespread use of vaccines is one of the greatest public health achievements of the twentieth century. Other than safe drinking water, no other modality has had a greater impact on reducing mortality from infectious diseases. The first accounts of deliberate inoculation to prevent disease date back as far as the tenth century. However it wasn't until 1798 that Edward Jenner published his work on inoculation of natural cowpox as a means to prevent infection with smallpox. This was the first scientific attempt to prevent infection by inoculation. Since 1900, vaccines have been developed against more than 20 diseases, with half of these recommended for routine use. The widespread use of vaccines has resulted in the eradication of smallpox worldwide and wild-type poliovirus from the Western hemisphere. There have also been dramatic declines in the incidence of diphtheria, pertussis, tetanus, measles, mumps, rubella, and *Haemophilus influenzae* type b.

❶ *Vaccines provide active immunity against a variety of viral and bacterial infections.* Most vaccines are designed to prevent acute infections that can be rapidly controlled and cleared by the immune system. Successful immunization involves activation of antigen-presenting cells with processing of the antigen by lysosomal or cytoplasmic pathways. T and B lymphocytes will be activated to replicate and differentiate to form large pools of memory cells for protection against subsequent exposure to the antigen.[1]

Vaccines against viral infections may be **attenuated** live viruses or inactivated viral particles. Attenuation may be accomplished by several methods to decrease the viruses' virulence while retaining their **immunogenicity**. Bacterial vaccines utilize antigenic particles of the outer membrane to elicit an immune response. ❷ *Outer membrane polysaccharides are poorly immunogenic in children less than 2 years of age* unless conjugated with a carrier protein. Also, bacterial toxins may undergo chemical treatment to render them non-toxic to form **toxoids** against infectious agents.

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Patient Encounter 1

A 1-year-old child is brought to the pediatrician's office for a routine 1-year checkup. The child is healthy and meeting all growth and developmental targets. The child has received all vaccinations to date. The pediatrician discusses with the mother the need for more vaccinations during this visit.

- Which vaccine should the child receive during this visit?
- Is there a way to minimize the number of shots the child receives?
- What risks are involved with vaccinating this child?

COMMON TERMINOLOGY

Often the terms vaccination and immunization are used interchangeably even though they are very distinct concepts. Vaccination refers to the act of administering a vaccine, while immunization refers to the development of immunity to a pathogen. The delivery of a vaccine does not imply that the individual mounted an adequate immune response to the vaccine to elicit protection. However, immunization implies that the act of vaccination resulted in the development of protective immunity.

Herd immunity refers to high levels of immunization in one population resulting in protection of another unvaccinated population. For example, concentrated vaccination of children with the 7-valent pneumococcal conjugate vaccine resulted in decreased invasive *Streptococcus pneumoniae* infection not only in the vaccinated children, but also in elderly persons within the same community.

Cocoon immunization is a strategy used to immunize all persons surrounding another high-risk individual. This strategy is used to protect individuals who are not able to be vaccinated themselves, such as vaccinating parents, siblings, and grandparents of a new infant who is too young to be vaccinated.

THE ROUTINE VACCINES

Diphtheria, Tetanus, and Pertussis Vaccines

Diphtheria Toxoid

Diphtheria is a bacterial respiratory infection characterized by membranous pharyngitis. The membrane may cover the pharynx, tonsillar areas, soft palate, and uvula. Diphtheria may also cause anal, cutaneous, vaginal, and conjunctival infections. The impact of diphtheria is not from the causative bacteria, *Corynebacterium diphtheriae*, but rather from complications attributed to its exotoxin, such as **myocarditis** and peripheral **neuritis**. In the late 1800s, death due to diphtheria ranged from 46 to 196 cases per 100,000 annually. Mortality from diphtheria dropped in the 1900s mostly due to the availability of diphtheria antitoxin, which elicited passive immunity. Diphtheria is rarely reported in the United States since the introduction of vaccination with diphtheria toxoid; however, diphtheria continues to be a major problem in developing countries.

In the early 1900s, a balanced mixture of diphtheria toxin and antitoxin was found to produce active immunity in both animals and humans. This preparation gained widespread acceptance and protected approximately 85% of recipients. Several years later, diphtheria toxoid was developed by treating the toxin with small amounts of formalin. This process caused the toxin to lose its toxic properties while maintaining its immunogenic properties. In the mid-1920s, the addition of an alum precipitate enhanced the immunogenic properties of the toxoid.

In the 1940s, diphtheria toxoid was combined with tetanus toxoid and whole cell pertussis vaccines, and later with the acellular pertussis vaccine. The diphtheria toxoid, tetanus toxoid, and acellular pertussis vaccine are part of the routine childhood immunization schedule. Diphtheria toxoid is also combined with tetanus toxoid and is commonly used as a booster vaccine. The pediatric product (DT) has a higher amount of diphtheria toxoid than does the adult product (Td). Diphtheria toxoid is not available as an individual vaccine.

Recent outbreaks of diphtheria have demonstrated that immunity wanes in adulthood. Approximately 50% of all adults no longer have immunity to diphtheria. Regular boosters with tetanus and diphtheria toxoids every 10 years will provide adequate recall immunity to diphtheria provided the adult was previously immunized.[2]

Tetanus Toxoid

The tetanus vaccine differs from others in that it does not protect against a contagious disease such as diphtheria, but rather against an environmental pathogen. *Clostridium tetani* is widely found in the environment, especially in dirt and soils. Additionally, animals and humans may harbor and excrete the organism. *C. tetani* produces two neurotoxins, tetanospasmin and tetanolysin, which are responsible for producing the painful muscular contractions associated with tetanus. Tetanus continues to be a major problem in the developing world, causing approximately 1 million deaths each year. Approximately 40% of the cases are neonatal tetanus most likely associated with the use of non-sterile instruments or poultices on the umbilical cord. Tetanus is rarely seen in developed countries.

Immunity to tetanus decreases with increasing age, therefore a regular booster every 10 years with tetanus toxoid is recommended. The preferred agent to use in adults is tetanus and diphtheria toxoid (Td) in order to give a booster for diphtheria. Tetanus immunization status should be assessed in the management of wounds in individuals seeking medical care. A tetanus booster should be administered if a tetanus-containing

vaccine has not been given in the preceding 5 years for moderate and severe wounds or contaminated wounds. If the wound is minor and uncontaminated, then a tetanus booster is needed if the previous tetanus vaccination was more than 10 years ago.

Pertussis

Pertussis is a highly contagious respiratory tract infection caused by the bacteria *Bordetella pertussis*. Pertussis is characterized by a protracted severe cough with or without posttussive vomiting, whoop, difficulty breathing, difficulty sleeping, and rib fractures. It is often referred to as "whooping cough" or the 100-day cough. In the pre-vaccine era, pertussis accounted for more than 250,000 cases of severe illness and 10,000 deaths per year in the United States. Pertussis has always been thought of as a pediatric disease since most cases occurred in preschool-aged children with relatively no cases seen in adolescents and adults. The first pertussis vaccine was introduced in the 1940s and within 30 years resulted in a 99% reduction in disease. However, during the past two decades there has been a steady increase in reported cases of pertussis among adolescents and adults, indicating a waning immunity after primary immunization.[4]

The first pertussis whole cell vaccine was a mixture of killed organisms that was associated with frequent local and systemic reactions. In the late 1980s, an acellular pertussis vaccine was introduced that contains purified pertussis components that are immunogenic but associated with fewer adverse reactions. Acellular pertussis vaccine is available in combination with tetanus and diphtheria toxoids. Pertussis is not available as a separate vaccine component. In the spring of 2005, the Food and Drug Administration (FDA) approved tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines for use in adolescents and adults.

Use of Diphtheria, Tetanus, and Acellular Pertussis Vaccine

Diphtheria and tetanus toxoids and acellular pertussis (Dtap) vaccine should be administered in a five-shot series to all children beginning at 2 months of age (Table 83–1). The shots are given at 2, 4, 6, and 15 to 18 months, and 4 to 6 years. Complete immunity to diphtheria and tetanus is achieved after the third vaccination.

Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) is recommended as a single booster for the following groups in place of a tetanus booster.

- Adolescents 11 to 18 years of age: An interval of 5 years, with a minimum of 2 years, between the last tetanus-containing vaccine is recommended to minimize local and systemic adverse events; however, shorter intervals may be used.
- Adults 19 to 64 years of age: Tdap should replace the next routine tetanus booster. Intervals as short as 2 years between Tdap and Td may be used.
- Tetanus prophylaxis in wound management: Adolescents and adults 11 to 64 years of age, who have completed a primary series and require a tetanus-containing product should receive Tdap instead of Td if they have not already received Tdap.
- Prevention of pertussis in infants less than 12 months of age: Adults who have close contact with infants less than 12 months of age, especially parents, grandparents, and child care providers, should receive a single dose of Tdap. An interval of at least 2 years since the last tetanus-containing vaccine was given is suggested, but shorter intervals may be used. Ideally, Tdap should be given 1 month prior to contact with the infant.
- Postpartum women: Women should receive a single booster of Tdap in the immediate postpartum period if Tdap has not been previously received.

Haemophilus influenzae Type b Vaccine

Haemophilus influenzae is a bacterial respiratory pathogen that causes a wide spectrum of disease ranging from colonization of the airways to bacterial meningitis. It causes considerable morbidity and mortality, especially in children less than 5 years of age. *H. influenzae* is either encapsulated or unencapsulated. The encapsulated strains can be further differentiated into six antigenically distinct serotypes, a through f. *H. influenzae* type b was primarily found in cerebrospinal fluid and blood of children with meningitis, while the unencapsulated strains were found in the upper respiratory tract of adults. Before the introduction of the vaccine, *H. influenzae* was responsible for 20,000 to 25,000 cases of invasive disease annually and was the most common cause of bacterial meningitis. Since the introduction of the vaccine, invasive disease due to *H. influenzae* type b has been nearly eliminated.

The first *H. influenzae* type b vaccine was an aqueous solution of capsular polysaccharide, polyribosylribitol phosphate. As with all polysaccharide vaccines, it showed poor immunogenicity in children less than 2 years of age. This vaccine is no longer used.

The current *H. influenzae* type b vaccine is a protein conjugate that utilizes a carrier-hapten for antigen presentation. The polysaccharide is conjugated to an immunogenic protein carrier, which is recognized by T cells and macrophages that stimulates T-dependent immunity. The conjugated vaccine elicits an immune response characterized by T-helper cell activation. The T-dependent antigens induce an enhanced immune response in younger children. Within 10 years of its introduction, the *H. influenzae* type b vaccine use has resulted in widespread herd immunity.

H. influenzae type b conjugate vaccine is a recommended routine childhood vaccine given at 2, 4, 6, and 12 to 15 months of age. Adolescents and adults with functional or anatomic asplenia should also receive a booster dose of *H. influenzae* type b vaccine. The currently available vaccines are labeled for pediatric use, but can be used in adults when vaccination is indicated. There are several *H. influenzae* type b vaccines on

TABLE 83–1. Vaccine Dosing

Vaccine	Common Abbreviation	Dose	Route	Cautions
Diphtheria and tetanus toxoid	DT	0.5 mL	Intramuscular	
Diphtheria, tetanus, acellular pertussis	Dtap	0.5 mL	Intramuscular	• Systemic neurologic reaction from previous vaccine • Brachial neuritis • Cried for 3 hours non-stop after previous dose • Temperature greater than 40.5°C (105°F)
Haemophilus influenzae type b	HIB	0.5 mL	Intramuscular	
Hepatitis A	HAV	C: 0.5 mL A: 1 mL	Intramuscular	
Hepatitis B	HBV	C: 0.5 mL A: 1 mL	Intramuscular	• Allergic reaction to yeast (baking yeast)
Inactivated influenza	TIV	0.5 mL	Intramuscular	• Severe egg allergy • History of Guillain-Barré syndrome
Live attenuated influenza	LAIV	0.5 mL	Intranasal	• Severe egg allergy • Asthma • Chronic health problems • Immunocompromised host • Pregnant women • History of Guillain-Barré syndrome
Measles, mumps, rubella	MMR	0.5 mL	Subcutaneous	• Allergic reaction to gelatin or neomycin • Pregnant women • Immunocompromised host • Recently received a blood transfusion • Severe egg allergy
Meningococcal polysaccharide	MPSV4	0.5 mL	Subcutaneous	• History of Guillain-Barré syndrome
Meningococcal conjugate	MCV4	0.5 mL	Intramuscular	• History of Guillain-Barré syndrome
Pneumococcal 7-valent conjugate	PCV7	0.5 mL	Intramuscular	
Pneumococcal polysaccharide	PPV23	0.5 mL	Intramuscular route preferred; subcutaneous	• Children less than 2 years of age
Poliovirus, inactivated	IPV	0.5 mL	Intramuscular, subcutaneous	• Allergic reaction to neomycin, streptomycin, polymyxin B
Rotavirus vaccine		2 mL	Oral	• Immunocompromised host
Tetanus and diphtheria toxoid	Td	0.5 mL	Intramuscular	
Tetanus, reduced diphtheria, acellular pertussis	Tdap	0.5 mL	Intramuscular	• History of Guillain-Barré syndrome • Systemic neurologic reaction from previous vaccine
Varicella	VAR	0.5 mL	Subcutaneous	• Allergic reaction to gelatin or neomycin • Pregnant women • Immunocompromised host • Recently received a blood transfusion • Hematopoietic stem cell transplant

C, children; A, adult.

the market that differ in the size of the polysaccharide and type of carrier protein; however, the immune response to *H. influenzae* type b is similar among the different vaccines. The different brands are interchangeable without affecting the primary immune response or booster response.

H. influenzae type b and influenza vaccines have the potential for confusion and medication errors because of the similarity of the names. Care should be taken when ordering, dispensing, and administering these vaccines.

Hepatitis A Vaccine

Hepatitis A virus continues to be a frequent cause of illness despite the availability of a highly effective vaccine. Hepatitis A typically has an abrupt onset of symptoms including fever, malaise, nausea, abdominal discomfort, and jaundice. Frequently children less than 6 years of age are asymptomatic while adults typically have symptomatic disease. Symptoms may persist for 2 months or longer. There is wide geographic variation in the incidence of hepatitis A infection, with the number of cases ranging from 50 to more than 700 cases per 100,000 persons annually. The economic burden of hepatitis A is estimated to be greater than $300 million annually in combined direct and indirect costs. Widespread use of the vaccine offers the opportunity to substantially decrease the disease burden caused by hepatitis A infection.[5]

Hepatitis A vaccine was licensed in the United States in 1995. It is an inactivated whole virus vaccine that is administered in a

two-dose series. More than 94% of children, adolescents, and adults will have protective antibodies 1 month after receiving the first dose and 100% following the second dose.[5] Recommended use of the hepatitis A vaccine utilizes an incremental implementation schedule beginning with high-risk populations or those at increased risk for serious complications from the disease. Currently hepatitis A vaccine is recommended for all children following the first birthday, with the second dose administered 6 months later. Adults who are at high risk for hepatitis A should receive two doses at least 6 months apart. High-risk adults include persons with clotting disorders or chronic liver disease, men who have sex with men, illicit drug users, international travelers going to areas with high to intermediate endemicity of hepatitis A, or any other person who wishes to become immune.

Hepatitis B Vaccine

Hepatitis B virus is a blood-borne or sexually transmitted virus. Most acute infections occur in adults, while chronic infections usually occur in individuals infected as infants or children. However, about 10% of adults who contract hepatitis B virus will fail to clear their infection and develop chronic hepatitis B infection. Individuals with chronic hepatitis B infection are at risk for cirrhosis or hepatocellular carcinoma. Vaccination with hepatitis B vaccine is the most effective way to prevent hepatitis B infection.[6]

Hepatitis B vaccine is manufactured using recombinant DNA technology to express hepatitis B surface antigen (HBsAg) in yeast. This is further purified with biochemical separation techniques to produce the vaccine. The vaccines are formulated to contain 10 to 40 mcg of HBsAg protein/mL. Hepatitis B vaccine is available as a single component or in combination vaccines.

Hepatitis B vaccine is recommended for routine use in children. The first dose should be given within 12 hours of birth. The second and third doses are given at 2 months and 6 months after the first dose if using the single component vaccine, or at 2, 4, and 6 months if using combination vaccines. If the infant weighs less than 2000 g at birth, the birth dose is not counted in the three-dose series. Infants less than 2000 g do not produce an adequate immune response to the birth dose of hepatitis B vaccine. Adolescents should receive the three-dose series if not previously vaccinated.[6]

Adults at high risk for hepatitis B because of occupation or lifestyle should receive the hepatitis B vaccine series. The typical series has the second and third doses given 1 month and 6 months after the first dose. Accelerated schedules may also be used. Frequently, individuals do not follow through with the complete three-dose series and questions arise about restarting the series. Hepatitis B vaccine produces an amnesic response; therefore the series may be continued at any time in order to complete the three doses.

Following vaccination with hepatitis B vaccine, hepatitis B virus serologic markers will remain negative with the exception of anti-HBs (antibody to hepatitis B surface antigen), which will be positive indicating immunity. Persons with anti-HBs concentration greater than 10 mIU/mL after vaccination will have complete protection against acute and chronic infection.[6] It is unclear if a booster dose of hepatitis B vaccine should be administered when anti-HBs concentrations fall below 10 mIU/mL, since a good memory response will occur following exposure to hepatitis B virus.

Influenza Vaccine

Influenza is a contagious viral respiratory infection that usually occurs during the winter months in the Northern Hemisphere and all year round in the Southern Hemisphere. All age groups are affected by influenza; however, children have the highest rate of infection. Serious illness and death due to influenza usually occurs in extremes of age, those over 65 years or under 2 years. Influenza is responsible for approximately 36,000 deaths annually in the United States.[7]

Influenza A and B viruses are responsible for causing human disease. Influenza A is further categorized into subgroups by its surface antigens, hemagglutinin and neuraminidase (e.g., influenza A H1N1 virus). Influenza B virus is not sub-typed. Both influenza A and B undergo frequent antigenic drift, creating new influenza variants. Immunity to the surface antigens decreases the likelihood of infection. Unfortunately, antibody to one influenza subgroup does not give complete protection against other influenza sub-types. Therefore, annual influenza vaccination is recommended during October and November and continuing until the vaccine supply is exhausted.

The best way to protect against influenza is through vaccination. The influenza vaccine is composed of two influenza A sub-types and one influenza B sub-type. The viral sub-types contained in the vaccine usually changes each year. The exact composition is selected by a panel of experts and announced by the Centers for Disease Control and Prevention (CDC) in March or April each year. The vaccine becomes available for use in late August and September. Two types of influenza vaccine are licensed for use in the United States; both vaccines contain the same viral subunits. The influenza viruses for both vaccine preparations are grown in eggs. Therefore, the vaccines are contraindicated in individuals with severe allergy to eggs.

The trivalent inactivated influenza vaccine can be administered to all age groups and risk populations. It is recommended that the vaccine be administered yearly to children older than 6 months of age at risk for complications from influenza, such as those with asthma, cardiac disease, sickle cell disease, human immunodeficiency virus (HIV) infection, diabetes, and other conditions that compromise respiratory function. Healthy children 6 to 23 months of age should be vaccinated because of the increased risk for influenza-related

hospitalizations. Other groups of healthy children may also be vaccinated since this is a significant population for transmission to older adults. It is postulated that vaccination of young children may produce herd immunity and elicit protection in older adults who may not produce a fully protective immune response to the vaccine. If the child is less than 8 years old and is receiving influenza vaccine for the first time, two doses separated by 4 to 6 weeks should be given.

Influenza vaccine should be given yearly to all adults 50 years of age or older. Younger adults with chronic disorders of the cardiovascular or pulmonary systems, chronic metabolic diseases, renal dysfunction, immunosuppression, or disorders that compromise respiratory function should also be vaccinated. Women who will be pregnant during the winter months should be vaccinated against influenza.

Healthy individuals 5 to 49 years of age can receive the live attenuated influenza vaccine instead of the inactivated vaccine. There are limited data on transmission of the vaccine strain following intranasal vaccination; however, **secondary transmission** does not appear to be a concern.

Measles, Mumps, and Rubella Vaccine

Measles

Measles, also known as rubeola, is characterized by a rash that is often complicated by diarrhea, middle ear infection, or pneumonia. Encephalitis occurs in 1 of every 1000 reported cases. Individuals who recover from encephalitis usually have permanent brain damage. Death occurs in 1 to 2 of every 1000 reported measles cases.[8]

Prior to measles vaccine availability the number of cases of measles approached the birth rate of approximately 3 to 4 million annually. The first measles vaccine was licensed in 1963. Since that time there has been a 99% reduction in reported measles cases. Currently, there is a goal to eliminate measles transmission in the United States through aggressive immunization programs.

There have been several types of measles vaccines used since its introduction. There have been inactive and live attenuated vaccines using different strains of the virus. The current vaccine uses a live attenuated preparation of the Enders-Edmonston virus strain. Following vaccination with measles-containing vaccine, a mild non-communicable infection develops. Approximately 95% of individuals will develop antibodies following a single dose if administered after 12 months of age. More than 99% of individuals who receive two inoculations will develop long-term, probably lifelong, immunity to measles.[8]

Mumps

Mumps is usually thought of as a disease of children, but it has also gained notoriety as a prominent illness affecting military units. Mumps produces a typical acute parotitis, but may also cause nonspecific respiratory symptoms. In post-pubertal males, mumps may also cause orchitis in 38% of those infected, which may result in infertility.[8]

Since the introduction of the mumps vaccine in 1967 there has been a 99% reduction in reported cases. The mumps vaccine is a live virus preparation of the Jeryl-Lynn strain. It produces a sub-clinical, non-communicable infection following vaccination. Single doses of mumps vaccine will elicit immunity in 75% to 95% of individuals. Vaccine-induced immunity lasts for more than 30 years.

Rubella

German measles, also known as rubella, is a mild exanthematous illness in children and young adults; however, rubella infection in pregnant women can cause a variety of congenital malformations in the infant. Congenital rubella syndrome occurs in approximately 25% of infants whose mother acquires rubella during the first trimester. Congenital rubella syndrome is characterized by congenital cataracts, heart disease, deafness, thrombocytopenia, mental retardation, and numerous other abnormalities.[8]

The first rubella vaccine was licensed in 1969. Initial vaccination campaigns were targeting young children, since this age group had the highest rate of rubella infection. This strategy significantly decreased rubella cases in children, but did not have the desired effect on infection in adolescents and adults or on congenital rubella syndrome. Adolescents, especially young girls, were then targeted for vaccination. This has resulted in a significant reduction in the number of cases of congenital rubella syndrome.

The live rubella vaccine available in the United States contains the RA 27/3 strain of the virus. Following a single dose of rubella vaccine after the first birthday, more than 90% of individuals will develop long-term immunity. Rarely has congenital rubella syndrome been reported in infants born to mothers with adequate rubella immunization.

Use of Measles, Mumps, and Rubella Vaccine

Measles, mumps, and rubella vaccines are available as single component vaccines or as combinations. Most authorities recommend use of the measles, mumps, and rubella combination vaccine and discourage use of the single- or double-component vaccines. Two doses of the measles, mumps, and rubella vaccine are recommended for all individuals born after 1957. The first dose should be administered soon after the first birthday and the second prior to entering school. For high-risk adolescents and adults who do not have adequate immunity, two doses of the vaccine should be separated by a minimum of 28 days.[8]

Measles, mumps, and rubella vaccine is a live virus vaccine that should be used with caution in immunosuppressed children, such as those with cancer receiving chemotherapy, solid organ or bone marrow transplantation, or receiving other immunosuppressive drugs, such as steroids in a dose



Patient Encounter 2

An 18-year-old male is having a routine physical before leaving for college. He will be a freshman and is looking forward to dormitory life. The health care provider recommends some vaccinations be given at this visit.

- Which vaccines should be administered?
- What is the risk of not receiving the vaccines?

equivalent to prednisone 1 mg/kg per day or higher or 20 mg per day for 2 weeks or longer. If possible, vaccines should be given prior to becoming immunosuppressed. Otherwise, it may be prudent to defer the vaccine until after the immunosuppression resolves.

Meningococcal Vaccines

Neisseria meningitidis is a significant cause of meningitis and severe sepsis. Meningococcus causes an estimated 2500 cases of invasive disease each year in the United States. Invasive meningococcal disease is associated with an estimated 15% mortality rate. Morbidity in survivors is substantial, with approximately 20% having loss of limb or neurologic sequelae. The highest rates of meningococcal disease are among young children; however, rates have been increasing in adolescents and young adults. Thirteen meningococcal serogroups have been identified; however, five serogroups, A, B, C, Y, and W-135, are responsible for epidemic and endemic disease worldwide. Despite the availability of highly active antibacterial agents against *N. meningitidis,* there has been little impact on decreasing the morbidity and mortality due to invasive meningococcal disease.[9]

A meningococcal polysaccharide vaccine containing serogroups A, C, Y, and W-135 has been available in the United States for a number of years. Meningococcal polysaccharide vaccine is similar to other polysaccharide vaccines, in that it is poorly immunogenic in infants and children less than 2 years of age, and does not produce lasting immunity. Meningococcal polysaccharide vaccine produces a T-cell–independent response and fails to induce a memory response. Repeated vaccination results in hyporesponsiveness to serogroups A and C; the clinical implication of this finding is unknown.

In January 2005, a new meningococcal polysaccharide diphtheria toxoid conjugate vaccine was approved by the FDA. This vaccine also contains meningococcal serogroups A, C, Y, and W-135. Polysaccharide-protein conjugate vaccines are known to produce improved immunogenicity and memory responses. Meningococcal conjugate vaccine has shown similar immunologic response for all four serogroups when compared to meningococcal polysaccharide vaccine. However, this vaccine does not offer protection against diphtheria.

Meningococcal conjugate vaccine is recommended for routine vaccination of young adolescents 11 to 12 years of age. This may be done at the routine preadolescent health care visit. Routine meningococcal vaccination is also recommended for persons at increased risk for meningococcal disease, such as college freshman living in dormitories, microbiologists who are routinely exposed to isolates of *N. meningitidis*, military recruits, persons who travel to or reside in countries in which *N. meningitidis* is hyperendemic or epidemic, persons who have terminal complement component deficiencies, and persons who have anatomic or functional asplenia. Meningococcal conjugate vaccine is preferred for persons 11 to 55 years of age. Meningococcal polysaccharide vaccine should be used in persons 2 to 10 years of age and those greater than 55 years of age. Routine revaccination is not recommended at this time.[9]

Pneumococcal Vaccines

Streptococcus pneumoniae is the most common bacterial cause of community-acquired respiratory tract infections. *S. pneumoniae* causes approximately 3000 cases of meningitis, 50,000 cases of bacteremia, 500,000 cases of pneumonia, and over 1 million cases of otitis media each year. The increasing prevalence of drug-resistant *S. pneumoniae* has highlighted the need to prevent infection through vaccination. Both licensed pneumococcal vaccines are highly effective in preventing disease from the common *S. pneumoniae* serotypes that cause human disease.

The 23-valent pneumococcal polysaccharide vaccine contains 23 serotypes that are responsible for causing more than 80% of invasive *S. pneumoniae* infections in adults. The vaccine includes those serotypes that are associated with drug resistance. Use of the vaccine will not prevent the development of antibiotic-resistant *S. pneumoniae*, but is likely to prevent infection from drug-resistant strains. The 23-valent pneumococcal polysaccharide vaccine has demonstrated good immunogenicity in adults, but an individual will not develop immunity to all 23 serotypes following vaccination.[10]

The 23-valent pneumococcal polysaccharide vaccine is recommended for use in all adults 65 years of age or older and adults less than 65 years who have medical comorbidities that increase the risk for serious complications from *S. pneumoniae* infection, such as chronic pulmonary disorders, cardiovascular disease, diabetes mellitus, chronic liver disease, chronic renal failure, functional or anatomic asplenia, and immunosuppressive disorders. Alaskan natives and certain Native American populations are also at increased risk. Children over the age of 2 years may be vaccinated with the 23-valent pneumococcal polysaccharide vaccine if they are at increased risk for invasive *S. pneumoniae* infections, such as children with sickle cell anemia or those receiving cochlear implants.

Revaccination with the 23-valent pneumococcal polysaccharide vaccine is recommended for adults over the age of 65 years if the first dose was administered when they were less than 65 years

of age and at least 5 years have passed. Revaccination results in a blunted immune response and increased local adverse reactions, therefore routine revaccination is not recommended.[10] Adults vaccinated at age 65 or greater do not require revaccination.

The 7-valent pneumococcal conjugate vaccine was licensed in February 2000 for use in children. It induces good immunogenicity in children under the age of 2 years. It is now part of the routine childhood immunization schedule beginning at 2 months of age. It is given at 2, 4, 6, and 12 to 18 months of age. The 7-valent pneumococcal conjugate vaccine has been shown to decrease the carriage rate of *S. pneumoniae* and the incidence of invasive disease in vaccinated populations. Widespread use of the 7-valent pneumococcal conjugate vaccine has also shown herd immunity and decreased the incidence of invasive *S. pneumoniae* disease among unvaccinated adults over 20 years of age.[10]

Poliovirus Vaccine

Poliomyelitis is a highly contagious disease that is often asymptomatic; however, approximately 1 in every 100 to 1000 cases will develop a rapidly progressive paralytic disease. Polio is caused by poliovirus which has three serotypes; type 1 is most frequently associated with paralytic disease. Poliovirus replicates in the oropharynx and intestinal tract and is excreted in oral secretions and feces, which can infect others. As a result, more than 90% of unvaccinated individuals will become infected with poliovirus following household exposure to wild-type poliovirus. Since the introduction of the first poliovirus vaccine, there has been a significant reduction in the number of polio cases. Today, polio caused by wild-type poliovirus has been eradicated from the Western Hemisphere with the goal of eradicating it from the world.[11]

The first inactivated poliovirus vaccine was introduced in the 1950s in an injectable formulation, and replaced in the 1960s by a live oral poliovirus vaccine. The oral poliovirus vaccine not only elicits systemic immunogenicity but also a localized immune response in the intestinal tract. Unfortunately, the oral poliovirus vaccine has the risk of vaccine-associated paralytic poliomyelitis occurring in approximately 1 case of every 2.4 million doses distributed. The risk with the first dose of oral poliovirus vaccine is 1 case in 750,000 doses.[11]

The last reported case of indigenous wild-type poliovirus in the United States was in 1979; subsequent cases were all vaccine-associated. In 1997, a transition period to the inactivated poliovirus vaccine was begun to reduce the risk of vaccine-associated paralytic poliomyelitis. By January 2000, the oral vaccine was no longer recommended for routine use. Currently, the inactivated poliovirus vaccine is recommended for routine use in the United States. The oral poliovirus vaccine is still widely used in some countries where poliovirus eradication has been more difficult.

The enhanced potency inactivated poliovirus vaccine contains all three serotypes. After two doses, more than 90% of those vaccinated will have immunity to the three serotypes and 99% after three doses. Inactivated poliovirus vaccine is recommended to be given at 2, 4, 6 to 18 months, and 4 to 6 years of age.

Rotavirus Vaccine

Rotavirus is the most common cause of diarrhea worldwide. Most children will become infected by the age of 5 years. In the United States, rotavirus is responsible for approximately 50,000 hospitalizations for severe diarrhea and dehydration, and 20 to 40 deaths annually. Most hospitalizations occur in children less than 3 years of age.

The first rotavirus vaccine was a tetravalent rhesus rotavirus strain. It was licensed in the United States in 1998 and subsequently withdrawn from the market due to an association with **intussusception**. A pentavalent human-bovine reassortant rotavirus vaccine was approved by the FDA in February 2006. The exact mechanism by which the vaccine produces an immune response is unknown; however, this live virus vaccine replicates in the small intestines and induces immunity.

The rotavirus vaccine is a three-dose series that is orally administered. The first dose is given to infants between 6 and 12 weeks of age with subsequent doses administered 4 to 10 weeks apart.

Varicella Vaccine

Varicella zoster virus causes two distinct diseases, chickenpox (varicella) and herpes zoster, also known as shingles. Chickenpox is one of the most common childhood diseases. It has always been thought to be a benign disease causing few serious complications in children. The rate of chickenpox prior to the vaccine becoming available was thought to approximate the birth rate with 3 to 4 million cases annually resulting in 11,000 hospitalizations and 100 deaths. Adults who develop chickenpox have a 25% greater risk for developing serious complications from varicella compared to children. Chickenpox is highly contagious and has a secondary household transmission rate of 87%.

Later in life, approximately 15% of the population will develop herpes zoster. Herpes zoster is the reactivation of latent varicella zoster virus in the sensory ganglia. Approximately 20% of persons with herpes zoster will develop post-herpetic **neuralgia**, which is a painful debilitating condition that can persist for months after resolution of the herpes zoster rash.

The varicella vaccine is relatively new and has only been recommended for use since 1996, therefore its true impact on chickenpox and herpes zoster is not yet known. Its continued use will undoubtedly change the epidemiology of these diseases.

The varicella vaccine is made up of an attenuated Oka strain of varicella zoster virus. This is a live attenuated vaccine. Attenuation was achieved by performing serial passages through human embryonic lung cells, embryonic guinea pig cells, and human diploid cells.

Children less than 12 years of age will have a 97% seroconversion rate following a single vaccination. Adolescents and adults more than 13 years old will only have 78% seroconversion after a single inoculation, but will have 99% conversion after the second vaccination administered 4 to 8 weeks after the first. Antibody titers appear to persist for at least 20 years following immunization. Despite excellent seroconversion rates, breakthrough chickenpox is reported at a rate of 1 case per 10,000 doses distributed. Most cases occurred within the first year following vaccination, and were due to wild-type varicella zoster virus. The majority of breakthrough cases were mild and of short duration.[12]

Secondary transmission to household contacts is always a concern with administration of a live vaccine. There are a few cases of possible secondary transmission of varicella following vaccination. Of the cases that varicella typing was done, 62% were wild-type virus, indicating exposure to an unvaccinated person. There are less than 10 confirmed cases of secondary transmission of the Oka vaccine strain following vaccination. A mild rash occurring in less than 5% of persons has been reported following vaccination. The varicella virus may be shed from the rash. Rashes due to the Oka vaccine strain typically occur more than 20 days following vaccination.[12]

Varicella vaccine should be administered after 12 months of age and a second dose at 4 years of age. Adolescents and adults without evidence of immunity to varicella zoster should receive two doses of varicella vaccine given 4 to 8 weeks apart. Varicella vaccine is available as a single-component vaccine or in combination with measles, mumps, and rubella vaccine.

COMBINATION VACCINES

The childhood immunization schedule is complex and requires a large number of injections. In small infants the large number of injections can be intolerable to the infant, parent, and health care provider. Limiting the number of injections at each visit can lead to missed vaccinations and increased expense for return visits. ❸ *Use of combination vaccines decreases the number of injections and increases the likelihood that the immunization schedule would be completed.*

Many factors have to be considered when developing combination vaccines. First the selected components need to be given on a similar schedule and all components should already be licensed in the United States. The excipients contained in the individual vaccines may interfere with another component when combined, altering a component's immunogenicity. Finally, the immunogenicity of the combination must be similar (within 10%) to the immune response when the components are administered separately. This has been problematic with combinations containing *Haemophilus influenza* type b vaccine, for which the immune response has been significantly blunted in some combinations.[13]

There are several combination vaccines available in the United States. One of the most popular pediatric combinations is Pediarix® a combination of diphtheria and tetanus toxoids, acellular pertussis, inactivated poliovirus, and hepatitis B vaccines. ComVax® is a combination of *Haemophilus influenzae* type b and hepatitis B vaccines. The most recent combination is ProQuad® which contains measles, mumps, rubella, and varicella vaccines. The only combination available for adults is Twinrix® which has hepatitis A and hepatitis B vaccines.

VACCINE ADMINISTRATION SCHEDULES

Most vaccines are administered in two- to four-shot series in order to elicit the best protection. Childhood and adult immunization schedules are revised frequently and published annually by the CDC Advisory Committee on Immunization Practices. Current immunization schedules can be found at www.cdc.gov/nip/. The childhood schedule is published in January and the adult schedule in October of each year. Recommendations will be published throughout the year in the Morbidity and Mortality Weekly Report (MMWR) as new vaccines are licensed or new information necessitates a change in previous recommendations.

VACCINE SAFETY

Vaccination is one of the most powerful tools used to prevent disease. As with all drugs, most vaccines have been reported to cause adverse reactions. The reactions are either acute, such as local reactions, or are related to risk of developing another disease. Health care professionals are to give vaccine information sheets to individuals or caregivers prior to vaccination; these provide information about the risks and benefits of each vaccine.

Vaccine safety is monitored by the FDA and CDC through a passive reporting system that allows anyone, health professionals or lay public, to report any event. ❹ *Health care professionals are bound by federal regulation to report certain adverse events* (Table 83–2). Additionally, any serious, life-threatening or unusual reactions should also be reported. The Vaccine Adverse Event Reporting System (VAERS) can be found at http://vaers.hhs.gov.

The VAERS database is continually monitored to determine if the prevalence of reactions is changing and to identify previously unreported reactions to a particular vaccine. One of the limitations of the VAERS data is that it does not contain denominator data. Therefore it is not possible to calculate a true rate of reaction occurrence: the number of cases of reaction per dose of vaccine administered. Rates are usually calculated using the number of doses distributed from the manufacture as the denominator. This makes the assumption that each dose distributed is administered.

TABLE 83–2. Vaccine Reportable Events

Vaccine/Toxoid	Event	Interval from Vaccination
Tetanus in any combination; (DTaP, DTP, DTP-Hib, DT, Tdap, Td, or TT)	Anaphylaxis or anaphylactic shock	7 days
	Brachial neuritis	28 days
	Systemic allergic reaction	7 days
	Systemic neurologic reaction	
Pertussis in any combination; (DTaP, DTP, DTP-Hib, or Tdap)	Anaphylaxis or anaphylactic shock	7 days
	Encephalopathy or encephalitis	7 days
	Progressive neurologic disorders, such as infantile spasms or uncontrolled epilepsy	7 days
Measles, mumps, and rubella in any combination; (MMR, MR, M, or R)	Anaphylaxis or anaphylactic shock	7 days
	Encephalopathy or encephalitis	15 days
Rubella in any combination; (MMR, MR, or R)	Chronic arthritis	42 days
Measles in any combination; (MMR, MR, or M)	Thrombocytopenic purpura	7–30 days
	Vaccine strain measles in immunodeficient recipient	6 months
Oral polio (OPV)	Paralytic polio	30 days to 6 months
	Vaccine strain polio infection	30 days to 6 months
Inactivated polio (IPV)	Anaphylaxis or anaphylactic shock	7 days
	Systemic allergic reaction	7 days
Hepatitis B	Anaphylaxis or anaphylactic shock	7 days
	Systemic allergic reaction	7 days
Haemophilus influenzae type b (conjugate)	Anaphylaxis or anaphylactic shock	7 days
	Systemic allergic reaction	7 days
Varicella (chickenpox)	Anaphylaxis or anaphylactic shock	7 days
	Systemic allergic reaction	7 days
Rotavirus	Intussusception	30 days
Pneumococcal conjugate	Anaphylaxis or anaphylactic shock	7 days
	Systemic allergic reaction	7 days

Local Reactions

Pain at the injection site is one of the most commonly reported adverse effects of vaccination. The reaction is usually mild with complaints of pain and tenderness at the injection site that may or may not be accompanied by erythema. Local reactions tend to be more frequent with repeated doses or booster doses of vaccine. The frequency and degree of the reactions appear to be related to the amount of preformed antibodies and rapid immunologic responses reflective of priming from previous doses. More serious Arthus reactions are infrequently reported. Arthus reactions are classified as type III hypersensitivity reactions, and are characterized by a massive local response involving the entire thigh or deltoid. Arthus reactions are also related to preformed antibody complexes that induce an inflammatory lesion.[14]

Tetanus-containing vaccines are well known for causing localized reactions; however, all vaccines can cause local reactions.

Fever

Fever is the most frequently reported adverse effect in children and adolescents. Fever associated with vaccination is defined as a temperature of greater than or equal to 38°C (100.4°F) measured at any site using a validated device. Fever is caused by a complex reaction induced by the production of cytokines that affect the hypothalamic neurons. This results in raising the hypothalamic set point. Temperature elevations above 40°C (104°F) can result in cellular and multi-organ dysfunction. Excessive temperature elevations rarely result from fever alone, but are usually coupled with other thermoregulatory dysfunction.[15]

The whole cell pertussis vaccine has been highly associated with temperature elevations; however, the prevalence has significantly decreased since the introduction of the acellular pertussis vaccine. Live virus vaccines are also associated with fever.

Guillain-Barré Syndrome

Guillain-Barré syndrome is a transient neurologic disorder involving inflammatory demyelination of the peripheral nerves. The syndrome is characterized by progressive symmetric weakness of the legs and arms with loss of reflexes. Occasionally sensory abnormalities and paralysis of respiratory muscles will occur.[16]

The etiology of Guillain-Barré syndrome is unknown, but increasing evidence suggests it is probably a humoral and

cellular autoimmune disease induced by infection with a variety of microorganisms. The background rate of Guillain-Barré syndrome is one to two cases per 100,000 persons annually. Guillain-Barré syndrome has been associated with several vaccines. An influenza vaccine used in the mid-1970s (swine flu vaccine) increased the incidence of Guillain-Barré syndrome by a factor of eight.[16] Warnings about Guillain-Barré syndrome continue to be given with annual influenza vaccinations. The hepatitis B vaccine derived from pooled plasma was also associated with Guillain-Barré syndrome; however, Guillain-Barré has not been reported with use of the currently available hepatitis B vaccines produced through recombinant DNA technology. Most recently, Guillain-Barré syndrome has been reported to occur with the meningococcal conjugate vaccine.

Other Safety Concerns

A clear cause-and-effect relationship between vaccine administration and chronic diseases, such as diabetes mellitus, multiple sclerosis, and chronic arthritis, has never been scientifically proven.

Thimerosal is a preservative used in vaccines that has been purported to cause autism in children. The assumption is that thimerosal, also known as ethyl mercury, causes similar effects as methyl mercury, which has neurotoxic and nephrotoxic effects at high doses. Several epidemiologic studies have not shown a higher rate of autism among children receiving thimerosal-containing vaccines when compared to the normal background rate of autism. Additionally, the mercury exposure with vaccination is much lower than through many other environmental exposures. Despite the lack of evidence of thimerosal causing neurologic disorders, vaccine manufacturers are producing vaccines that are thimerosal-free or only contain trace amounts of thimerosal.[14]



Patient Encounter 3

A 7-year-old child with acute leukemia is 1 year post–bone marrow transplantation. The child's clinical course has been uneventful since transplantation and everything is going as expected. The physician discusses with the child's parents the continued need for protection against infections and suggests that the child should receive some vaccinations.

- When should the child begin receiving vaccinations?
- Which vaccines should be administered and on what schedule?
- Should any vaccines be avoided?
- Which vaccines should household contacts receive?

SPECIAL POPULATIONS

Immunocompromised Host

The number of immunocompromised persons is continually increasing as advances are made in medicine. The life expectancy for persons with cancer, HIV infection, and solid organ or bone marrow transplantation is increasing. Vaccination provides one tool to prevent infection in the immunocompromised host; however, the individual's immunosuppressed state will alter the response to vaccine. In general all vaccinations should be updated prior to the person becoming immunosuppressed, if possible. ❺ *Once a person becomes significantly immunosuppressed, live virus vaccines should be avoided.*

Adults with HIV infection should be vaccinated with the 23-valent pneumococcal polysaccharide and hepatitis B vaccines as early in the course of the disease as possible. Inactivated influenza vaccine should be given yearly. Children should continue to receive vaccinations on the standard childhood immunization schedule. The individual may experience a transient elevation in HIV viral load following vaccination.[17]

Following hematopoietic stem cell transplantation the patient will need virtually all routine vaccines to be administered again; however, the patient will not be able to mount an adequate response for 6 to 12 months post-transplant. Diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b, hepatitis B, pneumococcal, and inactivated poliovirus should be given at 12, 14, and 24 months post–hematopoietic stem cell transplantation. Inactivated influenza vaccine should be given yearly, starting 6 months after transplant. Measles, mumps and rubella can be given 2 years after transplant and varicella vaccine is contraindicated.[16]

Solid organ transplant recipients have a blunted immune response to vaccines because the immunosuppressive regimens used to prevent organ rejection inhibit both T- and B-cell proliferation. Many of these patients will also have secondary hypogammaglobulinemia post-transplantation. Prior to transplant, children should complete primary immunization schedules if possible; accelerated schedules may be used. Adults should have all vaccinations updated prior to transplantation.[16]

Household contacts of immunocompromised persons should have all routine vaccines as scheduled, including yearly influenza vaccination. Children in the household may receive live virus vaccines without special precautions; however, if a rash develops following varicella vaccination, contact should be avoided with the immunocompromised host until the rash resolves.

Pregnancy

Immunization during pregnancy is done to ensure that the infant has sufficient antibodies during the period he or she is

most vulnerable to disease. Maternal antibodies are actively transported to the fetus throughout the pregnancy. However, in the last 4 to 6 weeks of gestation the active transport of immunoglobulins substantially increases. Vaccines administered during pregnancy should produce high antibody concentrations following a single vaccination and are administered in the second and third trimester, but no later than 2 weeks prior to delivery. Maternal vaccination has not shown any harmful effects to the developing fetus. However, live virus vaccines are avoided due to theoretical concerns of the virus being transported across the placenta and infecting the fetus. It is recommended that pregnant women be up to date on tetanus vaccine and receive the influenza vaccine if the second and third trimester will occur during the winter months.[18]

Health Care Workers

Most health care workers are at risk for exposure to many diseases in the normal course of their work. Additionally, health care workers may transmit vaccine-preventable diseases to their patients. At the time of employment and on a regular basis, health care workers should be screened for immunity to measles, rubella, and varicella; if found to be non-immune, the measles, mumps, and rubella, and varicella vaccines should be administered. The hepatitis B series should be given if not already completed. Tetanus should be updated and given every 10 years. Health care personnel in hospitals and ambulatory settings with direct patient contact should receive Tdap if not already received; an interval as short as 2 years from the last tetanus-containing vaccine should be used. Priority for receiving Tdap should be given to personnel with direct contact with infants less than 12 months of age.

All health care personnel should be strongly encouraged to receive the influenza vaccine yearly in order to prevent transmission of influenza within the health care facility and to decrease employee absenteeism for influenza-related reasons. The vaccine should be made available to employees at the workplace, free of charge. Employees should be asked to sign a declination if refusing to receive the influenza vaccine. Additionally, health care facilities should report the number of health care personnel receiving influenza vaccine as a patient safety measure.[19]

OUTCOME MEASURES

❻ *Vaccines are a cost-effective means for disease prevention.* It is estimated that for every dollar spent on routine childhood vaccines there will be a savings of $0.90 to $24.00 in direct medical expense. The rates of vaccination for children are well over 90%. This has been attributed to the requirements for proof of vaccination by states for enrollment into day care centers and school. Additionally, children (less than or equal to 18 years of age) may receive routine vaccinations free of charge through state health departments or other assistance programs, such as the national Vaccines for Children program. Many states have developed universal immunization databases to document pediatric and adult vaccination status. This eliminates the problems of lost immunization records if a child changes health care providers.

The vaccination rate in adults is much lower than that in children. Only 50% to 60% of adults who meet criteria have received pneumococcal or influenza vaccination. Comprehensive initiatives need to be implemented to increase the adult vaccination rate. Some proven concepts are providing reminders to patients that vaccines are due and implementation of standing orders for vaccines. This latter concept allows nurses and pharmacists to screen patients to see if pneumococcal, influenza, or other vaccines are needed and to vaccinate without a physician's order.

The Centers for Medicare and Medicaid Services has incorporated pneumococcal and influenza immunization rates into some of their quality standards. Patients admitted to a hospital for community-acquired pneumonia should be screened for, offered, and vaccinated with pneumococcal and influenza vaccines prior to discharge if not previously administered. In physicians' office practice, all persons over 65 years of age who have been hospitalized in the past year should be screened for, offered, and vaccinated with pneumococcal and influenza vaccines if not previously administered. Both of these standards will affect payment if the standard is not met. The Joint Commission on Accreditation of Healthcare Organizations has also incorporated these standards into their accreditation reviews of health care facilities.

ABBREVIATIONS

anti-HBs:	antibody to hepatitis B surface antigen
CDC:	Centers for Disease Control and Prevention
DT:	diphtheria and tetanus toxoid vaccine (pediatric)
Dtap:	diphtheria and tetanus toxoids and acellular pertussis vaccine
FDA:	Food and Drug Administration
HBsAg:	hepatitis B surface antigen
HIV:	human immunodeficiency virus
Td:	tetanus and diphtheria toxoid vaccine (adult)
Tdap:	tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine
VAERS:	Vaccine Adverse Event Reporting System

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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84 Human Immunodeficiency Virus Infection

Amanda Corbett, Rosa Yeh, Julie Dumond, and Angela D.M. Kashuba



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Explain the routes of transmission for HIV, and its natural disease progression.
2. Identify typical and atypical signs and symptoms of acute and chronic HIV infection.
3. Identify the desired therapeutic outcomes for patients with HIV infection.
4. Recommend appropriate first-line pharmacotherapy interventions for patients with HIV infection.
5. Recommend appropriate second-line pharmacotherapy interventions for patients with HIV infection.
6. Describe the components of a monitoring plan to assess effectiveness and adverse effects of pharmacotherapy for HIV infection.
7. Educate patients about the disease state, appropriate lifestyle modifications, and drug therapy required for effective treatment.

Key Concepts

❶ The treatment goals for HIV infection are to maximally and durably suppress HIV replication, avoid the development of drug resistance, restore and preserve immune function, prevent opportunistic infections, and minimize adverse effects.

❷ HIV RNA plasma concentrations and CD4+ T-cell counts are used to assess risk of progression to AIDS (or risk for opportunistic infection) and to monitor efficacy and durability of treatment.

❸ Effective and complete treatment of HIV infection involves a multidisciplinary approach, which includes pharmacists, clinicians, social workers, and others. Treatment of HIV infection always requires combination prescription antiretroviral therapy, and may include prescription treatment or prophylaxis for opportunistic infections, and prescription or nonprescription treatment for adverse effects.

❹ Treatment with two nucleoside reverse transcriptase inhibitors (NRTIs) *and* either a nonnucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) is the mainstay of treatment for HIV infection.

❺ All patients with HIV infection relapse if medication is withdrawn. Therefore, long-term maintenance treatment is required.

❻ Eventually, HIV becomes resistant to current medication therapy. To prolong this time to resistance, strict adherence to the drug regimen is critical.

❼ The majority of antiretroviral medications are metabolized by the cytochrome P-450 enzyme system (CYP). Therefore, it is important to review patient medication profiles for drugs that may interact with antiretroviral drugs.

❽ Most antiretroviral medications cause acute and chronic adverse effects. Patients should be closely monitored for these toxicities.

The acquired immune deficiency syndrome (AIDS) was first recognized in 1981, and described in a cohort of young homosexual men with significant immune deficiency. Since then, human immunodeficiency virus type 1 (HIV-1) has been clearly identified as the major cause of AIDS.[1] HIV-2 is much less prevalent than HIV-1, but also causes AIDS. HIV primarily targets CD4+ lymphocytes, which are critical to proper immune system function. If left untreated, patients experience a prolonged asymptomatic period followed by rapid, progressive immunodeficiency. Therefore, most complications experienced by patients with AIDS involve opportunistic infections and cancers.

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HIV is primarily transmitted by sexual contact, by contact with blood or blood products, and from mother to child during gestation, delivery, or breast-feeding. The prevalence and incidence of HIV is rising globally, and to date there are no treatments which eradicate HIV from the body. Combinations of potent antiretroviral agents (called highly active antiretroviral therapy, or HAART) can suppress HIV replication to undetectable levels, delay the onset of AIDS, and prolong survival. However, there are a number of drug-induced long-term toxicities that challenge effective patient management. This chapter will address HIV treatment options and challenges, and give practical suggestions for patient management.

EPIDEMIOLOGY

Since the first cases of AIDS were identified in 1981, over 25 million people have died as a result of HIV infection. This makes AIDS one of the most destructive epidemics in recorded history. The epidemic remains extremely dynamic, and no country in the world remains unaffected. It is estimated that HIV currently infects approximately 40 million people worldwide. Approximately 65% of these cases are in sub-Saharan Africa, with a prevalence of approximately 7%. East Asia, Central Asia, and Eastern Europe are also seeing rapidly rising infection rates.

Five million people were newly infected with HIV in 2005 alone. Most of these infections were acquired through heterosexual transmission. As of December 2005, women accounted for 46% of all people living with HIV worldwide; in sub-Saharan Africa, women account for 57%. Persons aged 15 to 24 years accounted for nearly one-half of new HIV infections worldwide.

At the end of 2003, an estimated 1,039,000 to 1,185,000 persons were living with HIV/AIDS in the United States, with 24% to 27% undiagnosed and unaware of their HIV infection (who may be unknowingly transmitting the virus to others). Of the total number of HIV-infected patients, approximately 4% (42,514) were diagnosed with AIDS in 2004, and 2% (18,017) died with AIDS. The cumulative estimated number of diagnoses of AIDS through 2004 was 944,305, one-half of whom (529,113) had died.

Compared with their distribution in the overall population, African-American and Hispanic populations are disproportionately affected by HIV/AIDS, representing 50% and 18% of cases, respectively. HIV/AIDS is among the top three causes of death for African-American men aged 25 to 54 years, is among the top four causes of death for African-American women aged 20 to 54 years, and is the number one cause of death for African-American women aged 25 to 34 years. From 2000 through 2004, HIV/AIDS rates for African-American males were eight times those for white males and three times those for Hispanic males. HIV/AIDS rates for African-American females were 23 times the rates for white females and 5 times the rates for Hispanic females.

ETIOLOGY AND PATHOGENESIS

HIV-1 is a retrovirus and member of the genus *Lentivirus*. These viruses have a characteristically prolonged latency period. There are two molecularly and serologically distinct but related types of HIV: HIV-1 and HIV-2. HIV-2 is a less common cause of the epidemic and is found primarily in West Africa. HIV-1 is categorized by phylogenetic lineages into three groups (M [main], N [new], and O [outlier]). HIV-1 group M can be further categorized into nine subtypes: A through D, F through H, and J and K. HIV-1 sub-type B is primarily responsible for the North American and Western European epidemic.

Evidence suggests that HIV in humans is the result of cross-species transmission from primates infected with simian immunodeficiency virus (SIV). HIV-2 is closely related to the SIV found in sooty mangabeys in West Africa, and HIV-1 is similar to the SIV found in chimpanzees. The earliest known human HIV infection was in central Africa in 1959. Cultural practices such as the preparation and eating of bushmeat, or keeping primates as pets, may have allowed the virus to transmit from animal to human. The rapid spread of the virus throughout the world can be primarily attributed to high mobility due to modern transportation, sexual promiscuity, and drug abuse.

HIV infection occurs through three primary modes of transmission: sexual, parenteral, and perinatal. The most common method for transmission is receptive anal and vaginal intercourse, with the probability of transmission up to 3% per sexual contact for the former, and up to 0.2% per sexual contact for the latter. The probability of transmission increases when the index partner has a high level of viral replication (which occurs at the very beginning of infection or late in disease), or when the uninfected partner has ulcerative disease, compromised mucosal surfaces, or (in the case of men) has not been circumcised.

Parenteral transmission of HIV primarily occurs through injection drug use by sharing contaminated needles or injection-related supplies. As a result of a comprehensive North American screening program, less than 1% of all cases of HIV infection occurs as a result of transfusions of contaminated blood or blood products, or infected transplant organs. Health care workers have a 0.3% estimated risk of acquiring HIV infection through percutaneous needlestick injury.

Perinatal infection (also known as vertical transmission or mother-to-child transmission [MTCT]) can occur during gestation, at or near delivery, and during breast-feeding. The risk of MTCT up to and including delivery is approximately 25%, while the risk of transmission during breast-feeding is approximately 15% to 20% within the first 6 months of life. Since a high rate of HIV replication in the blood is a significant risk factor for transmission of HIV, it is important to treat women for their HIV infection during pregnancy. After delivery, mothers are strongly recommended not to breast-feed if safe alternatives are available.

It is important to understand the life cycle of the virus in order to understand how antiretroviral drugs are combined for optimal therapy (Fig. 84–1). Once HIV enters the body, an outer glycoprotein called gp120 binds to CD4 receptors found on the surface of dendritic cells, T lymphocytes, monocytes, and macrophages. This allows further binding to other chemokine receptors on the cell surface called CCR5 and CXCR4. Most newly infected patients have viruses that preferentially use CCR5 to enter the cell, and most patients with advanced disease have viruses that preferentially use CXCR4 to enter the cell. This becomes important in understanding the place in therapy for some of the new drugs in development.

After the virus has attached to CD4 and chemokine receptors, another viral glycoprotein (gp41) assists with viral fusion to the cell and internalization of the viral contents. The viral contents include single-stranded RNA, an RNA-dependent DNA polymerase (also known as reverse transcriptase), and other enzymes. Using the single-stranded viral RNA as a template, reverse transcriptase synthesizes a complementary strand of DNA. The single-stranded viral RNA is removed from the newly formed DNA strand by ribonuclease H, and reverse transcriptase completes the synthesis of double-stranded DNA. The viral reverse transcriptase enzyme is highly error-prone, and many mutations occur in the conversion of RNA to DNA. This inefficient reverse transcription activity is responsible for HIV's ability to rapidly mutate and develop drug resistance.

A chronic infection is established when the double-stranded DNA migrates to the host cell nucleus and is integrated into the host cell chromosome by an HIV enzyme called integrase. Once the cell becomes activated by antigens or cytokines, HIV replication starts: host DNA polymerase transcribes viral DNA into messenger RNA, and messenger RNA is translated into viral proteins. These proteins assemble beneath the bilayer of the host cell, a nucleocapsid forms containing these proteins, and the virus buds from the cell. After budding, the virus matures when an HIV protease enzyme cleaves large polypeptides into smaller functional proteins. Without this process, the virus is unable to infect other cells.

During the early stages of infection, approximately 10 billion viruses can be produced each day. Most of the cells containing these viruses will be lysed as a result of budding virions, killed by cytotoxic T-lymphocytes, or undergo apoptosis. However, virus will be protected within some cells, which can stay dormant for years. The initial immune response against

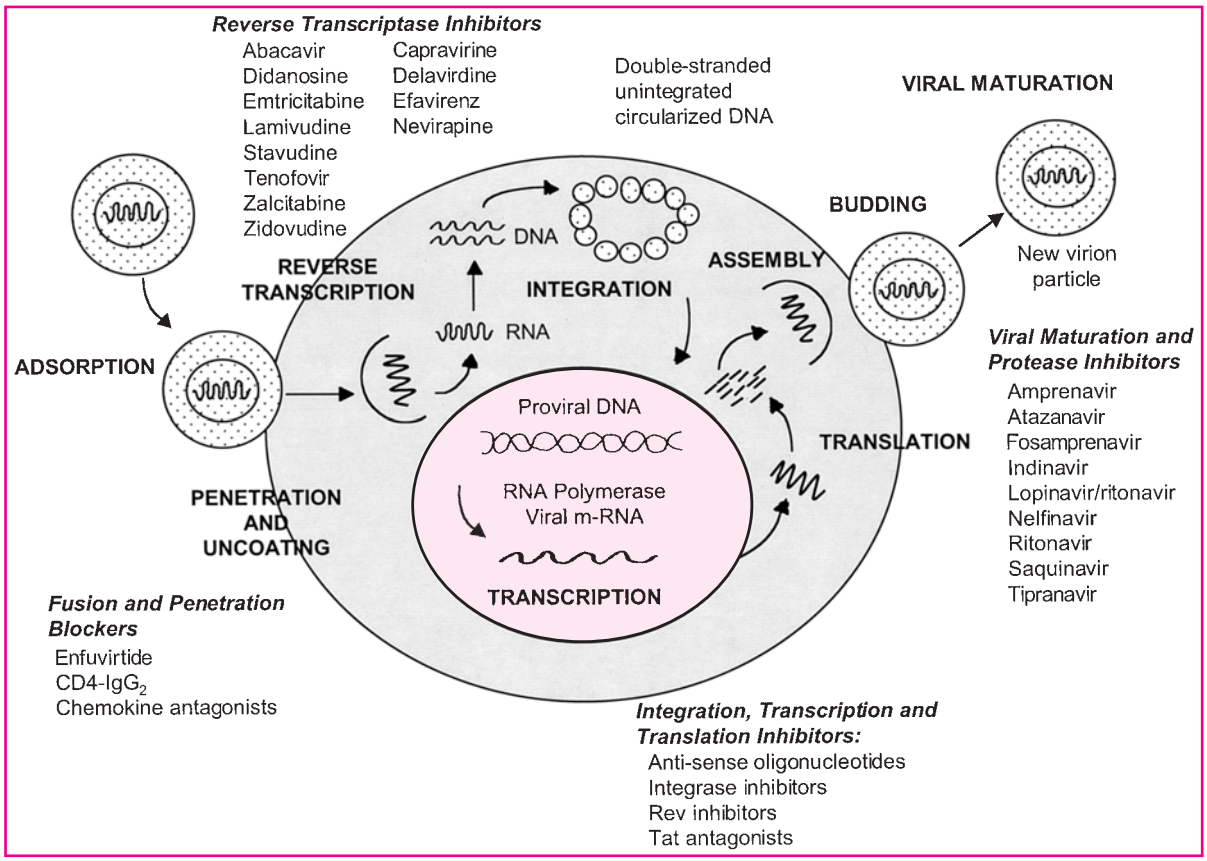


FIGURE 84–1. Life cycle of HIV and targets for antiretroviral drugs. (From Fletcher CV, Kakuda TN. Human immunodeficiency virus infection. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 2258, with permission.)

HIV is relatively effective, but it is unable to completely clear the infection, and the patient enters a latent, asymptomatic or mildly symptomatic stage lasting 5 to 15 years. During this time, a high rate of viral replication can be seen in the lymph nodes. Eventually immune deficiency occurs when the body is no longer able to replenish helper T cells at a rate equal to that at which HIV is destroying them.

❶ *Currently, the goal of therapy is to maximally and durably suppress HIV replication in order to restore and preserve immune system function and minimize morbidity and mortality*. Since HIV replication has been found in all areas of the body, it is important to use potent drug therapy that can achieve adequate concentrations in all tissues, including protected sites such as the brain and genital tract.

CLINICAL PRESENTATION AND DIAGNOSIS

HIV diagnosis is made either by a positive **HIV enzyme-linked immunosorbent assay (ELISA)** or rapid test (these tests may be positive as soon as 3 to 6 weeks after infection) and then confirmed by a positive confirmatory test, usually the HIV Western blot (Table 84–1).

Patients who are acutely infected with HIV may be asymptomatic or present with signs and symptoms associated with any viral infection, such as fever, myalgias, lymphadenopathy, pharyngitis, or rash. Taken together, these are the "acute retroviral syndrome." Providers should consider the possibility of HIV infection in any patients with these findings and inquire about recent high-risk sexual encounters or other modes of exposure. Risk factors for HIV/AIDS infection include: men who have sex with men; history of or current intravenous drug use (needle or equipment sharing); unprotected sexual intercourse with high-risk individuals; the presence of other sexually transmitted infections (e.g., *Chlamydia trachomatis* or *Neisseria gonorrhoeae*); persons with coagulation/hemophilia disorders; and previous blood product recipients. If patients are not identified during acute infection, they may later present with various nonspecific symptoms such as myalgias, fatigue, weight loss, thrush, or symptoms associated with opportunistic infections.

The diagnosis of HIV infection is made either by a baseline serologic screening test such as the ELISA or a rapid test. If reactive, then a confirmatory test is performed. The **Western blot (WB)** is the gold standard confirmatory test and is commonly used. The WB is considered reactive if two of the three major



Clinical Presentation of HIV

Patients with acute HIV infection may display symptoms described as "acute retroviral syndrome." Patients with chronic HIV infection may present with these same nonspecific symptoms and/or opportunistic infections.

Acute Retroviral Syndrome

The majority of patients may present with fever, lymphadenopathy, pharyngitis, and/or rash. Other symptoms include:

- Myalgia or arthralgia
- Diarrhea
- Headache
- Nausea and vomiting
- Hepatosplenomegaly
- Weight loss
- Thrush
- Neurologic symptoms (meningoencephalitis, aseptic meningitis, peripheral neuropathy, facial palsy, or cognitive impairment or psychosis)

Opportunistic Infections

Depending on the severity of immunosuppression (the CD4+ T lymphocyte count), patients may present with the following opportunistic infections (grouped by CD4+ count):

Any CD4+ count

- *Mycobacterium tuberculosis* disease
- Bacterial pneumonia (commonly *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*)
- Herpes simplex virus disease
- Varicella zoster virus disease
- Bacterial enteric disease (most commonly *Salmonella*, *Campylobacter*, and *Shigella*)
- Syphilis
- Bartonellosis

Less than 250 cells/microliter

- Coccidioidomycosis
- *Pneumocystis jiroveci* (formerly *carinii*) pneumonia (PCP)
- Oropharyngeal and esophageal candidiasis
- Kaposi's sarcoma or human herpesvirus-8 disease

Less than 150 cells/microliter

- Disseminated histoplasmosis

Less than 100 cells/microliter

- Cryptosporidiosis
- Microsporidiosis

Less than 50 cells/microliter

- Disseminated *Mycobacterium avium* complex disease
- Cytomegalovirus disease
- Cryptococcosis, aspergillosis, and *Toxoplasma gondii* encephalitis

TABLE 84–1. Available HIV Tests

Test	Minimum Time to Detection after Exposure	Sample(s) Tested	Comments
Initial Screening Tests			
Enzyme-linked immunosorbent assay (ELISA)	3–6 weeks	Plasma	If nonreactive, no further testing is required, unless acute infection suspected
HIV RNA assay	Up to 14 days	Plasma	Obtain if recent high-risk exposure; if initially negative, repeat at months 1, 3, and 6
Rapid tests (currently FDA-approved products)	Detects HIV antibodies within minutes of sample application		
OraQuick ADVANCE	3–6 weeks	Whole blood, plasma, or oral fluid	Detects HIV-1 and HIV-2
Reveal Rapid HIV-1 Antibody Test	3–6 weeks	Plasma or serum	Detects HIV-1
Uni-Gold Recombigen HIV Test	3–6 weeks	Whole blood, plasma, or serum	Detects HIV-1
Confirmatory Tests			
Western blot (WB)	3–6 weeks	Plasma	Gold standard confirmatory test
Indirect immunofluorescence assay (IFA)	3–6 weeks	Plasma	Simple to perform, but requires expertise to interpret results

FDA, Food and Drug Administration; HIV, human immunodeficiency virus.

bands (p24, gp41, and/or gp120/160) change color. The test is nonreactive if no viral bands are visible. If the test is indeterminate (one band visible), patients are retested in 2 to 3 months. This is most likely if a recent (i.e., less than 3 to 6 weeks) infection has occurred, and HIV antibodies have not yet been fully formed. In this case, a plasma HIV RNA concentration (reverse transcriptase polymerase chain reaction [RT-PCR]) should be evaluated. Patients with acute infection will generally have HIV RNA concentrations greater than 10^6/μL. ❷ HIV severity is determined by following: (1) the CD4+ lymphocyte count (CD4 count) and percentage and (2) HIV RNA (viral load). The CD4 percentage is followed because the absolute count may fluctuate and does not necessarily indicate a change in the patient's condition.

TREATMENT

❶ *The goals of treatment are to maximally and durably suppress viral replication, avoid the development of drug resistance, restore and preserve immune function, prevent opportunistic infections, and minimize drug adverse effects*. Elimination of HIV is not possible with currently available therapies. ❷ Instead, maximal suppression of viral replication (defined as HIV RNA concentrations undetectable by the most sensitive assay available) is desired. After the initiation of antiretroviral therapy, a rapid decline to undetectable HIV RNA in 16 to 24 weeks has been shown to be a predictor of improved clinical outcomes.[2]

❷ *Degree of immune function preservation also correlates with decreased viral replication, and is measured by CD4+ T-cell counts. CD4 measures are the best predictor of progression to AIDS, and help decide when to initiate treatment*. At CD4+ T-cell counts of 200 cells/mm^3 and lower, patients require drug prophylaxis for opportunistic infections. Table 84–2 details the monitoring endpoints of HIV treatment for HIV RNA and CD4+ T-cell counts.

Four classes of drugs are available to treat HIV infection: **nucleoside (NRTI)/nucleotide (NtRI) reverse transcriptase inhibitor, protease inhibitor (PI), nonnucleoside reverse transcriptase inhibitor (NNRTI),** and fusion inhibitor. ❸ *Currently, combination antiretroviral drug therapy with three or more drugs is the standard of care*, which increases the durability of viral suppression and decreases the potential for the development of resistance. ❹ *Two nucleoside (nucleotide) reverse transcriptase inhibitors and either a nonnucleoside reverse transcriptase inhibitor or a protease inhibitor are the mainstay regimens of combination therapy*. In the late 1980s, when only zidovudine was available, achieving and maintaining viral suppression for more

TABLE 84–2. Monitoring Endpoints for CD4+ T-Cell Counts and HIV RNA

CD4+ T-Cell Counts			HIV RNA Concentration		
When to Monitor	**Why**	**Goal**	**When to Monitor**	**Why**	**Goal**
Initial diagnosis	Assess need for ART	Start therapy in appropriate patients	Initial diagnosis	Establish baseline and assess need for ART	Start therapy in appropriate patients
	Assess need for OI chemoprophylaxis	Start therapy when less than 200 cells/mm^3	2–8 weeks after starting or changing ART	Early assessment of regimen efficacy	Decrease of at least 1.0 $\log_{10}$ copies/mL
Every 3–6 months	Receiving ART: monitor success of treatment	Average increase of 100–150 cells/mm^3 per year	3–4 months after starting ART	Assess virologic efficacy of regimen	Undetectable
	Not receiving ART: assess need to begin therapy	Start therapy in appropriate patients	Every 3–4 months	Receiving ART: assess durability of RNA suppression with current regimen	Steadily decreasing and/or consistently low
	Assess need for OI chemoprophylaxis	Start therapy when less than 200 cells/mm^3		Not receiving ART: monitor changes in RNA	Start therapy in appropriate patients
Clinical event	Assess need for ART	Start therapy in appropriate patients	Clinical event or decrease in CD4+ T-cell count	Receiving ART: assess if event is due to virologic failure	Change regimen if needed (drugs or doses)
	Assess need for OI chemoprophylaxis	Start therapy when less than 200 cells/mm^3		Not receiving ART: assess need to begin therapy	Start therapy in appropriate patients

ART, antiretroviral therapy; HIV, human immunodeficiency virus; OI, opportunistic infection. (Adapted from the DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, April 7, 2005.)

than 4 months was rarely possible. As more agents became available in the mid-1990s (most notably the protease inhibitors), HIV RNA was suppressed to undetectable concentrations and maintained there for long periods of time. Currently recommended combination regimens decrease HIV RNA to less than 50 copies/mL in 50% to 80% of patients in clinical trials. Therefore monotherapy, or the use of two NRTIs alone, are no longer treatment options at any time during HIV infection. Figure 84–1 details the mechanisms of action of the drug classes within the life cycle of HIV.

Nonpharmacologic Interventions

❻ *Patient adherence is a key component in treatment success.* Drug therapy is required for a lifetime, as the virus begins to replicate at high levels when medications are stopped. Early HIV combination therapy was exceedingly complicated for patients, with multiple daily doses, varying food restrictions, and large pill burdens. Advances in delivery and formulations now make possible once- or twice-daily dosing with fewer than six pills per day. Recently, a combination of tenofovir + emtricitabine + efavirenz was approved as a one pill, once per day regimen (Atripla™). The use of low-dose ritonavir to enhance the concentrations of other protease inhibitors (known as pharmacokinetic enhancement or "boosting") allows for significantly fewer doses and lower pill burdens. These advances, however, do not replace the need for patient counseling by a trained pharmacist and a multidisciplinary approach to promoting adherence.

Counsel all patients initially and repeatedly on ways to prevent viral transmission. Preventing the spread of resistant virus is particularly important. Patients receiving antiretroviral therapy can still transmit virus to sexual partners, and to those with whom they share needles or other drug equipment. Where both partners are HIV-positive, safe sex and needle practices reduce the risk of superinfection with differing strains of HIV and the transmission of other sexually transmitted diseases. General guidelines for preventing viral transmission include using condoms with a water-based lubricant for vaginal or anal intercourse, using condoms without lubricant or dental dams for oral sex, and not sharing equipment used to prepare, inject, or inhale drugs.

❸ *Nutrition and dietary counseling should also be included in the care of the HIV patient, as poor nutrition leads to poorer outcomes and complicates treatment.* Antiretroviral therapy itself introduces a host of nutritional issues, including drug-food interactions, gastrointestinal adverse effects that may affect appetite and limit dietary intake, lipid abnormalities, and fat redistribution. The American Dietetics Association currently recommends assessing HIV-infected patients for their level of nutritional risk and involving a registered dietician as part of the clinical team for optimal nutrition care.[3]

Pharmacologic Therapy for Antiretroviral-Naïve Patients

Two major panels of experts publish guidelines for the treatment of HIV-infected individuals. Although the recommendations are quite similar, slight differences do exist between the Department of Health and Human Services (DHHS) Guidelines[2] and the International AIDS Society-USA (IAS-USA) Panel Recommendations.[4] The DHHS Guidelines are updated every 6 months and current and archived versions are available online at www.aidsinfo.nih.gov. The IAS-USA Guidelines were last updated in 2006, and in 2004 prior to that revision. Due to the intense research and constant modifications to therapeutic approaches in the treatment of HIV, the majority of the treatment algorithms and recommendations presented herein follow the most up-to-date information found in the DHHS recommendations.

❷ *The decision of when to begin antiretroviral therapy is complex. Recommendations are based on the CD4+ T-cell count (which predicts disease-free survival) with consideration given to HIV RNA* (Table 84–3). Other factors to consider include the patient's willingness to begin therapy and maintain medication adherence, and the risk versus benefit of treating an asymptomatic patient. Once the decision is made to initiate treatment, the regimen is selected based on patient-specific factors. ❹ *All recommended regimens contain either an NNRTI or a PI in combination with two NRTIs (or NtRI)*. The preferred regimens are:

1. Efavirenz *and* (zidovudine or tenofovir) *and* (lamivudine *or* emtricitabine)
2. Lopinavir/ritonavir *or* atazanavir/ritonavir *or* fosamprenavir/ritonavir *and* (zidovudine) *or* tenofovir *and* (lamivudine *or* emtricitabine)

The decision to choose a NNRTI-based or PI-based regimen as initial therapy is based on many patient- and clinician-specific factors. NNRTI-based regimens have low pill burdens and may have decreased incidences of long-term adverse effects (e.g., dyslipidemia) in comparison to some PI-based regimens. However, this class also has a low threshold for drug resistance (the K103N mutation causes high level cross-class resistance), and patient adherence is a critical consideration. In pregnant women, or women with the potential to become pregnant, a PI-based regimen is preferred due to the potential teratogenicity of efavirenz (pregnancy category D). If a patient is at risk for having contracted a resistant virus (i.e., from someone currently on antiretroviral therapy) genotyping of the virus may assist in selecting the most appropriate drug regimen.

In patients who cannot tolerate the above preferred first-line therapies, or have a compelling reason to choose a different agent, the following first-line therapies are recommended. These regimens tend to be more complex and have higher pill burdens, but may be necessary in order to treat a specific patient:

1. Efavirenz *and* (didanosine *or* abacavir *or* stavudine) *and* (lamivudine *or* emtricitabine)
2. Nevirapine in place of efavirenz in selected populations (due to a more frequent incidence of hepatotoxicity, nevirapine should only be used in patients with low to moderate CD4+ T-cell counts: less than or equal to 250 cells/mm^3 for females, less than or equal to 400 cells/mm^3 for males)
3. Atazanavir *or* fosamprenavir *or* nelfinavir *or* saquinavir/ritonavir, *and* zidovudine *or* stavudine *or* tenofovir *or* abacavir *or* didanosine, *and* lamivudine *or* emtricitabine
4. Lopinavir/ritonavir, *and* abacavir *or* stavudine *or* tenofovir *or* didanosine, *and* lamivudine *or* emtricitabine

Triple NRTI therapy is recommended *only* when a first-line or alternative first-line therapy with either an NNRTI-based or PI-based regimen cannot be used. Abacavir plus zidovudine plus lamivudine is the only regimen approved by the DHHS. The following triple nucleoside therapy combinations have shown poor or limited efficacy, and should be avoided: abacavir plus tenofovir plus lamivudine (or emtricitabine), and didanosine plus tenofovir plus lamivudine (or emtricitabine).

Therapies *not recommended* for initial treatment due to poor potency or significant toxicity include delavirdine, nevirapine in patients with moderate to high CD4+ T-cell counts, indinavir or saquinavir used without ritonavir ("unboosted"), ritonavir used without another protease inhibitor, and tenofovir plus didanosine with an NNRTI.

Drugs that should *not be combined* due to overlapping toxicities include: amprenavir oral solution plus ritonavir oral solution, atazanavir plus indinavir (due to enhanced hyperbilirubinemia), and any combination of didanosine, stavudine, and zalcitabine. Emtricitabine and lamivudine should not be combined because of their similar chemical structures, and antagonism can result when lamivudine is combined with zalcitabine, or stavudine is combined with zidovudine.

TABLE 84–3. Summary of Recommendations for Initiating Antiretroviral Therapy

CD4+ T-Cell Count	Qualifier	Recommendation
Any	AIDS-defining illness	Begin treatment
	Severe HIV infection	
Less than 200 cells/mm^3	Asymptomatic	Begin treatment
201–350 cells/mm^3	Asymptomatic	Offer treatment
Greater than 350 cells/mm^3	HIV RNA greater than 100,000 copies/mL	May offer or defer treatment
	HIV RNA less than 100,000 copies/mL	Defer treatment

AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus. (Adapted from the DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, April 7, 2005.)

Pharmacologic Therapy for Antiretroviral-Experienced Patients

❻ *Ongoing viral replication, whether at low levels in the face of adequate drug concentrations or at higher levels due to inconsistent systemic concentrations (or low concentrations in sanctuary sites; e.g., male and female genital fluids, cerebrospinal fluid, or lymph nodes), will eventually lead to resistance to the prescribed medications.* There is no consensus on the optimal time to change therapy based on virologic or immunologic failure (Table 84–4). ❷ Virologic failure is defined as HIV RNA greater than 400 copies/mL after 24 weeks, greater than 50 copies/mL after 48 weeks, or a repeated HIV RNA greater than 400 copies/mL after prior suppression to less than 400 copies/mL.[2] Some clinicians may change therapy with any repeated, detectable viremia (HIV RNA greater than 50 to 400 copies/mL), while others will set arbitrary thresholds of 1,000 to 1,500 copies/mL. Immunologic failure is defined as having an increase of less than 25 to 50 cells/mm^3 in CD4+ T lymphocyte count above baseline after 1 year of therapy, or a decline in CD4+ cell count below baseline while taking antiretroviral therapy.

Treatment considerations for antiretroviral-experienced patients are much more complex than for patients who are naïve to therapy. Prior to changing therapy, the reasons for treatment failure should be identified. A comprehensive review of the patient's severity of disease, antiretroviral treatment history, adherence to therapy, intolerance or toxicity, concomitant drug therapies, co-morbidities, and results of current and past HIV resistance testing should be performed. If patients fail therapy due to poor adherence, the underlying reasons must be determined and addressed prior to initiation of new therapy. Reasons for poor adherence include: problems with medication access, active substance abuse, depression and/or denial of the disease, and a lack of education on the importance of 100% adherence to therapy. Medication intolerance or toxicity can be remedied with therapy for the adverse event, exchanging the drug causing the toxicity with another in the same class, or changing the entire regimen. Pharmacokinetics or systemic drug exposure can be optimized by ensuring maximal drug absorption (taking the drug with or without food can alter exposure by up to 30%), and avoiding interactions with concomitant prescription or over-the-counter medications and dietary supplements or natural products (e.g., antacids, St. John's wort, and garlic). When causes for treatment failure are identified, appropriate strategies for therapy can be determined.

TABLE 84–4. Treatment Options Following Virologic Failure with the Initial Regimen

Initial Regimen	Recommended Change
2 NRTIs + NNRTI	• 2 NRTIs (based on resistance testing) + PI (with or without low-dose ritonavir)
2 NRTIs + PI (with or without low-dose ritonavir)	• 2 NRTIs (based on resistance testing) + NNRTI
3 NRTIs	• 2 NRTIs (based on resistance testing) + NNRTI **or** PI (with or without low-dose ritonavir) • NNRTI + PI (with or without low-dose ritonavir) • NRTI (based on resistance testing) + NNRTI + PI (with or without low-dose ritonavir)

NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
(Adapted from the DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, April 7, 2005.)

Drug interactions between antiretrovirals and between antiretrovirals and concomitant medications should be evaluated for each patient to avoid under- and/or overexposure of either therapy. ❼ *NNRTIs and PIs are metabolized by CYP450 enzymes and are inducers and/or inhibitors of this enzyme system.* In addition, some of the antiretrovirals are substrates, inhibitors, and/or inducers of transporters such as P-glycoprotein, and therefore may lead to drug interactions. Information provided in Table 84–5 describes the drug interaction potential of each antiretroviral. Due to the ever-changing drug interactions with this class of medications, the regularly updated DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1–Infected Adults and Adolescents are a recommended source of specific drug interactions.[2]

The goals of therapy differ for antiretroviral-experienced patients that have limited drug exposure (i.e., developing resistance to their first antiretroviral regimen) versus those with extensive exposure (i.e., developing resistance to their third or fourth antiretroviral regimen). It is reasonable to expect maximal viral suppression in those with limited drug exposure. However, this may not be feasible for patients with prior exposure to multiple medications. ❶ *In antiretroviral-experienced patients, a reasonable goal is to simply preserve immune function and prevent clinical progression.*

Several issues need to be considered in choosing a salvage regimen for HIV infection. Knowing prior medication exposure can assist in identifying which drugs to avoid. However, direct HIV resistance testing can better identify the resistance and susceptibility patterns of the major viral strains. Since HIV may be susceptible to certain components of the failing antiretroviral regimen, these drugs can be recycled into future regimens. Resistance testing should be used when initiating therapy in patients with acute HIV infection, in patients with virologic failure on a current ARV regimen, or with suboptimal suppression after initiation of ARV therapy. For resistance testing to be useful, the patient should have a plasma HIV RNA of at least 1,000 copies/mL, and should be currently taking their antiretroviral medications (or be within 4 weeks of discontinuing antiretroviral therapy). The former is because this concentration will yield reliable amplification of the virus, and the latter is because the dominant viral species reverts to wild-type within 4 to 6 weeks after medications are stopped.

TABLE 84–5. Summary of Currently Available Antiretroviral Agents

Drug Name Generic/(Abbreviation)/ Trade Name	Dosage Forms	Commonly Prescribed Doses	Dose Adjustments	Food Restrictions	Significant Adverse Events	Drug Interaction Potential
Nucleoside (tide) Reverse Transcriptase Inhibitors						
Abacavir (ABC) Ziagen®	300-mg tab; 20 mg/mL oral solution	150 mg bid or 300 mg qday qday	None	None Alcohol ↑ ABC conc. by 41%	Potentially fatal hypersensitivity reaction (rash, fever, malaise, nausea, vomiting, shortness of breath, sore throat, loss of appetite)	Alcohol dehydrogenase and glucuronyl transferase, 82% renal excretion of metabolites
Didanosine (ddI) Videx EC® Generic didanosine EC (same dosing as Videx EC®)	125-, 200-, 250-, 400-mg cap	Greater than 60 kg: 400 mg qday Less than 60 kg: 250 mg qday	**CrCl (mL/minute)** / **Greater than 60 kg** / **Less than 60 kg** 30–59 / 200 mg / 125 mg 10–29 / 125 mg / 100 mg Less than 10 / 125 mg / 75 mg	Take 30 minutes prior or 2 hours after meal (conc. ↓55% with food)	Pancreatitis; peripheral neuropathy; nausea; diarrhea	Renal excretion
Emtricitabine (FTC) Emtriva™	200-mg cap; 1 mg/mL oral solution	200 mg qday; 240 mg (24 mL) oral solution qday	**CrCl (mL/minute)** / **capsule** / **solution** 30–49 / 200 mg q48hours / 120 mg q24hours 15–29 / 200 mg q72hours / 80 mg q24hours Less than 15/HD / 200 mg q96hours / 60 mg q24hours (dose after dialysis on dialysis days)	None	Minimal	Renal excretion
Lamivudine (3TC) Epivir®	150-mg and 300-mg tabs or 10 mg/mL oral solution	150 mg bid or 300 mg qday	**CrCl (mL/minute)** / **Dose** 30–49 / 150 mg qday 15–29 / 150 mg × 1, then 100 mg qday 5–14 / 150 mg × 1, then 50 mg qday Less than 5/HD / 50 mg × 1, then 25 mg qday (dose after dialysis on dialysis days)	None	Minimal	Renal excretion
Stavudine (d4T) Zerit®	15-, 20-, 30-, 40-mg caps or 1 mg/mL for oral solution	Greater than 60 kg: 40 mg bid Less than 60 kg: 30 mg bid	**CrCl (ml/minute)** / **Dose greater than 60 kg** / **less than 60 kg** 26–50 / 20 mg q12hours / 15 mg q12hours 10–25/HD / 20 mg q24hours / 15 mg q24hours (dose after dialysis on dialysis days)	None	Peripheral neuropathy; lipodystrophy; rapidly progressive ascending neuro-muscular weakness (rare); pancreatitis; lactic acidosis with hepatic steatosis (higher incidence with d4T than with other NRTIs); hyperlipidemia	Renal excretion
Tenofovir disoproxil fumarate (TDF) Viread®	300 mg tab	300 mg qday	**CrCl (mL/minute)** / **Dose** 30–49 / 300 mg q48hours 10–29 / 300 mg twice weekly ESRD/HD / 200 mg q7days (dose after dialysis on dialysis days)	None	Asthenia, headache, diarrhea, nausea, vomiting, and flatulence; renal insufficiency	Renal excretion

(Continued)

TABLE 84–5. Summary of Currently Available Antiretroviral Agents *(Continued)*

Drug Name Generic/(Abbreviation)/ Trade Name	Dosage Forms	Commonly Prescribed Doses	Dose Adjustments	Food Restrictions	Significant Adverse Events	Drug Interaction Potential
Zalcitabine (ddC) Hivid® (anticipated discontinuation of distribution in 2006)	0.375-, 0.75-mg tab	0.75 mg tid	**CrCl (mL/minute)** **Dose** 10–40 0.75 mg bid less than 10 0.75 mg qday No data on hemodialysis	None	Peripheral neuropathy; stomatitis, lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs); pancreatitis	Renal excretion
Zidovudine (AZT, ZDV) Retrovir®	100-mg caps, 300-mg tabs, 10 mg/mL intravenous solution, 10 mg/mL oral solution	300 mg bid	100 mg tid in severe renal impairment or HD	None	Bone marrow suppression: macrocytic anemia or neutropenia; gastrointestinal intolerance, headache, insomnia, asthenia	Glucuronyl transferase and renal
Zidovudine + lamivudine (AZT/3TC) Combivir®	AZT 300 mg + 3TC 150 mg tab	1 tablet bid	Do not use with CrCl less than 50 mL/minute	None	See adverse events for AZT and 3TC	See AZT and 3TC
Abacavir + lamivudine + zidovudine (ABC/3TC/ AZT) Trizivir®	ABC 300 mg + 3TC 150 mg + AZT 300 mg tab	1 tablet bid	Do not use with CrCl less than 50 mL/minute	None	See adverse events for AZT, 3TC, and ABC	See AZT, 3TC, and ABC
Abacavir + lamivudine (ABC/3TC) Epzicom®	ABC 600 mg + 3TC 300 mg tab	1 tablet bid	Do not use with CrCl less than 50 mL/minute	None	See adverse events for ABC and 3TC	See ABC and 3TC
Tenofovir + emtricitabine (TDF/FTC) Truvada™	TDF 300 mg + FTC 200 mg tab	1 tablet bid	**CrCl (mL/minute)** **Dose** 30–49 1 tablet q48hours Less than 30 Not recommended	None	See adverse events fo TDF and FTC	See TDF and FTC
Nonnucleoside Reverse Transcriptase Inhibitors						
Delavirdine (DLV) Rescriptor®	100-, 200-mg tabs	400 mg tid (100 mg tabs can be dispersed in greater than or equal to 3 oz of water to produce slurry); 200 mg tabs should be administered whole; separate dosing from buffered DDI or antacids by 1 hour	Use with caution in patients with hepatic impairment	None	Rash; increased LFTs, headaches	Metabolized by cytochrome P-450 (CYP); CYP3A inhibitor; 51% excreted in urine (less than 5% unchanged); 44% in feces

Efavirenz (EFV) Sustiva®	50-, 100-, 200-mg caps or 600-mg tabs	600 mg qday at or before bedtime	Use with caution in patients with hepatic impairment	Take on an empty stomach (high-fat/calorie meals ↑ C_{max} of caps 39% and C_{max} of tabs 79%	Rash; central nervous system symptoms (insomnia, irritability, lethargy, dizziness, vivid dreams) usually resolve in 2 weeks; increased LFTs; false-positive cannabinoid test; teratogenic in monkeys	Metabolized by CYP2B6 and CYP3A (3A mixed inducer/inhibitor); 14–34% excreted in urine (glucuronidated metabolites, less than 1% unchanged); 16–61% in feces
Nevirapine (NVP) Viramune®	200-mg tabs or 50 mg/5 mL oral suspension	200 mg qday for 14 days; then 200 mg bid	Use with caution in patients with hepatic impairment	No food restrictions	Rash including Stevens-Johnson syndrome; symptomatic hepatitis, including fatal hepatic necrosis	Metabolized by CYP2B6 and CYP3A (3A inducer); 80% excreted in urine (glucuronidated metabolites; less than 5% unchanged); 10% in feces
Tenofovir + Emtricitabine + Efavirenz (TDF/FTC/EFV) Atripla™	TDF 300 mg + FTC 200 mg + EFV 600 mg	1 tablet once daily	Do not use in patients with CrCl less than 50 ml/minute	High-fat/high caloric meals increase peak plasma concentrations of EFV capsules by 39% and EFV tablets by 79%; take on an empty stomach	See adverse events of TDF, FTC, and EFV	See TDF, FTC, and EFV
Protease Inhibitors						
Amprenavir (APV) Agenerase®	5 mg/mL oral solution	1,400 mg bid (Note: APV and RTV oral solution should not be co-administered due to competition of the metabolic pathway of the two vehicles)	Oral solution not recommended in patients with renal oral hepatic failure	Avoid high fat meal (AUC? ↓ 21%); can be taken with or without food	GI intolerance, nausea, vomiting, diarrhea; rash; oral paresthesias; hyperlipidemia; LFT elevation; hyperglycemia; fat maldistribution; possible increased bleeding episodes in patients with hemophilia (Note: oral solution contains propylene glycol; contraindicated in pregnant women, children less than 4 years old, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole)	CYP3A4 inhibitor, inducer, and substrate
Atazanavir (ATV) Reyataz™	100-, 150-, 200-mg caps	400 mg qday *If taken with efavirenz or tenofovir use the following:* ATV 300 mg qday + RTV 100 mg qday	**Child-Pugh Class** / **Dose** 7–9 / 300 mg qday Greater than 9 / Not recommended	Take with food (AUC ↑ 30%); pH-sensitive dissolution—avoid antacids or proton pump inhibitors; separate histamine blockers by taking 10 hours before ATV and if dosed twice daily, second dose 2 hours after ATV	Indirect hyperbilirubinemia; prolonged PR interval (asymptomatic first-degree AV block); use with caution in patients with underlying conduction defects or on concomitant medications that can cause PR prolongation; hyperglycemia; fat maldistribution; increased bleeding episodes in patients with hemophilia	CYP3A4 inhibitor and substrate; UGT1A1 inhibitor

(Continued)

TABLE 84–5. Summary of Currently Available Antiretroviral Agents (*Continued*)

Drug Name Generic/(Abbreviation)/ Trade Name	Dosage Forms	Commonly Prescribed Doses[a]	Dose Adjustments	Food Restrictions	Significant Adverse Events	Drug Interaction Potential[b]
Darunavir (DRV) Prezista™	300 mg tablet	DRV 600 mg + RTV 100 mg twice daily	Use with caution in patients with hepatic impairment	Should be given with food	Skin rash (has a sulfonamide moiety, Stevens Johnson & erythema multiforum have been reported); diarrhea, nausea; headache; hyperlipidemia; transaminase elevation; hyperglycemia; fat maldistribution; possible increased bleeding episodes in patients with hemophilia	CYP3A4 inhibitor and substrate
Fosamprenavir (fAPV) Lexiva™	700-mg tabs	*ARV-naïve pts:* fAPV 1,400 mg bid or fAPV 700 mg + RTV 100 mg bid *PI-experienced pts:* fAPV 700 mg + RTV 100 mg bid *Co-administration w/EFV:* fAPV 700 mg + RTV 100 mg bid or fAPV 1400 mg + RTV 300 mg qday	**Child-Pugh Class** **Dose** 5–8 700 mg bid 9–12 Not recommended Ritonavir should not be used in patients with hepatic impairment	None	Skin rash; diarrhea, nausea and vomiting; headache; hyperlipidemia; LFT elevation; hyperglycemia; fat maldistribution; increased bleeding episodes in patients with hemophilia	CYP3A4 inhibitor, inducer, and substrate
Indinavir (IDV) Crixivan®	200-, 333-, 400-mg caps	800 mg q8hours; IDV 800 mg + RTV 100 bid; IDV 800 mg + RTV 200 mg bid	Mild to moderate hepatic insufficiency due to cirrhosis: 600 mg q8hours	*For unboosted IDV:* Take 1 hour before or 2 hours after heavy meals, or concomitantly with low-fat meal No restrictions when used with RTV	Nephrolithiasis; GI intolerance, nausea; indirect hyperbilirubinemia; hyperlipidemia; headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, hemolytic anemia; hyperglycemia; fat maldistribution; increased bleeding episodes in patients with hemophilia	CYP3A4 inhibitor (less than RTV)
Lopinavir + ritonavir (LPV/r) Kaletra®	LPV 200 mg + RTV 50 mg tablet, LPV 400 mg + RTV 100 mg/5 mL oral solution (contains 42% alcohol)	2 tablets or 5 mL bid 4 tablets qday *With EFV or NVP:* 3 tablets or 6.7 mL bid	Use with caution in patients with hepatic impairment	Take with food (AUC ↑ 48–80%)	Nausea, vomiting, diarrhea; asthenia; hyperlipidemia; LFT elevation; hyperglycemia; fat maldistribution; increased bleeding episodes in hemophiliacs	CYP3A4 inhibitor and susbstrate

Nelfinavir (NFV) Viracept®	250- 625-mg tabs, 50 mg/g oral powder	1,250 mg bid or 750 mg tid	Use with caution in patients with hepatic impairment	Take with meal or snack	Diarrhea; hyperlipidemia; hyperglycemia; fat maldistribution; increased bleeding in hemophiliacs; LFT elevation	CYP3A4 inhibitor and substrate
Ritonavir (RTV) Norvir®	100-mg caps, 600 mg/7.5 mL solution	600 mg bid (when ritonavir is used as sole PI); 100–200 mg/dose when used as pharmacokinetic enhancer	No dosage adjustment in mild hepatic impairment No data for moderate to severe impairment; use with caution	Take with food to improve tolerability	GI intolerance, nausea, diarrhea; paresthesias; hyperlipidemia; hepatitis; asthenia; taste perversion; hyperglycemia; fat maldistribution; increased bleeding in hemophiliacs	CYP3A4 greater than 2D6; potent (3A4 inhibitor)
Saquinavir tablets and hard gel capsules (SQV) Invirase®	200-mg capsules, 500-mg tablets	Unboosted SQV not recommended *With RTV:* (RTV 100 mg + SQV 1,000 mg) two times/day	Use with caution in patients with hepatic impairment	Take within 2 hours of a meal when taken with RTV	Nausea, diarrhea; headache; LFT elevation; hyperlipidemia; hyperglycemia; fat maldistribution; increased bleeding in hemophiliacs	CYP3A4 inhibitor and substrte
Tipranavir (TPV) Aptivus®	250-mg capsules	500 mg twice daily with RTV 200 mg twice daily	Contraindicated in patients with moderate to severe hepatic insufficiency	Take with food	Hepatotoxicity; skin rash; hyperlipidemia; hyperglycemia; fat maldistribution; possible increased bleeding in hemophiliacs	TPV/RTV mixed CYP inhibitor/ inducer; TPV is CYP3A4 substrate
Fusion Inhibitors						
Enfuvirtide (T20) Fuzeon™	Injectable, in lyophilized powder Each single-use vial contains 108 mg of enfuvirtide to be reconstituted with 1.1 mL of sterile water for injection for delivery of approximately 90 mg/1 mL	90 mg (1 mL) subcutaneously two times/day	No dosage recommendation	N/A	Local injection site reaction (pain, erythema, induration, nodules and cysts, pruritus, eachymosis) in most patients; increased rate of bacterial pneumonia; less than 1% hypersensitivity reaction (rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases); do not rechallenge	Catabolism to amino acids, with subsequent recycling in the body pool

AUC, area under the time-concentration curve; ARV, antiretroviral; AV, atrioventricular; C_{max}, maximum concentration; CrCl, creatinine clearance; ESRD, end-stage renal disease; GI, gastrointestinal; HD, hemodialysis; LFT, liver function test; NRTI, nucleoside reverse transcriptase inhibitor; UGT, uridine diphosphate-glucuronsyltransferase.
(Adapted from the DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, October 12, 2006.)

Two types of HIV resistance testing are available, genotyping and phenotyping. Genotyping involves detecting mutations by genetically sequencing the virus, while phenotyping determines the ability of the virus to replicate in the presence of varying ARV concentrations. Genotyping is more rapid and less costly than phenotyping, but results in a list of mutations that may be more difficult to interpret than phenotyping. A report known as the *virtual phenotype* may also be reported when genotypes are ordered.[5–12] This compares the patient's viral sequence to a database of matched genotypes and drug susceptibilities. Since the predictability of *virtual phenotypes* are dependent on the robustness of the database from which they are derived, some clinicians believe their utility is limited. A number of web-based tools are available to assist with interpretation of resistance mutations (e.g., Stanford University's HIV Drug Resistance Database; http://hivdb.stanford.edu/index.html). However, expert interpretation of genotype and phenotype reports is recommended.

Certain guiding principles should be considered when treating ARV-experienced patients, and expert opinion is advised before selecting therapy. ❹ *As with ARV-naïve patients, three or more active drugs should be prescribed.*[8,13–15] Since considerable cross-resistance can occur between medications within an antiretroviral class, simply using drugs to which the patient has not been exposed may be insufficient. Complete cross-resistance occurs within the NNRTI class, whereas the NRTIs and PIs have variable overlapping resistance patterns. For this reason, HIV resistance assays are important tools for choosing subsequent effective therapies. The following factors are associated with superior virologic response: lower viral load at the time therapy is changed, using a new class of antiretroviral agent, and using ritonavir-enhanced PIs in patients previously exposed to PIs.[16,17]

Table 84–4 provides general treatment options based on previous drug use. If patients fail therapy with resistance to only one drug, one or two active agents may be substituted for this drug while retaining the remaining drugs in the regimen. If patients fail therapy with resistance to more than one drug, changing classes of antiretrovirals and/or adding new active drugs is warranted. Some patients may have partial response to ARV therapy, and continue to have detectable plasma HIV RNA. In this case, intensification of the current therapy with the addition of a new agent (such as tenofovir) or pharmacokinetic enhancement of a current PI-based regimen with the addition of ritonavir, may lead to complete response. New NRTIs should be selected from resistance testing. If this is not available, the assumption should be made that resistance has developed to all NRTIs used in the failing regimen. In general, HIV that is resistant solely to lamivudine and/or emtricitabine will be susceptible to other NRTIs. If HIV develops resistance solely to tenofovir, then it may have reduced susceptibility to didanosine, but should remain susceptible to zidovudine, stavudine, lamivudine, emtricitabine, and abacavir. Cross-resistance occurs between zidovudine and stavudine.

If a patient appears to fail an antiretroviral regimen without detectable HIV resistance, adherence should be investigated, and the adequacy of the plasma HIV RNA concentration in the resistance sample confirmed. Options include continuing the current regimen or starting a new regimen and repeating the resistance test 2 to 4 weeks after adherence is verified. An increasing number of patients have extensive HIV resistance, such that antiretroviral regimens cannot be designed to which the virus is fully susceptible. For these patients, continuing the current regimen may be beneficial because drug-resistant virus may have a compromised **replication capacity**. Other strategies may be considered for this type of patient, including pharmacokinetic enhancement with ritonavir, re-treatment with prior antiretroviral agents, treatment with multi-drug regimens (four or more antiretroviral drugs), and the use of new agents through expanded access programs or clinical trials.

Treatment Considerations in Special Populations

Acute HIV Infection Diagnosis of acute HIV infection is difficult, since many patients are asymptomatic, or have non-specific clinical symptoms similar to other common respiratory infections. If acute HIV infection is suspected, HIV antibody tests and a plasma HIV RNA concentration should be obtained. A clear diagnosis is made when an HIV antibody test is negative and the plasma HIV RNA concentration is high. There are limited outcomes data for treating acutely infected patients. Treatment of acute infection can decrease the severity of acute disease and decrease the viral set point; this may decrease progression rates and reduce the rate of viral transmission.[18–22] Limitations include an increased risk of chronic drug-induced toxicities and the development of viral resistance.

Adolescent Patients As a result of similar modes of HIV transmission, adolescents infected after puberty are treated with similar considerations as adults. In this population, dosing of antiretroviral drugs should not be based on age, but on the Tanner stage (which considers external primary and secondary sexual characteristics). Adolescents in early puberty should be dosed according to pediatric guidelines, while those in late puberty should be dosed as adults. During growth spurts, adolescents should be monitored closely for drug efficacy and toxicity, since rapid changes in weight can lead to altered drug concentrations. Adherence is of concern in this population due to denial of the disease, misinformation, distrust of health care professionals, low self-esteem, and lack of family and/or social support. Additionally, asymptomatic patients this age find it more difficult to adhere to therapy while feeling well.

Pediatric Patients There are unique considerations in the treatment of HIV-infected children. Specific treatment guidelines exist,[23] but a thorough review is outside the scope of this chapter. Most children acquire HIV infection through

perinatal transmission either in utero, intrapartum, or postpartum through breast-feeding, although antiretroviral interventions have dramatically reduced transmission rates.[2] Antiretroviral therapy is limited in pediatric patients, as some drugs have no dosing recommendations for this population, or are not available in a formulation that can be easily administered to children. Additionally, drug exposures can change dramatically during ontogeny due to altered drug-metabolizing enzyme and drug transporter activities.

Drugs of Abuse Treatment challenges in illicit drug users include comorbidities (such as hepatitis infection), limited access to care, inadequate adherence to therapy, side effects and toxicities, and the need for treatment of substance abuse which can lead to drug interactions. ❼ *Many drugs of abuse have the potential to interact with antiretroviral medications, and a number of case reports have documented drug overdose when combined with protease inhibitor therapy.*[24] In these populations, without addiction control, adherence is suboptimal and treatment failure is common.[2] Most protease inhibitors and nonnucleoside reverse transcriptase inhibitors decrease methadone concentrations up to 50%. As this can result in the development of withdrawal symptoms, patients should be closely monitored for 4 to 8 weeks after initiation of antiretroviral therapy. Withdrawal symptoms can be alleviated with a methadone dose increase of 5 to 10 mg. Although there are fewer data, buprenorphine concentrations may be similarly affected, and therefore this drug requires close monitoring.

Pregnancy and Women of Reproductive Potential The goals of antiretroviral therapy for women of reproductive age and pregnant women are the same as for other adult patients. Specific guidelines for HIV-infected pregnant women are available.[25] Recommended therapies in pregnancy include zidovudine, lamivudine, nelfinavir, lopinavir/ritonavir, and if the CD4+ count is less than 250 cells/mm^3, nevirapine. Drugs to be avoided include efavirenz (due to potential teratogenicity), the combination of didanosine and stavudine (due to a high incidence of lactic acidosis), nevirapine in patients with a CD4 count greater than 250 cells/mm^3 (due to an increased risk of hepatotoxicity), and the liquid formulation of amprenavir (due to high concentrations of propylene glycol). The goal of therapy is to reduce plasma HIV RNA below 1,000 copies/mL and prevent mother-to-child transmission of HIV. Limited data are available on antiretroviral pharmacokinetics in pregnancy, and standard doses of antiretroviral drugs are currently recommended with close HIV RNA and CD4 monitoring in the third trimester of pregnancy.

Women of reproductive potential prescribed efavirenz should be counseled on its potentially teratogenic effects and the importance of birth control. ❼ *Additionally, nevirapine, nelfinavir, ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir have been shown to decrease the concentrations of estrogens and/or progestins in oral contraceptives, which could lead to failure.*[2] For patients prescribed these drugs, barrier forms of contraception are preferred to prevent pregnancy. DepoProvera may be a safe alternative, as it does not affect nelfinavir, efavirenz, or nevirapine concentrations; although the effect of antiretrovirals on medroxyprogesterone concentrations has not been examined, no evidence of ovulation has been seen in women on these combinations.[26]

Hepatitis B Co-Infection HIV-infected patients co-infected with hepatitis B virus (HBV) have higher concentrations of DNA and hepatitis B early antigen (HBeAg), and higher rates of HBV-associated liver disease. Therapy for HBV should be offered to patients who are HBeAg-positive, or have HBV DNA greater than 10^5 copies/mL and have either liver serologies (alanine aminotransferase) greater than 2 times the upper limit of normal or histologic evidence of moderate disease or fibrosis. Options include interferon alfa 2a or 2b and nucleoside/tide analogs. Nucleoside/tide analogs that treat HBV but not HIV are adefovir and entecavir. Nucleoside/tide analogs that treat HBV and HIV are lamivudine, emtricitabine, and tenofovir. These latter agents should be considered when treating HIV infection in HBV co-infected patients.

Hepatitis C Co-Infection Patients co-infected with hepatitis C virus (HCV) and HIV have a three-fold increase in rate of progression to cirrhosis compared to those with HCV alone. Therapy for HCV is considered in patients with detectable plasma HCV RNA and a liver biopsy showing bridging or portal fibrosis. Patients with HCV genotype 2 and 3 (and a CD4 count greater than 200 cells/mm^3) treated with pegylated interferon plus ribavirin have a better sustained viral response at 48 weeks (60% to 70%) compared to those with HCV genotype 1 (15% to 28%). Comprehensive treatment guidelines for HIV/HCV co-infected patients are available.[27] Important considerations addressed in these guidelines include avoiding the combination of ribavirin with didanosine (due to increased risk of pancreatitis and/or lactic acidosis), and ribavirin with zidovudine (due to increased risk of anemia). Growth factors may be needed to treat neutropenia from interferon and anemia from ribavirin. Antiretrovirals such as nevirapine, efavirenz, and tipranavir are hepatotoxic and in most cases should be avoided in HCV/HIV-infected patients.

OUTCOME EVALUATION

❶ *The success of antiretroviral therapy is measured by the degree to which the therapy (1) restores and preserves immunologic function, (2) maximally and durably suppresses HIV RNA, (3) improves quality of life, and (4) reduces HIV-related morbidity and mortality.* ❷ *The major outcome parameters are CD4+ lymphocyte absolute count and percentage, and plasma HIV RNA.* Adequate immunologic response in antiretroviral-naïve patients consists of an increase in CD4+ cell count that averages 100 to 150 cells/mm^3 per year (with a faster response in the first 3 months), and a 1 log decrease in HIV RNA by 2 to 8 weeks after starting

medications, followed by concentrations less than 50 copies/mL by 12 to 16 weeks (if HIV RNA less than 100,000/μL) or by 16 to 24 weeks (if HIV RNA greater than 100,000/μL). HIV RNA and CD4 count are monitored generally every 3 to 6 months. In highly treatment-experienced patients, adequate immunologic response may be a stable or slightly increasing CD4 T-cell count, and a stable HIV RNA to prevent clinical progression.

❺ *Currently, treatment of HIV infection is lifelong.* Treatment interruption may be necessary due to drug toxicity or illness that precludes administration of oral therapy. Occasionally, patients may experience treatment fatigue and can benefit from a temporary halt of their antiretroviral therapy. The duration of this "holiday" depends on the patient's HIV RNA and CD4+ count prior to initiation of their first antiretroviral regimen. Patients with higher CD4+ counts and lower viral loads prior to therapy maintain their immunologic status for longer periods of time compared to those who began therapy with more advanced disease. Ultimately, antiretroviral therapy will need to be reinstituted.

Each patient should have a plan to assess the effectiveness of antiretroviral therapy after initiation. At each clinic visit, patients should be evaluated for the presence of adverse drug reactions, drug allergies, medication adherence, and potential drug interactions. ❽ *Antiretrovirals have both class-associated and drug-specific adverse effects* (see Table 84–5). If the patient experiences any of the serious, life-threatening effects (Table 84–6), the offending agent should be discontinued promptly, and in most cases the patient cannot be rechallenged. Potential long-term complications that may reduce the quality of life are listed in Table 84–7. For drugs with a high likelihood of intolerability (such as nelfinavir-associated diarrhea), patients should be counseled to anticipate these effects and have concomitant prescriptions available for preemptive management (such as an antidiarrheal agent). Patients should have follow-up within the first week after initiating a new drug regimen. If the patient does not tolerate a medication despite all efforts to the contrary, consider changing the drug.



Patient Encounter, Part 1

A 46-year-old man with a history of hypertension and gastroesophageal reflux disease comes to your clinic complaining of increased fatigue, shortness of breath, and cough. He has noticed feeling tired more easily for the past 3 months, but the difficulty breathing and cough appeared 2 weeks ago. After questioning him further, he says has sex with men, but he has had the same sexual partner for the past 8 years. They do not use condoms. He also says that he smokes about 1 pack of cigarettes per day.

1. What information is suggestive of HIV/AIDS?
2. What risk factors are present for having HIV/AIDS?
3. What additional information do you need to know before creating a treatment plan for this patient?

Part 2

The Medical History, Physical Exam, and Diagnostic Tests

PMH

Hypertension for 5 years; it is often not well controlled because of poor patient adherence
Gastroesophageal reflux disease (GERD), currently controlled on histamine antagonists
History of hepatitis B

FH

Father died of myocardial infarction at the age of 68 years; mother is still alive with history of diabetes

SH

Works as a truck driver; reports distant history of intravenous drug use in his 20s; drinks alcohol occasionally

Meds

Hydrochlorothiazide 25 mg PO once daily
Famotidine 20 mg PO twice daily

ROS

(+) weight loss, decreased appetite, shortness of breath, and cough; (–) chest pain, nausea, vomiting, diarrhea

PE

VS: Blood pressure 144/84 mm Hg, pulse 100 bpm, respiratory rate 22/minute, temperature 38.3°C (100.9°F)
HEENT: Mild thrush on tongue
CV: RRR, normal S_1, S_2; no murmurs, rubs, gallops
Abd: Soft, nontender, nondistended; (+) bowel sounds, no hepatosplenomegaly
Rectal: Deferred

Labs

Sodium 135 mEq/L (135 mmol/L), potassium 3.6 mEq/L (3.6 mmol/L), chloride 100 mEq/L (100 mmol/L), bicarbonate 24 mEq/L (24 mmol/L), blood urea nitrogen 14 mg/dL (5 mmol/L), creatinine 1.0 mg/dL (88.4 μmol/L), WBC $5.2 \times 10^3/mm^3$, hemoglobin 11.5 g/dL, hematocrit 34.1%, platelets $151{,}000/mm^3$, neutrophils 58%, bands 9%, lymphocytes 32%, monocytes 1%, eosinophils 0%, basophils 0%, CD4 150 cells/mm^3
HIV ELISA: Pending
Chest x-ray: Diffuse interstitial infiltrates bilaterally

1. Given this additional information, what is your assessment of the patient's condition?
2. What other laboratory tests would you recommend?
3. Identify your treatment goals for the patient.
4. What nonpharmacologic and pharmacologic alternatives are available for the patient?

TABLE 84–6. Serious Adverse Effects and Management

Adverse Effects	Drug	Signs and Symptoms	Risk Factors	Prevention/Monitoring	Management
Hepatotoxicity	NVP	**Onset** Up to 18 weeks post initiation **Symptoms** Abrupt onset of flu-like symptoms, abdominal pain, jaundice, fever ± rash	1. Increased CD4 + count at initiation 2. Female 3. Elevated baseline AST/ALT 4. Any liver disease 5. High NVP conc	AST/ALT ⇒ every 2 weeks for first month, monthly for 3 months, then every 3 months	D/C antiretrovirals; D/C all hepatotoxic agents; rule out other causes; do not rechallenge with NVP
	Other NNRTIs, PIs, and NRTIs	**Onset** NNRTI—60% within first 12 weeks PI—weeks to months NRTI—months to years **Symptoms** NNRTI—asymptomatic to nonspecific symptoms, such as anorexia, weight loss, or fatigue PI—generally asymptomatic, some with anorexia, weight loss, jaundice NRTI—ZDV, ddI, d4T may cause hepatotoxicity associated with lactic acidosis; 3TC, FTC, or TDF may cause HBV flare when these drugs are withdrawn	1. HBV or HCV coinfection 2. Alcoholism 3. Concomitant hepatotoxic drugs	Monitor LFTs at least every 3–4 months	Rule out other causes; for symptomatic patients: D/C all antiretrovirals and other potential hepatotoxic agents; after symptoms and LFTs normalize, begin new antiretroviral regimen (without the potential offending agents); for asymptomatic patients: If ALT greater than 5–10x ULN, may consider D/C antiretrovirals or continue with close monitoring; after symptoms and LFTs normalize, begin new antiretroviral regimen (without the potential offending agents)
Lactic acidosis/ hepatic steatosis +/– pancreatitis	NRTIs (esp. d4T, ddI, ZDV)	**Onset** Months after initiation **Symptoms** Nonspecific gastrointestinal (nausea, anorexia, abdominal pain, vomiting, weight loss, fatigue) Laboratory values: ↑lactate, ↓ arterial pH, ↓serum bicarbonate, ↑AST/ALT, ↑PT, ↑T.bili, ↑amylase/lipase (with pancreatitis)	1. d4T + ddI 2. Female 3. Obesity 4. Pregnancy 5. ddI + hydroxyurea or ribavirin	None unless symptoms present ⇒ Consider lactate concentrations in patients with ↓ serum bicarbonate or ↑ anion gap	D/C all antiretrovirals; symptomatic support with fluids; some patients require IV bicarbonate, hemodialysis, parenteral nutrition, or mechanical ventilation; once syndrome resolves, consider using NRTIs with ↓ mitochondrial toxicity (ABC, TDF, 3TC, or FTC); monitor lactate after restarting NRTIs; some clinicians use NRTI-sparing regimens.
Stevens-Johnson syndrome/toxic epidermal necrosis	NVP greater than EFV, DLV; Also, APV, f-APV, ABC, ZDV, ddI, IDV LPV/r, ATV	**Onset** First days to weeks after therapy start **Symptoms** Skin eruption with mucosal ulcerations; fever, tachycardia, malaise, myalgia, arthralgia	NVP—female, black, Asian, Hispanic	Use 2-week lead in ⇒ 200 mg qday, then 200 mg bid Avoid corticosteroid use during dose escalation—may ↑rash incidence	D/C all antiretrovirals as well as any other possible cause; aggressive symptom support; do not rechallenge patient with offending agent; if caused by NVP, avoid NNRTI class, if possible

(Continued)

TABLE 84–6. Serious Adverse Effects and Management *(Continued)*

Adverse Effects	Drug	Signs and Symptoms	Risk Factors	Prevention/Monitoring	Management
Hypersensitivity reaction (HSR)	ABC	**Onset** Median = 9 days; 90% within first 6 weeks **Symptoms** Acute onset of symptoms (most frequent to least): high fever, diffuse skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, respiratory symptoms	1. HLA-B*5701, HLA-DR7, HLA-DQ3 2. Antiretroviral-naïve patients 3. Higher incidence with 600 mg qday compared to bid dosing	Educate patients about signs and symptoms of HSR and the need of prompt report	D/C ABC and other antiretrovirals; rule out other causes of symptoms, most signs and symptoms resolve 48 hours after ABC/DC; do not rechallenge with ABC after suspected HSR
Bleeding episodes	PIs	**Onset** Few weeks **Symptoms** ↑Spontaneous bleeding tendency (in joints, muscles, soft tissues, and hematuria)	PI use in hemophiliac patients TPV and anticoagulants (risk of intracranial hemorrhage)	Consider using a NNRTI-based regimen	May require increased use of factor VIII products
Bone marrow suppression	ZDV	**Onset** Few weeks to months **Symptoms** Fatigue, risk of ↑ bacterial infections due to neutropenia; anemia, neutropenia	1. Advanced HIV 2. High dose ZDV 3. Preexisting anemia or neutropenia 4. Concomitant use of bone marrow suppressants	Avoid in patients with high risk for bone marrow suppression; avoid other suppressing agents; monitor CBC with differential at least every 3 months	Switch to another NRTI; D/C concomitant bone marrow suppressant, if possible; for anemia: Identify and treat other causes; consider erythropoietin treatment or blood transfusion, if indicated; for neutropenia: Identify and treat other causes; consider filgrastim treatment, if indicated
Nephrolithiasis/ urolithiasis/ crystalluria	IDV	**Onset** Any time after initiation of therapy, especially if ↓ fluid intake **Symptoms** Flank pain and/or abdominal pain, dysuria, frequency; pyuria, hematuria, crystallauria; rarely, ↑serum creatinine and acute renal failure	1. History of nephrolithiasis 2. Patients unable to maintain adequate fluid intake 3. High peak IDV concentration 4. ↑Duration of exposure	Drink at least 1.5–2 L of non-caffeinated fluid per day; ↑fluid intake at first sign of darkened urine; monitor urinalysis and serum creatinine every 3–6 months	Increased hydration; pain control; may consider switching to alternative agent; stent placement may be required
Nephrotoxicity	IDV potentially TDF	**Onset** IDV—months after therapy TDF—weeks to months after therapy **Symptoms** IDV—asymptomatic; rarely develop end-stage renal disease TDF—asymptomatic to symptoms of nephrogenic diabetes insipidus, Fanconi syndrome	1. History of renal disease 2. Concomitant use of nephrotoxic drugs	Avoid use of other nephrotoxic drugs; adequate hydration if on IDV; monitor creatinine, urinalysis, serum potassium and phosphorus in patients at risk	D/C offending agent, generally reversible; supportive care; electrolyte replacement as indicated

Pancreatitis	ddI; ddI + d4T; DDI + hydroxyurea (HU) or ribavirin (RBV); 3TC in children	**Onset** Usually weeks to months **Symptoms** Post-prandial abdominal pain, nausea, vomiting; ↑serum amylase and lipase	1. High intracellular and/or serum ddI concentrations 2. History of pancreatitis 3. Alcoholism 4. Hypertriglyceridemia 5. Concomitant use of ddI with d4T, HU, or RBV 6. Use of ddI + TDF without ddI dose reduction	ddI should not be used in patients with history of pancreatitis; avoid concomitant use of ddI with d4T, HU, or RBV; ↓ddI dose when used with TDF	D/C offending agents; symptomatic management of pancreatits—bowel rest, IV hydration, pain control, gradual resumption of oral intake
Skin rash	NVP greater than EFV, DLV APV, f-APV, TPV, ABC, ATV	**Onset** Within first few days to weeks after therapy initiation **Symptoms** Mild to moderate rash; diffuse maculopapular rash with or without pruritus; severe rash; see section on Stevens-Johnson syndrome (SJS)	NVP—see NVP SJS; APV, f-APV, TPV—sulfonamide derivative, potential for cross-reactivity with other sulfa drugs; EFV—↑ incidence in children	NVP—see SJS; advise patient to report first sign of rash; recommend avoiding other NNRTIs in patients with severe rash to one NNRTI	Mild to moderate rash: symptomatic treatment with antihistamine and continuation of offending agent; D/C offending drug if rash worsens to severe (blisters, fever, mucous membrane involvement, conjunctivitis, edema, or arthralgias) or if systemic symptoms are present

3TC, lamivudine; ABC, abacavir; APV, amprenavir; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ATV, atazanavir; CBC, complete blood cell count; D/C, discontinue; ddI, didanosine; d4T, stavudine; EFV, efavirenz; FTC, emtricitabine; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDV, indinavir; IV, intravenous; LFT, liver function tests; LPV/r, lopinavir + ritonavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; PT, prothrombin time; T.bili, total bilirubin; TDF, tenofovir disoproxil fumarate; TPV, tipranavir; ULN, upper limit of normal; ZDV, zidovudine.

TABLE 84–7. Other Adverse Effects and Management

Adverse Effects	Drug	Signs and Symptoms	Risk Factors	Prevention/Monitoring	Management
Potential Long-term Complications					
Cardiovascular	Potentially all PIs	Onset: months to years after therapy initiation	Other risk factors for CVD	Consider non-PI based regimen; lifestyle modification counseling	Early diagnosis, prevention, and pharmacologic therapy for hyperlipidemia, HTN, insulin-resistance/diabetes mellitus; assess cardiac risk factors; switch to NNRTI- or ATV-based regimen; avoid d4T
Hyperlipidemia	All PIs (except ATV); d4T; EFV (to a lesser extent)	Onset: weeks to months after therapy initiation; symptoms: All PIs except ATV—↑LDL and total cholesterol (TC), ↓HDL; LPV/r and RTV—disproportionate ↑TG, d4T—↑TG; may also ↑LDL and TC; EFV or NVP—↑HDL, slight ↑TG	Underlying hyperlipidemia PI TPV/r greater than LPV/r and RTV greater than NFV and APV greater than IDV and SQV greater than ATV; NNRTI: less than PIs; NRTI: d4T greater than ZDV and TDF	Use non-PI non-d4T–based regimens; use ATV-based regimen; monitor fasting lipid profile at baseline, 3–6 months after new regimen, then at least annually	Lifestyle modification; switch to antiretrovirals with fewer lipid effects; total cholesterol greater than 200 mg/dL, ↑LDL, TG 200–500 mg/dL ⇒ pravastatin or atorvastatin; TG greater than 500 mg/dL ⇒ gemfibrozil or micronized fenofibrate
Insulin resistance/ Diabetes mellitus	All PIs	Onset: weeks to months after therapy initiation; symptoms: polyuria, polydipsia, polyphagia, fatigue, weakness; exacerbation of hyperglycemia in patients with underlying diabetes	Underlying hyperglycemia, family history of diabetes mellitus 1. Diabetes 2. Prior steroid use 3. Advanced age 4. Alcohol use 5. Hyperlipidemia	Use PI-sparing regimens; monitor fasting blood glucose 1–3 months after starting new regimen, then at least every 3–6 months Risk reduction: for asymptomatic cases with less than 15% bony head involvement, monitor with MRI every 3–6 months × 1 y, then every 6 months × 1 y, then annually	Diet and exercise; consider switching to an NNRTI-based regimen; if need for pharmacologic therapy, consider metformin, sulfonylurea, "glitazones," or insulin, where indicated Conservative: reduce weight-bearing activity on affected joint; reduce risk factors; analgesics as needed; Surgical: core decompression +/– bone grafting (early disease); total joint arthroplasty (severe disease)
Osteonecrosis	All PIs	Onset: insidious; symptoms: mild to moderate periarticular pain; 85% of cases involve one or both femoral heads			
Quality of Life Complications					
Central nervous system effects	EFV	Onset: first few doses; symptoms: one or more of the following: drowsiness, insomnia, abnormal dreams, dizziness, impaired concentration, depression, hallucination; exacerbation of psychiatric disorders; psychosis; suicidal ideation	1. Preexisting or unstable psychiatric illness 2. Use of other drugs with CNS effects	Take no earlier than 2–3 hours before bedtime; take on an empty stomach; counsel patients to avoid operating machinery during first 2–4 weeks of therapy	Symptoms usually diminish or resolve after 2–4 weeks; may consider discontinuing therapy if symptoms persist and significantly impair daily function or exacerbate psychiatric illness

Fat maldistribution	PIs, d4T	Onset: gradually, months after therapy initiation; symptoms: lipoatrophy-peripheral fat loss (facial thinning, thinning of extremities and buttocks); lipohypertrophy—increase in abdominal girth, breast size, and dorsocervical fat pad (buffalo hump)	Lipoatrophy—low baseline body mass index	DEXA scan	Switching to other agents may slow or stop progression, but may not reverse effects; injectable poly-L-lactic acid for facial lipoatrophy
Gastrointestinal intolerance	All PIs, ZDV, ddI	Onset: first few doses; symptoms: nausea, vomiting, abdominal pain; diarrhea commonly seen with NFV, LPV/r, and ddI-buffered formulations	All patients	Taking with food may reduce symptoms (not for ddI or unboosted IDV); may preemptively need ntiemetics or antidiarrheals	May spontaneously resolve or become tolerable with time; nausea and vomiting: consider antiemetic prior to dosing; switch to less emetogenic agent; diarrhea: consider antimotility agents, calcium tablets, bulk-forming agents, and/or pancreatic enzymes
Injection site reactions	Enfuvirtide	Onset: first new doses; symptoms: pain, pruritus, erythema, ecchymosis, warmth, nodules, rarely injection site infection	All patients	Educate regarding use of sterile technique, solution at room temperature, rotation of injection sites, avoidance of sites with little subcutaneous fat or existing reactions	Massaging the area vigorously before and after injection may reduce pain; wear loose clothing around injection site areas; take warm shower or bath prior to injection; Rarely, warm compact or analgesics may be necessary
Peripheral neuropathy	ddI, d4T, ddC	Onset: weeks to months after therapy initiation; symptoms: begins with numbness and paresthesias of toes and feet; may progress to painful neuropathy; upper extremities less frequently involved; may be irreversible despite drug discontinuation	1. Preexisting peripheral neuropathy 2. Combined use of these NRTIs or other drugs which may cause neuropathy 3. Advanced HIV 4. High dose of offending drugs	Avoid using these agents in patients at risk, if possible; avoid combined use of these agents; ask patient at each encounter	Consider D/C offending agent prior to onset of disabling pain; pharmacologic treatment (variable effectiveness): gabapentin, tricyclic antidepressants, lamotrigine, oxcarbamazepine, topiramate, tramadol, narcotic analgesics, capsaicin cream, topical lidocaine

APV, amprenavir; ATV, atazanavir; CNS, central nervous system; CVD, cardiovascular disease; D/C, discontinue; ddC, zalcitabine; ddI, didanosine; DEXA, dual-energy x-ray absorptiometry; d4T, stavudine; EFV, efavirenz; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; HTN, hypertension; IDV, indinavir; LDL, low-density lipoprotein; LPV/r, lopinavir + ritonavir; MRI, magnetic resonance imaging; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RTV, ritonavir; SQV, saquinavir; TDF, tenofovir disoproxil fumarate; TG, triglyceride; TPV/r, tipranivir + ritonavir; ZDV, zidovudine.



Patient Encounter, Part 3

Creating a Care Plan

Based on the information presented, create a care plan for this patient's HIV/AIDS. Your plan should include: (a) a statement of the best drug combinations and reasons supporting each drug recommended, as well as any adverse effects or potential drug-related problems, (b) the goals of therapy, (c) a patient-specific, detailed therapeutic plan, and (d) a plan for follow-up to determine whether the goals have been achieved and adverse effects avoided.



Patient Encounter, Part 4

The Patient Returns

Your patient begins treatment with atazanavir 300 mg PO once daily, ritonavir 100 mg PO once daily, tenofovir 300 mg PO once daily, and lamivudine 300 mg PO once daily. He initially does well on this regimen, but after about 3 months, he has difficulty taking his medications at the same time every day due to his busy schedule. Because of his job, he relocated to Alabama, and has not been seen in your clinic for 2 years. He returns today to see you in clinic and complains of feeling tired, but otherwise no specific complaints.

1. What laboratory tests do you recommend?
2. What additional information do you need to know before creating a treatment plan for this patient?



Patient Care and Monitoring

Patient Assessment

1. Medication history
   - Get a thorough history of prescription, nonprescription, and natural drug product use. Determine what prior antiretroviral regimens, if any, were used in the past.
   - *Is the patient taking the appropriate dose of each medication? Are the doses adjusted for renal or hepatic failure? Are the doses adjusted for drug interactions with concomitant medications?*
   - Evaluate the patient for the presence of adverse drug reactions, drug allergies, and drug interactions.
   - Assess improvement in quality-of-life measures such as physical, psychological, and social functioning and well-being. *Is the patient experiencing any drug-induced adverse effects? What can you do to help manage these adverse effects?*
2. Review any available diagnostic data to determine status of his HIV/AIDS.
3. Determine if initiation of antiretroviral therapy is indicated. Evaluate the patient's ability to adhere to medications, daily routine, social support, and financial stability. *Is the patient taking any medications that may interfere with the individual components of potential regimens? Does the patient have medical insurance and prescription coverage?*
4. Develop a plan to assess the effectiveness and tolerability of antiretroviral therapy.

Patient Education

1. Educate the patient on HIV/AIDS disease and the importance of strict adherence to medication (the patient must ideally take his or her medications at the same time every day). Recommend a therapeutic regimen that is as easy as possible for the patient to take. Talk to the patient specifically about when and how the patient will be taking the medications. *What time do they eat meals? When do they wake up? What other medications are they taking at the same time?* Educate patients whether to take their medications with or without food.
2. Educate the patient on common adverse drug effects and a few of the key signs and symptoms of severe toxicity (i.e., jaundice and abacavir hypersensitivity reaction). Tell them to call their provider immediately if any of those symptoms occur. Make sure they have the correct telephone number for the clinic.



Patient Encounter Answer Key

Part 1

1. Presence of risk factors for HIV, symptoms of chronic disease and/or opportunistic infections
2. Sex with men, unprotected sex
3. Does this patient have an opportunistic infection that needs treating first? It is also important to know what other medications the patient is taking, drug allergies, and the patient's daily routine.

Part 2

1. This patient has the subjective symptoms of weight loss, decreased appetite, shortness of breath, and cough. Abnormal laboratory values include: elevated temperature, decreased hemoglobin and hematocrit, and decreased CD4 count. Chest x-ray shows diffuse interstitial infiltrates bilaterally. Physical exam reveals thrush. The assessment is possible AIDS with CD4 count of 150 cells/mm^3, thrush, a respiratory illness (possibly *Pneumocystis jiroveci* pneumonia), and anemia of chronic disease. He also has a history of hepatitis B, hypertension, and GERD (on famotidine), poor adherence to his antihypertensive medications, and likely has an irregular daily regimen due to his occupation as a truck driver.
2. For PCP: Oxygen saturation on room air, induced sputum or bronchoalveolar lavage for presence of *Pneumocystis jiroveci* organisms
   For HIV: HIV RNA, baseline HIV genotypic resistance test
   For HIV treatment: Hepatitis B tests (hepatitis B surface antibody and antigen, hepatitis B envelope antigen, and HBV DNA), liver function tests
3. a. Treat opportunistic infections such as thrush and PCP, if the diagnosis is made, prior to starting antiretroviral therapy. This is because treatment with antiretroviral therapy may cause immune reconstitution syndrome.
   b. Restore and preserve immunologic function
   c. Maximally and durably suppress HIV RNA
   d. Improve quality of life
   e. Reduce HIV-related morbidity and mortality
4. Nonpharmacologic: Prevention of viral transmission (use protective barrier for oral and sexual intercourse; do not share needles or other equipment used in preparing, injecting, or inhaling drugs), adequate nutritional intake
   Pharmacologic: For treatment-naïve patients, two regimens are preferred, either:
   Efavirenz *and* (zidovudine or tenofovir) *and* (lamivudine *or* emtricitabine)
   or
   Lopinavir/ritonavir *or* atazanavir/ritonavir *and* (zidovudine *or* fosamprenavir/ritonavir *or* tenofovir) *and* (lamivudine *or* emtricitabine).

Part 3

a. Any preferred regimen may be okay for this patient; however, due to the patient's lifestyle as a truck driver, the potential side effects of the drugs, and the patient's history of hepatitis B, the combination of efavirenz, tenofovir, and emtricitabine may be the best choice for him. This regimen is taken once daily. Use of efavirenz avoids the high likelihood of gastrointestinal adverse effects of lopinavir/ritonavir such as nausea and diarrhea, which would be inconvenient for him if he is driving long distances. Tenofovir has activity against both hepatitis B and HIV, so would be a good choice in him. Emtricitabine and lamivudine are similar NRTIs with similar resistance profiles. Both also have activity against hepatitis B and HIV. Because tenofovir was recommended, a combination tablet of tenofovir emtricitabine and efavirenz is available, decreasing his pill burden. Zidovudine may not be the best choice, as it may worsen his anemia.

b. Goals of therapy:
   1. Restore and preserve immunologic function
   2. Maximally and durably suppress HIV RNA
   3. Improve quality of life
   4. Reduce HIV-related morbidity and mortality

c. Talk to the patient and based on his sleep/wake schedule, food intake, and other daily routines, find specific times for him to take his medications, both HIV and non-HIV. Counsel the patient about the importance of adherence and the potential side effects of the drugs. Efavirenz (rash; central nervous system symptoms including insomnia, irritability, lethargy, dizziness, and/or vivid dreams which usually resolve in 2 weeks; increased LFTs; false-positive cannabinoid test, if the patient uses marijuana), tenofovir (asthenia, headache, diarrhea, nausea, vomiting, flatulence, and renal insufficiency), and emtricitabine (minimal).

d. Call the patient in the first week after starting medications to evaluate development of any side effects or problems in adherence. In 2 to 8 weeks after starting medications, the patient should have a follow-up visit and/or blood drawn for CD4+ lymphocyte absolute count and percentage and plasma HIV RNA. Adequate immunologic response in antiretroviral-naïve patients consists of an increase in CD4+ cell count that averages 100 to 150 cells/mm^3 per year (with a faster response in the first 3 months), and a 1 log decrease in HIV RNA by 2 to 8 weeks after starting medications, followed by concentrations less than 50 copies/mL by 12 to 16 weeks (if HIV RNA less than 100,000/μL) or by 16 to 24 weeks (if HIV RNA greater than 100,000/μL). HIV RNA and CD4 count are monitored generally every 3 to 6 months.

Part 4

1. The patient may be failing his current regimen due to nonadherence or a drug interaction with famotidine. Check HIV RNA and CD4 count to evaluate HIV treatment efficacy and complete blood count with differential, chemistry profile, and liver function tests for routine follow-up.
2. If the patient is failing his current antiretroviral regimen, ask if the patient is currently taking his medications. If he is, then obtain a resistance test to help determine the cause for failure. Question him further about his previous regimen regarding tolerability and adherence, other concomitant medications, new disease states, and drug allergies.

ABBREVIATIONS

3TC: lamivudine
ABC: abacavir
AIDS: acquired immune deficiency syndrome
ALT: alanine aminotransferase
APV: amprenavir
ARV: antiretroviral
AST: aspartate aminotransferase
ATV: atazanavir
CBC: complete blood cell count
CNS: central nervous system
CVD: cardiovascular disease
CYP: cytochrome P-450 isoenzyme
D/C: discontinue
ddC: zalcitabine
ddI: didanosine
DEXA: dual-energy x-ray absorptiometry
DHHS: Department of Health and Human Services
DRV: darunavir
d4T: stavudine
ELISA: enzyme-linked immunosorbent assay
EFV: efavirenz
FDA: Food and Drug Administration
FTC: emtricitabine
GERD: gastroesophageal reflux disease
HAART: highly active antiretroviral therapy
HBeAg: hepatitis B early antigen
HBV: hepatitis B virus
HCV: hepatitis C virus
HDL: high-density lipoprotein
HIV: human immunodeficiency virus infection
HTN: hypertension
IAS-USA: International AIDS Society-USA
IDV: indinavir
IFA: indirect immunofluorescence assay
IV: intravenous
LDL: low-density lipoprotein
LFT: liver function tests
LPV/r: lopinavir + ritonavir
MRI: magnetic resonance imaging
MTCT: mother-to-child transmission
NNRTI: nonnucleoside reverse transcriptase inhibitor
NRTI: nucleoside reverse transcriptase inhibitor
NtRI: nucleotide reverse transcriptase inhibitor
NVP: nevirapine
PCP: *Pneumocystis jiroveci* (formerly *carinii*) pneumonia
PI: protease inhibitor
PT: prothrombin time
RT-PCR: reverse transcriptase polymerase chain reaction
RTV: ritonavir
SIV: simian immunodeficiency virus
SQV: saquinavir
T.bili: total bilirubin
TDF: tenofovir disoproxil fumarate
TG: triglyceride
TPV: tipranavir
TPV/r: tipranivir + ritonavir
ULN: upper limit of normal
WB: Western blot
ZDV: zidovudine

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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85 Cancer Chemotherapy and Treatment

Dianne Brundage



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Describe the etiology of cancer.
2. Define the TNM system of cancer staging.
3. Classify each drug used in the treatment of cancer, and compare and contrast the mechanisms of action, uses, and side effects.
4. Outline actions for all health care providers to prevent medication errors with cancer treatments.
5. Describe the role of the health care practitioner in the care of cancer patients.

Key Concepts

❶ The word cancer covers a diverse array of tumors types that affect a significant number of Americans and are a significant cause of mortality.
❷ Numerous cellular changes occur in the genetic material of the cancer cell so that programmed cell death, or **apoptosis,** does not occur. Proliferation of cancer cells goes unregulated.
❸ Many tumors are staged according to the tumor, nodes, metastases (TNM) system. Metastases are cancer cells that have spread to sites distant from the primary tumor site and have started to grow. The most frequently occurring sites of metastasis of solid tumors are the brain, bone, liver, and lungs.
❹ Each category of chemotherapy drugs has similar side effects. Anthracyclines cause cardiac toxicity, which is related to the cumulative dose. Tubulin interactive agents are associated with neuropathy and ileus. Alkylating agents are associated with secondary malignancies.
❺ Because of the severe toxicities associated with many of the chemotherapy agents, safety precautions must be in place to prevent chemotherapy errors, accidental chemotherapy exposures, and overdosages.
❻ Clinicians should play a role in chemotherapy safety, patient education, and monitoring patient response to therapy. For example, cumulative doses of anthracyclines should be monitored along with signs and symptoms of heart failure. Clinicians also should monitor concurrent medications along with chemotherapy for drug interactions.

❶ *The word cancer covers a diverse array of tumors types that affect a significant number of Americans and are a significant cause of mortality.* The term *cancer* actually refers to more than 100 diseases. What is common to all cancers is the cancerous cell has uncontrolled growth so that it invades tissues and spreads to other parts of the body, called *metastasis*. In 2005, it is projected that over 1.3 million Americans will be diagnosed with cancer, whereas more than 560,000 Americans will die from the cancer.[1] Figure 85–1 reveals cancers by gender, new cases, and deaths.

A cancer patient may encounter many different health care professionals: phlebotomists, pathologists, surgeons, medical and radiation oncologists, physician assistants, pharmacists, nurses, counselors, dieticians, social workers, and chaplains all may be involved with a single patient. Each one plays an important role in care of the cancer patient. The pharmacist's role may include education of patients and family members, education of staff about new agents and safety issues, preparation of therapies, resolution of reimbursement issues, development of order sets, and participation in clinical trials. Each patient should have access to an interdisciplinary team to assist him or her during treatment.

Cancer treatments have exploded technologically in the last couple of decades. The fields of radiation therapy, surgery, and pharmaceuticals have had numerous developments, so patients are receiving not only less toxic treatments but also treatments that have improved outcomes over those of 15 years ago. Supportive-care therapies have improved, so patients may be at

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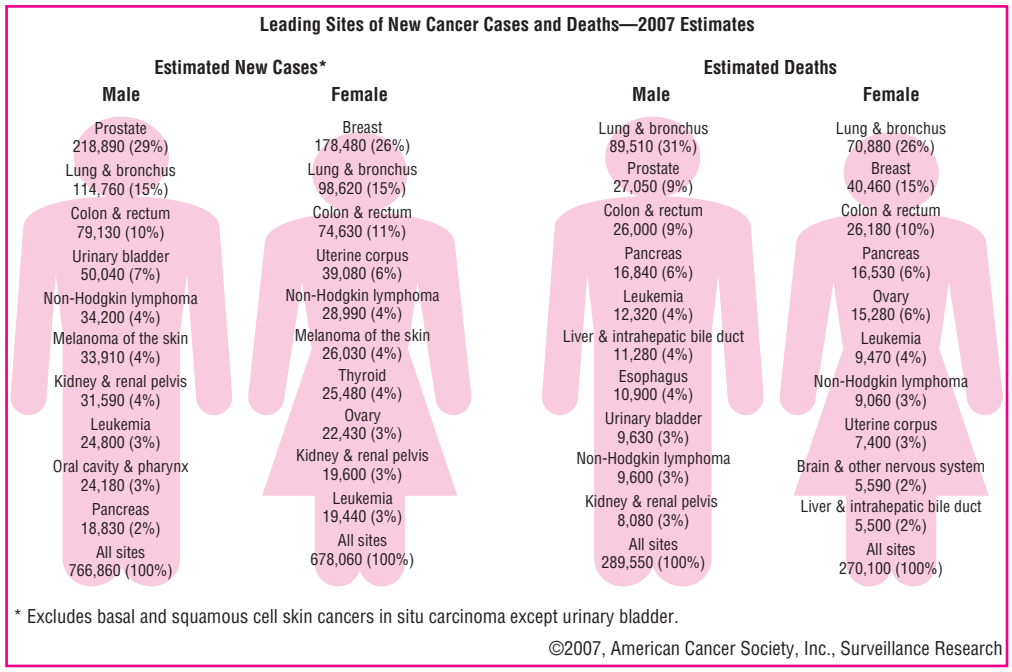


FIGURE 85–1. Cancer incidences (*left*) and deaths (*right*) in the United States for males and females estimate for 2007. (Reproduced from American Cancer Society. Cancer facts and figures—2007. Atlanta: American Cancer Society; 2007.)

less risk for toxicity and have a better **quality of life** than patients 10 to 15 years ago. In the early 1990s, most patients received chemotherapy while hospitalized because of side effects. Today, most patients receive chemotherapy in the clinic and/or are taking oral agents at home.

EPIDEMIOLOGY AND ETIOLOGY

Carcinogenesis

The exact cause of cancer remains unknown and probably is very diverse given the vast array of diseases called cancer. What is common to all cancer cells is that the usual cell cycle of proliferation and death no longer exists. Carcinogenesis may occur in the following steps: initiation, promotion, transformation, and progression. Initiation occurs when a carcinogenic substance encounters a normal cell to produce genetic damage, or a mutated cell. Environmental or other factors that favor the growth of the mutated cell refer to promotion. Transformation occurs when the mutated cell becomes malignant, and progression refers to the state where cell proliferation takes over, and the tumor spreads or develops metastases.

Carcinogenic agents include chemicals in the environment, such as aniline and benzene, which are associated with the development of bladder cancer and leukemia, respectively. Environmental factors, such as excessive sun exposure, also may result in cancer. Viruses, including the human papilloma virus and hepatitis B, may be associated with the development of cancer. Some of the chemotherapy agents cause secondary cancers after therapy has been completed. Numerous factors may contribute to the development of cancer.

Cancer Genetics

Since the human genome has been sequenced, and with the great improvements in genetic technology, there is an ever-increasing body of knowledge regarding the genetic changes of cancer. Currently, there are two major classes of genes involved in cancer: oncogenes and tumor-suppressor genes. Protooncogenes are normal genes that, through some genetic alteration caused by carcinogens, change into oncogenes. The oncogene produces abnormal or excessive gene product that disrupts normal cell growth and proliferation.[2] Table 85–1 provides examples of oncogenes.

Tumor-suppressor genes inhibit inappropriate cellular growth and proliferation by gene loss or mutation. The *p53* gene is one of the most common tumor-suppressor genes, and mutations of *p53* may occur in up to 50% of all malignancies. This gene stops the cell cycle to enable "repairs" of the cell. If *p53* is inactivated, then the cell allows the mutations to occur. While mutations of the *p53* gene are found in many tumors, it is also associated with drug resistance of cancer cells. DNA repair genes fix errors in DNA that occur because of environmental factors or errors in replication and sometimes are referred to as *tumor-suppressor genes*.

❷ *Numerous cellular changes occur in the genetic material of the cancer cell so that programmed cell death, or* ***apoptosis,*** *does not occur. Proliferation of cancer cells goes unregulated.* If mutations persist and cells aren't repaired or suppressed, cancer may develop. **Apoptosis,** or programmed cell death, may prevent the mutated cell from becoming cancerous. Loss of *p53* and overexpression of *bcl-2* are two examples of changes within the cell that occur to result in enhanced cell survival. *Cellular senescence* refers to cell death that occurs after a preset

TABLE 85–1. Examples of Oncogenes and Tumor-Suppressor Genes

Gene	Function	Associated Human Cancer
Oncogenes		
Genes for growth factors or their receptors		
EGFR or *ERB-B1*	Codes for epidermal growth factor (EGFR) receptor	Glioblastoma, breast cancer, squamous carcinoma
HER-2/neu or *ERB-B2*	Codes for a growth factor receptor	Breast, salivary gland, prostate, bladder and ovarian cancers
RET	Codes for a growth factor receptor	Thyroid cancer
Genes for cytoplasmic relays in stimulatory signaling pathways		
K-RAS		Lung, ovarian, colon, pancreatic binding cancers
N-RAS	Code for guanine nucleotide-proteins with GTPase activity	Neuroblastoma, acute leukemia
Genes for transcription factors that activate growth-promoting genes		
c-MYC		Leukemia and breast, colon, gastric, and lung cancers
N-MYC		Neuroblastoma, small cell lung cancer, and glioblastoma
Genes for cytoplasmic kinases		
BCR-ABL	Codes for a nonreceptor tyrosine kinase	Chronic myelogenous leukemia
Genes for other molecules		
BCL-2	Codes for a protein that blocks apoptosis	Indolent B-cell lymphomas
BCL-1 or *PRAD1*	Codes for cyclin D1, a cell cycle clock stimulator	Breast, head and neck cancers
MDM2	Protein antagonist of p53 tumor suppressor protein	Sarcomas
Tumor suppressor genes		
Genes for proteins in the cytoplasm		
APC	Step in a signaling pathway	Colon and gastric cancer
NF-1	Codes for a protein that inhibits the stimulatory Ras protein	Neurofibroma, leukemia, and pheochromocytoma
NF-2	Codes for a protein that inhibits the stimulatory Ras protein	Meningioma, ependymoma, and schwannoma
Genes for proteins in the nucleus		
MTS1	Codes for p16 protein, a cyclin-dependent kinase inhibitor	Involved in a wide range of cancers
RB1	Codes for the pRB protein, a master brake of the cell cycle	Retinoblastoma, osteosarcoma, and bladder, small cell lung, prostate and breast cancers
p53	Codes for the p53 protein, which can halt cell division and induce apoptosis	Involved in a wide range of cancers
Genes for protein whose cellular location is unclear		
BRCA1	DNA repair, transcriptional regulation	Breast and ovarian cancers
BRCA2	DNA repair	Breast cancer
VHL	Regulator of protein stability	Renal cell cancer
MSH2, MLH1, PMS1, PMS2, MSH6	DNA mismatch repair enzymes	Hereditary nonpolyposis colorectal cancer

From DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: Table 124–2.

number of cell doublings. Telomeres are DNA segments at the ends of chromosomes that shorten with each replication to the point where senescence is triggered.

Principles of Tumor Growth

It takes about 10^9 cancer cells to be clinically detectable by palpation. Figure 85–2 demonstrates the classic Gompertzian kinetics tumor-growth cycle. From the diagram, one can see that malignant cell growth occurs many times before a mass may be palpated. The number of malignant cells may plummet drastically because of surgery or in decreasing steps by each administration of chemotherapy. One dosing round, or cycle, of chemotherapy does not eliminate all malignant cells, and therefore, repeated cycles of chemotherapy are administered to eliminate tumor cell burden.

Metastases

A **metastasis** is a growth of the same cancer found at some distance from the primary tumor site.[3] The metastasis may be large, or it may be just a few cells that may be detected through polymerase chain reaction (PCR); however, the presence of metastasis at staging usually is associated with a poorer prognosis than the patient with no known metastatic disease. As the technology to find malignant cells evolves, the dilemma exists on how to treat patients based on current guidelines that were not based on cellular detection technology.

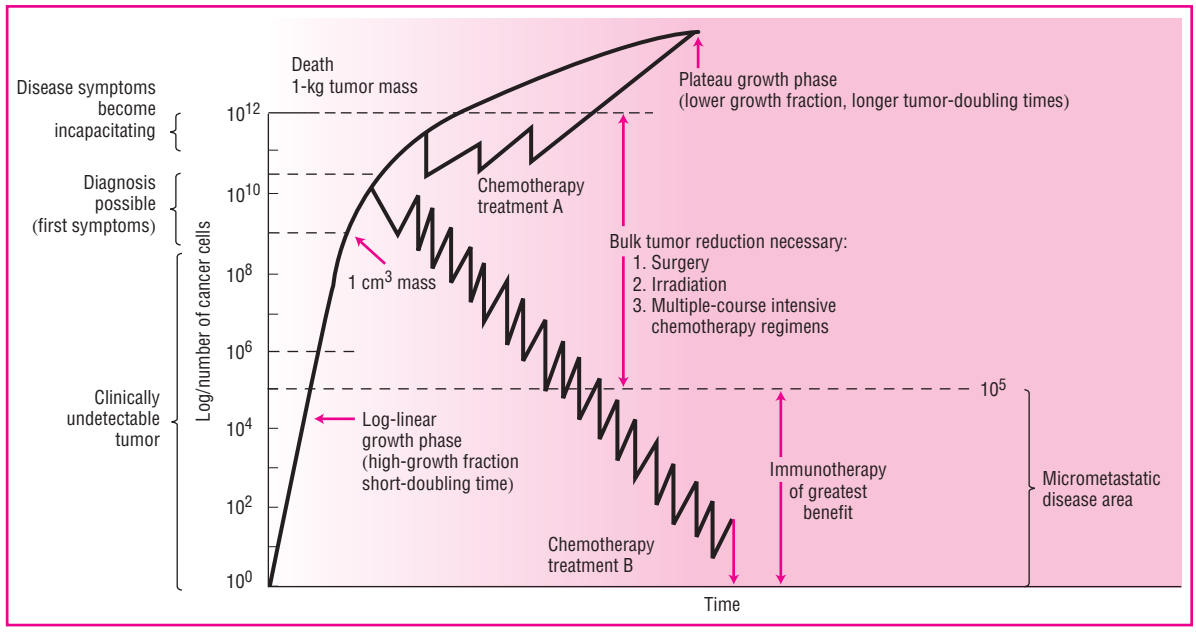


FIGURE 85–2. The Gompertzian growth curve demonstrating symptoms and treatments versus tumor volume. (From Buick RN. Cellular basis of chemotherapy. In: Dorr RT, Von Hoff DD, (eds.) Cancer Chemotherapy Handbook. 2nd ed. New York: Elsevier; 1994: 3–14.)

Cancers spread usually by two pathways: hematogenous (through the bloodstream) or through the lymphatics (drainage through adjacent lymph nodes). The malignant cells that split from the primary tumor find a suitable environment for growth. It is believed that malignant cells secrete mediators that stimulate the formation of blood vessels for growth and oxygen, the process of angiogenesis.

The usual metastatic sites for solid tumors are the brain, the bone, the lung, and the liver. It is important to realize and educate patients that breast cancer cells may metastasize to the brain, so the individual doesn't have brain and breast cancer but breast cancer metastases to the brain.

PATHOPHYSIOLOGY

Tumor Characteristics

Tumors are either benign or malignant.[4] Benign tumors often are encapsulated, localized, and indolent; they seldom metastasize; and they recur rarely once removed. Histologically, the cells resemble the cells from which they developed. Malignant tumors are invasive and spread to other locations, even if the primary tumor is removed. The cells no longer perform their usual functions, and their cellular architecture changes. *Anaplasia* is defined as the loss of structure and function.

Tumor Origin

Tumors may arise from epithelial, connective (i.e., muscle, bone, and cartilage), lymphoid, and nerve tissue. The suffix–*oma* is added to the name of the cell type if the tumor cells are benign. A *lipoma* is a benign growth that resembles fat tissue.

Precancerous cells have cellular changes that are abnormal but not yet malignant and may be described as *hyperplastic* or *dysplastic*. Hyperplasia occurs when a stimulus is introduced and reverses when the stimulus is removed. Dysplasia is an abnormal change in the size, shape, or organization of cells or tissues.

Malignant cells are divided into categories based on the cells of origin. Carcinomas arise from epithelial cells, whereas sarcomas arise from muscle or connective tissue. Adenocarcinomas arise from glandular tissue. *Carcinoma in situ* refers to cells limited to epithelial origin that have not yet invaded the basement membrane.

TREATMENT

Desired Outcome

While at the time of surgery the surgeon may be able to remove all macroscopic disease, microscopic cells may be present near the surgical site or may have traveled to other parts of the body. Thus, for chemotherapy-sensitive diseases, systemic therapies may be administered after surgery to destroy these microscopic malignant cells; this is called *adjuvant therapy*. The goals of **adjuvant** therapy are to decrease recurrence of the cancer and to prolong survival. Chemotherapy may be given prior to surgical resection of the tumor; this is referred to as *neoadjuvant therapy*. Chemotherapy given prior to surgery should decrease the tumor



Clinical Presentation and Diagnosis

Signs and Symptoms

The seven warning signs of cancer are:

- Change in bowel or bladder habits
- A sore that does not heal
- Unusual bleeding or discharge
- Thickening or lump in breast or elsewhere
- Indigestion or difficulty in swallowing
- Obvious change in wart or mole
- Nagging cough or hoarseness

The eight warning signs of cancer in children are:

- Continued, unexplained weight loss
- Headaches with vomiting in the morning
- Increased swelling or persistent pain in bones or joints
- Lump or mass in abdomen, neck, or elsewhere
- Development of a whitish appearance in the pupil of the eye
- Recurrent fevers not caused by infections
- Excessive bruising or bleeding
- Noticeable paleness or prolonged tiredness

Diagnostic Procedures

- Laboratory tests: Complete blood count, lactate dehydrogenase (LDH), renal function, and liver function tests
- Radiologic scans: x-rays, computed tomographic (CT) scans, magnetic resonance imaging (MRI), positron-emission tomography (PET)
- Biopsy of tissue or bone marrow with pathologic evaluation
- Cytogenetics
- Tumor markers
- Staging [determination of the primary tumor size, extent of lymph node involvement, and the presence or absence of metastases, or sometimes referred to the TNM system (Table 85–2)]. ❸ *Many tumors are staged according to the TNM system. Metastases are cancer cells that have spread to sites distant from the primary tumor site and have started to grow. The most frequently occurring sites of metastasis are the brain, bone, liver, and lungs.*
  From: DiPiro JT, Talbert RL, Yee GC, et al., (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: Tables 124–5, 124–6.

burden to be removed (which may result in a shorter surgical procedure) and make the surgery easier to perform because the tumor has shrunk away from vital organs or vessels.

Chemotherapy may be given to cure cancers that are curable, or it may be given to help control the symptoms of an incurable cancer, which is referred to as *palliative therapy*.

Response

The response to chemotherapy may be referred to as *complete response, partial response, stable disease*, or *disease progression*. A *cure* in oncology implies that the cancer is completely gone, and the patient will have the same life expectancy as a patient without cancer. A *complete response* (CR) refers to complete disappearance of all cancer for 1 month after treatment. A *partial response* (PR) is defined as a 50% decrease in tumor diameter along with no new disease for 1 month. The term *overall objective response rate* refers to the combination of PR and CR. *Stable disease* refers to tumor that has not grown and has shrunk by less than 25% of the diameter. *Disease progression* refers to tumor that has spread or the primary tumor has increased in size by 25%. Some cancers, such as leukemia, cannot be measured by size, so biopsy of the bone marrow provides a cellular indication of absence or presence of disease.

Cancer chemotherapy and the treatment of cancers are analogous to anti-infectives and the treatment of infections. Cancer cells may be *sensitive* to certain chemotherapy agents, but then with repeated exposure, the cells become *resistant* to treatment. The resistant cells then grow and multiply. While tumors may be tested for chemotherapy sensitivity, this area is still developing. Today, tumor sensitivity can demonstrate tumor resistance so that needless exposure to an inadequate therapy and its toxicity can be avoided.

Tumor cells may become resistant when genetic changes occur during cell proliferation. Resistant cancer cells with the *mdr-1* gene may possess a membrane-associated protein, p-glycoprotein, that facilitates efflux of chemotherapy agents out of the cells. Numerous attempts at blocking this efflux pump have been unsuccessful.

Nonpharmacologic Therapy

The four primary treatment modalities of cancer are surgery, radiation, chemotherapy, and biologic therapy. Surgery is useful to gain tissue for diagnosis of cancer and for treatment, especially those cancers with limited disease. Radiation plays a key role not only in the treatment and possible cure of cancer but also in palliative therapy. Together, surgery and radiation therapy may provide local control of symptoms of the disease. However, when cancer is widespread, surgery may play little or no role, whereas radiation therapy localized to specific areas may palliate symptoms.

Pharmacologic Therapy

Chemotherapy of cancer started in the early 1940s when nitrogen mustard was administered to patients with lymphoma. Since then, numerous agents have been developed for the treatment of different cancers.

Dosing of Chemotherapy

Many chemotherapy agents have significant organ toxicities that preclude using larger and larger doses to treat the cancer. The doses of chemotherapy must be spaced out to allow the patient to recover from the toxicity of the chemotherapy; each

TABLE 85–2. TNM Staging Classification System for Colorectal Cancer

Primary tumor (T)	
T_x	Primary tumor cannot be assessed
T_0	No evidence of primary tumor
T_{is}	Carcinoma in situ: intraepithelial or invasion of lamina propria
T_1	Tumor invades submucosa
T_2	Tumor invades muscularis propria
T_3	Tumor invades through the muscularis propria into the subserosa, or into nonperitonealized pericolic or perirectal tissues
T_4	Tumor perforates the visceral peritoneum, and/or directly invades other organs or structures
Regional lymph nodes (N)	
N_x	Regional lymph nodes cannot be assessed
N_0	No regional lymph node metastasis
N_1	Metastasis in one to three pericolic or perirectal lymph nodes
N_2	Metastasis in four or more pericolic or perirectal lymph nodes
Distant metastasis (M)	
M_x	Presence of distant metastasis cannot be assessed
M_0	No distant metastasis
M_1	Distant metastasis

Stage	Grouping			Dukes	Modified Astler-Collier
Stage 0	T_{is}	N_0	M_0		
Stage 1	T_1	N_0	M_0	A	A
	T_2	N_0	M_0	A	B1
Stage IIA	T_3	N_0	M_0	B	B2
Stage IIB	T_4	N_0	M_0	B	B2, B3
Stage IIIA	T_{1-2}	N_1	M_0	C	C1–3
Stage IIIB	T_{3-4}	N_1	M_0	C	C1–3
Stage IIIC	Any T	N_2	M_0	C	C1–3
Stage IV	Any T	Any N	M_0	"D"	D

From DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: Table 124–7.

period of chemotherapy dosing is referred to as a *cycle*. Each cycle of chemotherapy may have the same dosages, or the dosages may be modified based on toxicity, or a chemotherapy regimen may alternate from one set of drugs given during the first, third, and fifth cycles to another set of different drugs given during the second, fourth, and sixth cycles. *Dose density* of chemotherapy refers to shortening of the period between doses of chemotherapy. This can accomplish two things: First, the tumor has less time between doses of chemotherapy to grow, and second, patients receive chemotherapy over a shorter period of time and hopefully can get back to a normal life sooner. Usually dose-dense chemotherapy regimens require colony-stimulating factors to be administered to shorten the time period of neutropenia. The chemotherapy regimens that are dose-dense tend to be adjuvant regimens, where the tumor burden is not measurable, and the cancer outcome is a cure. When a chemotherapy regimen is used as palliative therapy (to control symptoms), the dosages of chemotherapy should be decreased based on toxicity, or the interval between dosages should be lengthened to maintain quality of life.

Patient and tumor biology also affect how cancer therapy is dosed. Patients with a uridine diphosphate–glucuronosyltransferease 1A1 enzyme deficiency can have life-threatening diarrhea and complications from irinotecan. The patient may have a blood test prior to therapy to determine if there is a genetic problem prior to receiving irinotecan. In the case of the some of the monoclonal antibodies, flow cytometry results will reveal whether the tumor has the receptor where the drug will bind and exert the pharmacologic effect.

Another consideration of chemotherapy administration is the patient. Factors that affect chemotherapy selection and dosing are age, concurrent disease states, and performance status. Performance status can be assessed through either the Eastern Cooperative Oncology Group Scale or the Karnofsky Scale (Table 85–3). The patient is evaluated on whether he or she is active to bedridden most of the day; performance status is a very important prognostic factor for many types of cancer. If a patient has kidney dysfunction, and the chemotherapy is eliminated primarily by the kidney, dosing adjustments will need to be made. If a patient has had a myocardial infarction recently, the clinician will weigh the risks of anthracycline therapy against the benefit of the treatment of the cancer.

Another important consideration for treatment of cancers is reimbursement by third-party payors for off-label use of chemotherapy agents because of the high expense. The American Association of Cancer Centers (www.accc-cancer.org) provides

TABLE 85–3. Performance Status Scales

Description: Karnofsky Scale	Karnofsky Scale (%)	Zubrod Scale (ECOG)	Description: ECOG Scale
No complaints; no evidence of disease	100	0	Fully active, able to carry on all predisease activity
Able to carry on normal activity; minor signs or symptoms of disease	90		
Normal activity with effort, some signs or symptoms of disease	80	1	Restricted in strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature
Cares for self; unable to carry on normal activity or to do active work	70		
Requires occasional assistance but is able to care for most personal needs	60	2	Out of bed more than 50% of time; ambulatory and capable of self-care, but unable to carry out any work activities
Requires considerable assistance and frequent medical care	50		
Disabled; requires special care and assistance	40	3	In bed more than 50% of time; capable of only limited self-care
Severely disabled; hospitalization indicated, although death not imminent	30		
Very sick; hospitalization necessary; requires active supportive treatment	20	4	Bedridden; cannot carry out any self-care; completely disabled
Moribund; fatal processes progressing rapidly	10		
Dead	0		

ECOG, Eastern Cooperative Oncology Group.
From DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: Table 124–9.

a drug compendium quarterly to which clinicians may refer to verify coverage by Medicare based on ICD-9 codes. The drugs used according to Food and Drug Administration (FDA)–approved indications are almost always reimbursed. If sufficient literature exists, an insurer may pay for an off-label use.

Combination Chemotherapy

Again, the analogy to antibiotic therapy can be made when deciding on monotherapy versus combination therapy for the treatment of cancer. The underlying principles of using combination therapy are to use (1) agents with different pharmacologic actions, (2) drugs with different organ toxicities, (3) agents that are active against the tumor and ideally synergistic when used together, and (4) agents that do not result in significant drug interactions (although these can be studied carefully and the interactions addressed). When two or more agents are used together, the development of resistance may be slowed, but increased toxicity may result. ❹ *Each category of chemotherapy drugs has similar side effects. Anthracyclines cause cardiac toxicity, which is related to the cumulative dose. Tubulin interactive agents are associated with neuropathy and ileus. Alkylating agents are associated with secondary malignancies.*

Currently, anticancer agents are categorized by the mechanism of action. As depicted in Fig. 85–3, different agents work in different parts of the cell.

Antimetabolites

Fluorouracil

5-Fluorouracil, commonly referred to as 5-FU, is an analog of the pyrimidine uracil. It is metabolized by dihydropyrimidine dehydrogenase. 5-FU ultimately is metabolized to fluorodeoxyuridine monophosphate (FdUMP), which interferes with the function of thymidylate synthase, which is required for synthesis of thymidine. The triphosphate metabolite of 5-FU is incorporated into RNA to produce the second cytotoxic effect of 5-FU. It appears that inhibition of thymidylate synthesis occurs with the continuous infusion regimens, whereas the triphosphate form is associated with bolus administration. Patients with low activity of dihydropyrimidine dehydrogenase appear to be at risk for life-threatening toxicities.[5] Folates appear to increase the stability of the FdUMP thymidylate synthase inhibition, which enhances the activity of the drug in certain cancers. 5-FU has shown to be useful in the treatment of cancers of the colon, rectum, gastric, head and neck, and breast. 5-FU is metabolized extensively by the liver, whereas up to 15% of a dose may be found unchanged in the urine. The clearance of 5-FU ranges from 155 L/m^2 per hour (range 56–466 L/m^2 per hour) in women to 179 L/m^2 per hour (range 29–739 L/m^2 per hour) in men. Age does not appear to alter the pharmacokinetics of 5-FU. Fluorouracil has shown clinical activity in the treatment of colorectal, breast, esophageal, pancreas, stomach, anal, and

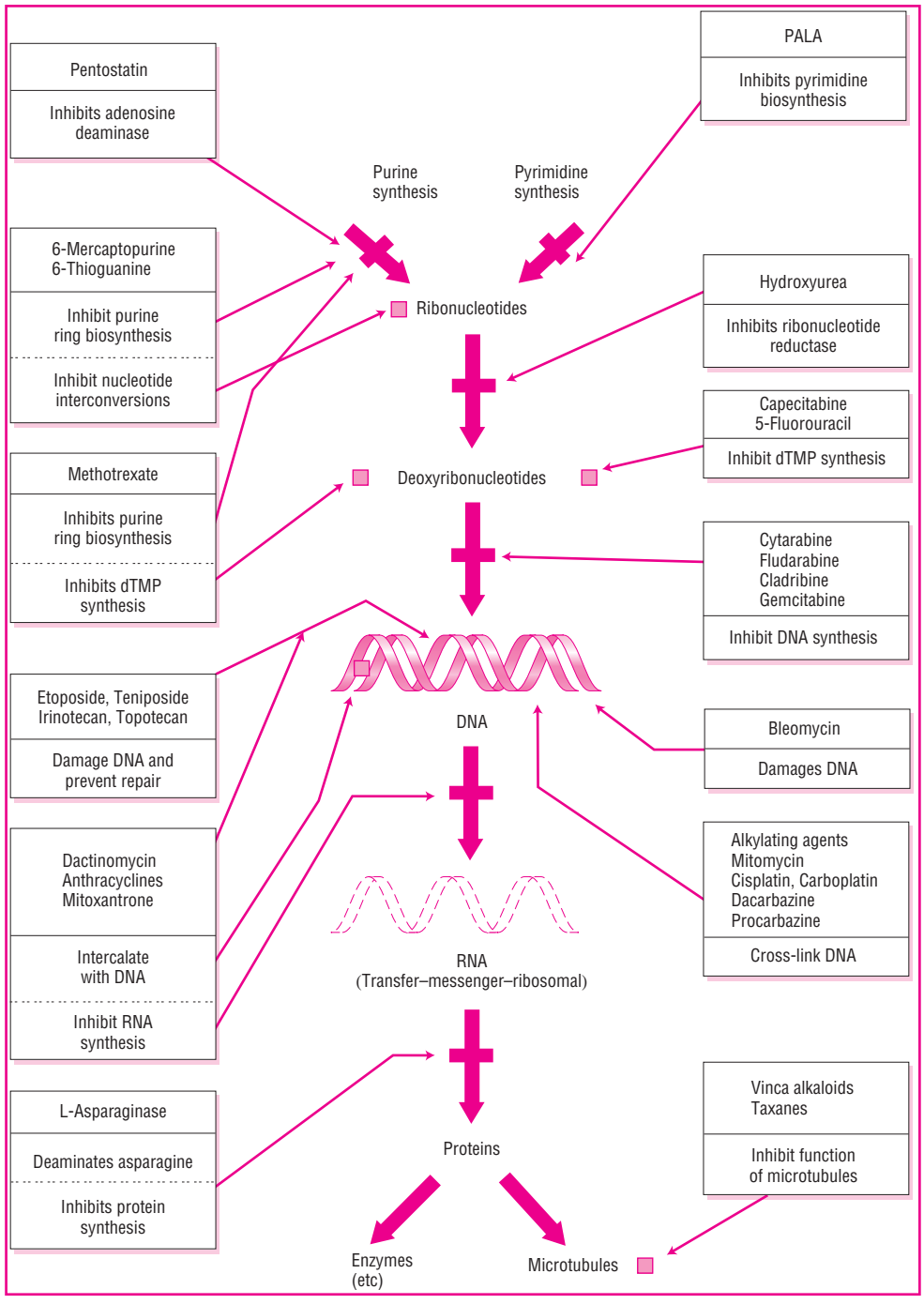


FIGURE 85–3. The mechanisms of action of antineoplastic agents. (From Chabner BA, Ryan DP, Paz-Ares L, et al. Antineoplastic agents. In: Hardman JG, Limbird LE, Gilman AG, (eds.) Goodman & Gilman's The Pharmacologic Basis of Therapeutics. 10th ed. New York: McGraw-Hill; 2001: 1381.)

head and neck cancers. Side effects of 5-FU include stomatitis, diarrhea, cardiac abnormalities, and rarely reported cerebellar toxicities. Esophagitis and gastric ulcerations also may occur. Some alopecia may occur, but hair regrowth may occur with subsequent doses. A recent study demonstrated that if the patient uses ice chips in the mouth for 30 minutes while receiving bolus 5-FU, **mucositis** may be decreased significantly. Neurotoxicity may consist of headaches, visual disturbances and cerebellar ataxia. Cardiac toxicity may consist of ST-segment elevation, which appears to be more common in patients with a prior history of coronary artery disease.

Capecitabine

Capecitabine is the prodrug of 5-FU and comes as oral tablets that are administered with food twice a day. Capecitabine has shown to be active in tumors of the colon, rectum, and breast. The toxicity profile of capecitabine is similar to that of 5-FU and includes diarrhea, mucositis, palmar-plantar erythrodysesthesia,

nausea, and **myelosuppression.** *Palmar-plantar erythrodyesthesia* refers to redness, itching, and blistering of the palms of the hands and soles of the feet. Patients should be educated to notify the prescriber when palmar-plantar erythrodyesthesia occurs. Significant increases in international normalization ratio (INR) and prothrombin time may occur within several days when capecitabine is started in patients who are on warfarin, and the INR should be monitored closely, or the patient may be switched to a low-molecular-weight heparin. Phenytoin levels may become elevated owing to possible CYP2C9 inhibition by capecitabine. Patients should be instructed to take capecitabine within 30 minutes of a meal.

Cytarabine

Cytarabine, often referred to as *Ara-C*, is an analog of cytosine and is phosphorylated intracellularly to the active triphosphate form, which inhibits DNA polymerase. The triphosphate form also may be incorporated into DNA to result in chain termination to prevent DNA elongation. The drug may be administered as a low-dose continuous infusion, high-dose intermittent infusion, and into the subdural space via intrathecal or intraventricular adminstration. There is also a liposomal formulation available for less frequent administration into the CNS. Cytarabine pharmacokinetics are best described by a two-compartment model, with an α half-life of 15 minutes and a β half-life of 2 hours. Cytarabine is eliminated by the kidney with a renal clearance of 90 mL/minute. Cytarabine has shown efficacy in the treatment of acute leukemias and some lymphomas. The toxicities of cytarabine include myelosuppression, cerebellar syndrome (i.e., nystagmus, dysarthria, and ataxia), and eye irritation with high doses that requires around-the-clock steroid eye drop administration. The risk of CNS toxicity is increased with the high-dose cytarabine regimen with renal dysfunction.

Gemcitabine

Gemcitabine is a deoxycytidine analog that is structurally related to cytarabine. Gemcitabine inhibits DNA polymerase activity and ribonucleotide reductase to result in DNA chain elongation. The pharmacokinetics of gemcitabine are best described by a two-compartment model, with a terminal half-life of 6 to 20 minutes. Approximately 5% of the dose is excreted unchanged by the kidney.[6] Gemcitabine has shown activity in cancers of the pancreas, breast, lung, ovary, and lung (non-small cell), along with some lymphomas. The toxicities include myelosuppression, flulike syndrome with fevers during the first 24 hours after administration, rash that appears 48 to 72 hours after administration, and hemolytic-uremic syndrome. While hemolytic-uremic syndrome is uncommon, it is a life-threatening side effect. Patients should be counseled about using acetaminophen to treat the fevers during the first 24 hours; however, fevers occurring 7 to 10 days after gemcitabine are likely to be febrile neutropenias and need prompt treatment with broad-spectrum antibiotics.

Azacitidine

Azacitidine, a cytidine analog, causes hypomethylation of DNA, which normalizes the function of genes that control cell differentiation to promote normal cell maturation. The suspension is administered as a subcutaneous injection daily for 7 days for the treatment of myelodysplastic syndrome, a preleukemia disease. The pharmacokinetics of azacitidine are best described by a two-compartment model, with a terminal half life of 3.4 to 6.2 hours, whereas peak concentrations are achieved 30 minutes after a subcutaneous injection.[7] Azacitidine has been shown to be clinically active in the treatment of myelodysplastic syndromes. The side effects include myelosuppression, renal tubular acidosis, renal dysfunction, and injection-site reactions.

Purines and Purine Antimetabolites

6-Mercaptopurine

6-Mercaptopurine (6-MP) is an oral purine analog that is converted to a ribonucleotide to inhibit purine synthesis. Mercaptopurine is converted into thiopurine nucleotides, which are catabolized by thiopurine *S*-methyltransferase (TPMT), which is subject to genetic polymorphisms and may cause severe myelosuppression. TPMT status may be assessed prior to therapy to reduce drug-induced morbidity and the costs of hospitalizations for neutropenic events. Mercaptopurine is poorly absorbed, with a time to peak concentration of 1 to 2 hours after an oral dose. The half-life is 21 minutes in pediatric patients and 47 minutes in adults. Mercaptopurine is used in the treatment of acute lymphocytic leukemia and chronic myelogenous leukemia. Significant side effects include myelosuppression, mild nausea, skin rash, and cholestasis. When allopurinol is used in combination with 6-MP, the dose of 6-MP must be reduced by 66% to 75% of the usual dose because allopurinol blocks the metabolism of 6-MP.

6-Thiogaunine

6-thioguanine (6-TG) is another oral purine analog that works similarly to 6-MP, and because of this, cross-resistance is observed. While little is known about the pharmacokinetics of thioguanine, it appears that absorption is incomplete and approximates 30% of the dose. Thioguanine may be used in the treatment of acute and chronic myelogneous leukemia. Side effects include myelosuppression, mild nausea, cholestasis, and rarely, veno-occlusive disease.

Fludarabine

Fludarabine is an analog of the purine adenine. It interferes with DNA polymerase to cause chain termination and inhibits transcription by its incorporation into RNA. Fludarabine is dephosphorylated rapidly and converted to 2-fluoro-Ara-AMP (2-FLAA), which enters the cells and is phosphorylated to 2-fluoro-Ara-ATP, which is cytotoxic. Fludarabine is converted rapidly to 2-FLAA. The pharmacokinetics of 2-FLAA

are best described by a two-compartment model, with an α half-life of 0.6 hours and a terminal half-life of 9.3 hours.[8] Fludarabine is used in the treatment of chronic lymphocytic leukemia, some lymphomas, and refractory acute myelogenous leukemia. This drug is given intravenously usually daily for 5 days every 4 weeks. Significant myelosuppression may occur, along with immunosuppression, so patients are susceptible to opportunistic infections. Mild nausea and vomiting and diarrhea have been observed. Rarely, interstitial pneumonitis has occurred.

Cladribine

Cladribine (2-chlorodeoxyadenosine, or 2-CDA) is a purine nucleoside that once it is in the triphosphate form is incorporated into DNA, which results in inhibition of DNA synthesis and chain termination. The pharmacokinetics of cladribine are best described by a two-compartment model, with an α half-life of 35 minutes and a terminal half-life of 6.7 hours.[9] It may be administered as a continuous 7-day intravenous infusion or as a 2-hour infusion daily for 5 days; both regimens deliver the same total dose of drug. Cladribine is used to treat hairy cell leukemia and, therefore, is myelosuppressive. Unfortunately, one of the other side effects of the drug is fever, so the clinician struggles with the dilemma of whether the fever is due to the drug or an infection. Rash occurs in approximately 50% of patients with hairy cell leukemia. Cladribine also may be used to treat chronic lymphocytic leukemia, refractory low-grade non-Hodgkin's lymphoma, and Waldenström's macroglobulinemia.

Antifolates

Folates carry one-carbon groups in transfer reactions required for purine and thymidylic acid synthesis. Dihydrofolate reductase is the enzyme responsible for supplying reduced folates intracellularly for thymidylate and purine synthesis.

Methotrexate

Methotrexate inhibits dihydrofolate reductase of both malignant and nonmalignant cells. When high doses of methotrexate are given, leucovorin, a reduced folate, is administered to bypass the methotrexate inhibition of dihydrofolate reductase of normal cells and is usually initiated 24 hours after methotrexate administration. For safety purposes, the term *folinic acid*, another term used for leucovorin, should not be used because of medication errors where folic acid was given instead. Methotrexate concentrations should be monitored to determine when to stop leucovorin administration. Generally, leucovorin administration may be stopped when methotrexate concentrations decrease to 5×10^{-8} M, although this may vary by the chemotherapy regimen. High dosages of methotrexate may cause methotrexate to crystallize out in the kidney, which may result in renal dysfunction and decreased methotrexate clearance. Intravenous hydration with sodium bicarbonate to maintain urinary pH greater than or equal to 7 helps to prevent methotrexate-induced renal dysfunction. The pharmacokinetics of methotrexate are best described by either a two- or three-compartment model. The α half-life is less than 1 hour, whereas the β half-life is 3 to 4 hours, and the γ half-life is 8 to 10 hours or longer with impaired kidney function. Approximately 60% to 100% of methotrexate is eliminated primarily as unchanged drug by the kidney. Since methotrexate is eliminated by tubular secretion, concomitant drugs that may inhibit or compete for tubular secretion should be avoided. Methotrexate doses must be adjusted for renal dysfunction. A recommended dosing adjustment is to divide the creatinine clearance of the patient by 70 mL/minute, which is the average creatinine clearance of patients who received methotrexate during clinical trials, and then to multiple this fraction by the dosage recommended for that disease state. Again, close monitoring of methotrexate concentrations in patients with renal impairment is advised. Methotrexate has shown activity in lymphoma, gastric, esophageal, bladder, and breast cancer and acute lymphocytic leukemia. Side effects of methotrexate include myelosuppression, nausea and vomiting, and mucositis. Methotrexate also may be administered via the intrathecal route at very low doses. Since methotrexate may be administered in doses as small as 12 mg intrathecally to 20 g intraveneously, it is crucial for the clinician to know the correct dose by the correct route in order to avoid substantial toxicity. Methotrexate also is administered as an intrathecal injection into the cerebrospinal fluid or directly into the ventricle via an Ommaya reservoir. The methotrexate used for intrathecal and intraventricular injection must be preservative-free. Drugs that may block the tubular secretion of methotrexate include probenecid, salicylates, penicillin G, and ketoprofen.

Pemetrexed

Pemetrexed inhibits at least three pathways in thymidine and purine synthesis. Pemetrexed is excreted primarly as unchanged drug by the kidney, with 70% to 90% of a dose recovered in 24 hours as unchanged drug in the urine. Patients with normal kidney function have a half-life of 3.5 hours.[10] Pemetrexed has shown activity in the treatment of mesothelioma and non–small cell lung cancer. Side effects include myelosuppression, rash, diarrhea, and nausea and vomiting. Patients should receive folic acid and cyanocobalamin to reduce bone marrow toxicity and diarrhea. Doses of folic acid of at least 400 mcg/day starting 5 days before treatment and continuing throughout therapy, as well as for 21 days after the last pemetrexed dose, have been used. Cyanocobalamin 1000 mcg intramuscularly is given the week prior to pemetrexed and then every three cycles thereafter. Dexamethasone 4 mg twice daily the day before, the day of, and the day after pemetrexed administration helps to decrease the incidence and severity of rash.

Tubulin Active Agents

The periwinkle, or vinca plant, served as a source for the drugs vincristine and vinblastine, which are commonly referred to as the *vinca alkaloids*. The vinca alkaloids inhibit the assembly

of microtubules, which interferes in the formation of the mitotic spindle. Care must be taken not to confuse the names and doses of vincristine and vinblastine.

Vincristine

Vincristine causes mitotic inhibition to arrest cells in metaphase. The pharmacokinetics of vincristine have been described by a three-compartment model, with an α half-life of 0.8 minutes, a β half-life of 7 minutes, and a γ half-life of 164 minutes.[11] Biliary excretion accounts for a significant portion of elimination of vincristine and its metabolites, so doses need to be adjusted for obstructive liver disease. Vincristine has been useful in the treatment of sarcomas, Wilms' tumor, many kinds of lymphoma, multiple myeloma, and acute lymphocytic leukemia. Vincristine is a **vesicant** that may cause significant neuropathy. Patients should be counseled regarding prevention of constipation and ileus caused by vincristine. Many clinicians cap intravenous vincristine doses at 2 mg to prevent severe neuropathic side effects. Several patients have died as a result of vincristine being administered intrathecally; it should only be administered intravenously, and appropriate labeling should be placed on all doses. Itraconazole has been reported to cause severe neurotoxicity when administered to patients receiving vincristine. Patients have been reported to experience paralytic ileus, neurogenic bladder, absence of deep reflexes, and severe paralysis of the lower extremeties within 10 days of starting itraconazole. Clinicians need to be aware of the potential interactions of the newer azoles with vincristine.

Vinblastine

Vinblastine is another vesicant vinca alkaloid that causes myelosuppression and less neurotoxicity than vincristine. The pharmacokinetics of vinblastine are best described by a three-compartment model, with an α half-life of 25 minutes, a β half-life of 53 minutes, and a terminal half-life of 19 to 25 hours.[12] Vinblastine has shown activity in the treatment of bladder, breast, and kidney cancer, as well as some lymphomas. The doses of vinblastine tend to be higher on a milligram per meter squared basis than vincristine. Nausea and vomiting are minimal with vinblastine. Other side effects include mild alopecia, rash, photosensitivity, and stomatitis.

Vinorelbine

The vesicant vinorelbine is structurally similar to vincristine and may cause many of the same side effects as vincristine. While this vesicant is administered intravenously over 6 to 10 minutes, patients should be counseled about neuropathy, ileus, and myelosuppression. The pharmacokinetics of vinorelbine are best described by a three-compartment model, with an α half-life of 2 to 6 minutes, a β half-life of 1.9 hours, and a γ half-life of 40 hours. Vinorelbine has shown efficacy in the treatment of breast cancer and non–small cell lung cancer. Additional side effects include myelosuppression, paresthesias, and mild nausea and vomiting.

Paclitaxel

Paclitaxel, a taxane, binds to tubulin to promote microtubule assembly and to prevent microtubule disassembly. The pharmacokinetics of paclitaxel can be described by a two-compartment model, with an α half-life of 30 to 45 minutes and a β half-life of 4 to 8 hours. Hepatic metabolism and biliary excretion account for the majority of paclitaxel's elimination. Paclitaxel has demonstrated activity in ovarian, breast, non–small cell lung, prostate, esophageal, gastric, and head and neck cancers. Considerable variability exists in paclitaxel dosing, from weekly 1-hour infusions to 24-hour infusions administered every 3 weeks. The diluent for paclitaxel, Cremophor EL, is composed of ethanol and castor oil. Infusions must be prepared and administered in non-PVC-containing bags and tubings, and solutions must be filtered. Patients receive dexamethasone, diphenhydramine, and an H_2 blocker to prevent hypersensitivity reactions from paclitaxel/Cremophor EL. Patients also may have asymptomatic bradycardia (i.e., heart rates around 45 beats per minute) during the infusion. Approximately 3 to 5 days after administration, patients may complain of myalgias and arthralgias that may last several days. Myelosuppression, flushing, neuropathy, ileus, and total-body alopecia are other common side effects. Since paclitaxel is a substrate for CYP 3A4, steady-state concentrations of paclitaxel were 30% lower in patients receiving phenytoin than in patients not receiving phenytoin. Paclitaxel clearance was decreased by 33% when it was administered following cisplatin, so paclitaxel is administered before cisplatin.

Recently, a nanoparticle albumin-bound paclitaxel product became available commercially for the treatment of metastatic breast cancer. This product does not have the serious allergic reactions encountered with paclitaxel in Cremophor EL, so premedication with H_1 and H_2 blockers and steroids is not necessary. The dose is infused over 30 minutes and does not require a special IV bag, tubing, or filter. The dosing of this product is different from that of the original paclitaxel, so practitioners need to be aware of which product is being prescribed. The pharmacokinetics of the albumin-bound paclitaxel display a higher clearance and larger volume of distribution than paclitaxel. The drug is eliminated primarily via fecal excretion.[13] The side effects of bone marrow suppression, neuropathy, ileus, arthralgias, and myalgias still occur.

Docetaxel

Docetaxel, another taxane, binds to tubulin to promote microtubule assembly. The pharmacokinetics of docetaxel are best described by a three-compartment model, with an α half-life of 0.08 hours, a β half-life of 1.6 to 1.8 hours, and a terminal half-life of 65 to 73 hours.[14] Docetaxel has activity in the treatment of breast, non–small cell lung, prostate, bladder, esophageal, stomach, ovary, and head and neck cancers. Dexamethasone, 8 mg twice daily for 3 days starting the day before treatment, is used to prevent the fluid retention syndrome associated with docetaxel and possible hypersensitivity reactions. The fluid

retention syndrome is characterized by edema and weight gain that is unresponsive to diuretic therapy and is associated with cumulative doses greater than 800 mg/m^2. Myelosuppression, alopecia, and neuropathy are other side effects associated with docetaxel treatment.

Estramustine

Estramustine, an oral drug, also inhibits microtubule assembly and has weak estrogenic activity at the estradiol hormone receptors of the cell. Approximately 75% of a dose of estramustine is absorbed.[15] The terminal half-life ranges between 20 to 24 hours, with nonrenal excretion as the major route of elimination. This drug is used primarily for the treatment of prostate cancer, but its use is limited by the side effects, which include nausea and vomiting, diarrhea, thromboembolic events, and gynecomastia.

Topoisomerase Inhibitors

Topoisomerase is responsible for relieving the pressure on the DNA structure during unwinding by producing strand breaks. Topoisomerase I produces single-strand breaks, whereas topoisomerase II produces double-strand breaks.

Etoposide

Etoposide causes multiple DNA double-strand breaks by inhibiting topoisomerase II. The pharmacokinetics of etoposide are described by a two-compartment model, with an α half-life of 0.5 to 1 hour and a β half-life of 3.4 to 8.3 hours. Approximately 30% of the dose is excreted unchanged by the kidney.[16] Etoposide has shown activity in the treatment of several types of lymphoma, testicular and lung cancer, retinoblastoma, and carcinoma of unknown primary. The intravenous preparation has limited stability, so final concentrations should be 0.4 mg/mL. Intravenous administration needs to be slow to prevent hypotension. Oral bioavailability is approximately 50%, so oral dosages are approximate two times those of intravenous doses; however, relatively low oral daily dosages are used for 1 to 2 weeks. Side effects include mucositis, myelosuppression, alopecia, phlebitis, hypersensitivity reactions, and secondary leukemias.

Teniposide

Teniposide, a topoisomerase II inhibitor, is administered as an infusion over 30 to 60 minutes to prevent hypotension. The pharmacokinetics are described by a three-compartment model, with an α half-life of 0.75 hours, a β half-life of 4 hours, and a terminal half-life of 20 hours. Considerable variability in clearance of teniposide in children has been reported.[17] Teniposide has shown activity in the treatment of acute lymphocytic leukemia, neuroblastoma, and non-Hodgkin's lymphoma. Side effects include myelosuppression, nausea, vomiting, mucositis, and venous irritation. Hypersensitivity reactions may be life-threatening.

Irinotecan

Irinotecan, a camptothecin analog, inhibits topoisomerase I to interfere with DNA synthesis through the active metabolite SN38, which is 100-fold more potent in vitro. The pharmacokinetics of irinotecan are best described by a three-compartment model, with an α half-life of 0.07 hours, a β half-life of 2.2 hours, and a terminal half-life of about 18 hours.[18] Irinotecan has shown activity in the treatment of cancers of the colon, rectum, cervix, and lung. Diarrhea owing to irinotecan may be life-threatening. Intravenous atropine should be used to treat diarrhea that occurs during the first 24 hours of administration. Loperamide 2 mg every 2 hours or 4 mg every 4 hours until diarrhea has stopped for 12 hours should be used for diarrhea occurring more than 24 hours after administration. Other side effects include myelosuppression, fatigue, and alopecia. Individuals homozygous for *UGT1A1*28* have an increased risk of febrile neutropenia and diarrhea and should be considered for an upfront dose reduction of one level; and heterozygotes should receive closer monitoring.

Topotecan

Topotecan inhibits topoisomerase I to cause single-strand breaks in DNA. The pharmacokinetics of topotecan can be described by a two-compartment model, with a terminal half-life of 80 to 180 minutes, with renal clearance accounting for approximately 70% of the clearance.[19] Topotecan has shown clinical activity in the treatment of ovarian and lung cancer, myelodysplastic syndromes, and acute myelogenous leukemia. The intravenous infusion may be daily for 5 days or once weekly. Side effects include myelosuppression, mucositis, and diarrhea.

Anthracyclines

All the anthracyclines contain a four-membered anthracene ring, a chromophore, with an attached sugar portion. Free radicals formed from the anthracyclines combine with oxygen to form superoxide, which can make hydrogen peroxide. Oxygen free-radical formation is a cause of cardiac damage and extravasation injury, which is common to these drugs. Daunorubicin, doxorubicin, epirubicin, and idarubucin cause cardiac toxicity, as manifested by a congestive heart failure/cardiomyopathy symptomotology, mucositis, myelosuppression, and tissue damage with extravasation.

Daunorubicin

Daunorubicin is an anthracycline that is sometimes referred to as an antitumor antibiotic. Daunorubicin inserts between base pairs of DNA to cause structural changes in DNA; however, the primary mechanism of cytotoxicity is the inhibition of topoisomerase II. The pharmacokinetics are best described by a two-compartment model, with a terminal half-life of about 20 hours. The predominant route of elimination of daunorubicin and hydroxylated metabolites is hepatobiliary

secretion. Daunorubicin has shown clinical activity in the treatment of acute lymphocytic leukemia, non-Hodgkin's lymphoma, neuroblastoma, and Ewing's and Kaposi's sarcoma. Myelosuppression is the major toxicity, along with alopecia, stomatitis, and mild to moderate nausea and vomiting, and it imparts a red to color to the urine so that patients need to be educated on side effects. Cardiac toxicity is manifested as congestive heart failure. The maximum cumulative dose in children older than 2 years of age is 300 mg/m^2, and the cumulative dose is 400 to 600 mg/m^2 in adults. Ventricular ejection fractions should be measured before therapy, and periodically if therapy is continued. Therapy should be halted if there is a 10% to 20% decrease from baseline in ejection fraction. Daunorubicin is a vesicant also.

Doxorubicin

The addition of a hydroxyl group to daunorubicin, resulted in the drug hydroxydaunorubicin (the H in CHOP therapy), or doxorubicin, which inhibits topoisomerase II. The pharmacokinetics of doxorubicin may be described by either a two- or three-compartment model, with a terminal half-life of 30 to 40 hours. Doxorubicin is metabolized extensively, and doxorubicinol, a major metabolite, is also a cardiotoxin. Biliary excretion accounts for about 40% of a dose; patients with cholestasis experience greater toxicity from standard doses. Doxorubicin has shown clinical activity in breast, esophageal, bladder, lung, ovarian, and head and neck cancers, along with lymphomas and multiple myeloma. This red drug causes a red-orange discoloration of the urine. Cumulative doses greater than 550 mg/m^2 are associated with cardiomyopathy. Doxorubicin is a vesicant and may cause significant pain when administered into the peritoneal cavity. Other side effects include myelosuppression, alopecia, mucositis, and nausea and vomiting.

Doxorubicin, Liposomal

Liposomal doxorubicin is an irritant, not a vesicant, and is dosed differently from doxorubicin, so clinicians need to be very careful when prescribing these two drugs. The pharmacokinetics of liposomal doxorubicin are best described by a two-compartment model, with a terminal half-life of 30 to 90 hours.[20] Liposomal doxorubicin has shown significant activity in the treatment of breast and ovarian cancer, along with multiple myeloma and Kaposi's sarcoma. Side effects include mucositis, myelosuppression, alopecia, and palmar-plantar erythrodysesthesia. The liposomal doxorubicin may be less cardiotoxic than doxorubicin.

Epirubicin

Epirubicin inhibits both DNA and RNA polymerases and thus inhibits nucleic acid synthesis and topoisomerase II enzymes. Epirubicin pharmacokinetics are best described by a three-compartment model, with an α half-life of 4 to 5 minutes, a β half-life of 2.4 hours, and a terminal half-life of 30 hours. Dosage alterations should be made in the presence of cholestasis because approximately 35% of a dose undergoes biliary excretion.[21] Epirubicin has shown clinical activity in the treatment of breast, esophageal, lung, ovary, and stomach cancers. Epirubicin also has been used in the treatment of lymphomas and soft tissue sarcomas. Cumulative doses of epirubicin greater than 900 mg/m^2 are associated with cardiomyopathy, so this drug may be less cardiotoxic on a milligram per milligram basis than doxorubicin. This topoisomerase II inhibitor may cause red-orange urine, myelosuppression, alopecia, and significant nausea and vomiting.

Idarubicin

Idarubicin inhibits both DNA and RNA polymerase, as well as topoisomerase II. The pharmacokinetics of idarubicin can best be described by a three-compartment model, with an α half-life of 13 minutes, a β half-life of 2.4 hours, and a terminal half-life of 16 hours.[22] Idarubicin is metabolized to an active metabolite, idarubicinol, which has a half-life of 41 to 69 hours. Idarubicin and idarubicinol are eliminated by the liver and through the bile. Idarubicin has shown clinical activity in the treatment of acute leukemias, chronic myelogenous leukemia, and myelodysplastic syndromes. Idarubicin causes cardiomyopathy at cumulative doses of greater than 150 mg/m^2 and produces cumulative cardiotoxic effects with other anthracyclines. Idarubicin is a vesicant and causes red-orange urine, mucositis, mild to moderate nausea and vomiting, and bone marrow suppression.

Mitoxantrone

This royal-blue-colored drug is an anthracenedione that inhibits DNA topoisomerase II. The pharmacokinetics of mitoxantrone may best be described by a three-compartment model, with an α half-life of 3 to 10 minutes, a β half life of 0.3 to 3 hours, and a median terminal half-life of 12 days. Biliary elimination appears to be the primary route of elimination, with less than 10% of the drug eliminated by the kidney.[23] Mitoxantrone has shown clinical activity in the treatment of acute leukemias, breast and prostate cancer, and non-Hodgkin's lymphomas. Myelosuppression, mucositis, nausea and vomiting, and cardiac toxicity are side effects of this drug. The total cumulative dose limit is 160 mg/m^2 for patients who have not received prior anthracycline or mediastinal radiation. Patients who have received prior doxorubicin or daunorubicin therapy should not receive a cumulative dose greater than 120 mg/m^2 of mitoxantrone. Patients should be counseled that their urine will turn a blue-green color.

Alkylating Agents

The alkylating drugs are the oldest category of chemotherapy agents. Globally, cytoxocity results from inhibition of DNA replication because interlinked strands do not separate.

Busulfan

Busulfan is an alkylating agent that forms DNA-DNA and DNA-protein cross-links to inhibit DNA replication. Oral busulfan is well absorbed, has a terminal half-life of 2 to 2.5 hours, and is eliminated primarily by metabolism. Busulfan has shown significant clinical activity in the treatment of acute myelogneous leukemia and chronic myelocytic leukemia. Side effects include bone marrow suppression, hyperpigmentation of skin creases, and rarely, pulmonary fibrosis. High doses used for bone marrow transplant preparatory regimens result in severe nausea and vomiting, tonic-clonic seizures, and sinusoidal obstruction syndrome (formerly known as *veno-occlusive disease*). Patients receiving high-dose busulfan should receive anticonvulsant prophylaxis.

Cyclophosphamide

Cyclophosphamide prevents cell division by cross-linking DNA strands. Cyclophophosphamide is activated to phosphoramide mustard and acrolein. Acrolein, which has no tumor activity, causes hemorrhagic cystitis of the bladder. The pharmacokinetics of cyclophosphamide are best described by a two-compartment model, with a terminal half-life that ranges from 4 to 10 hours. Approximately 15% of the dose is excreted unchanged by the kidney. Cyclophosphamide has shown clinical activity in numerous types of cancer, ranging from leukemias to lymphomas to breast and ovarian cancer. Whether the drug is administered orally or intravenously, patients need to be counseled on the importance of good hydration and frequent voiding to prevent hemorrhagic cystitis. Nausea and vomiting may occur 12 hours after administration, so patients need to have antiemetics available after the acute treatment period. Other side effects include myelosuppression, alopecia, SIADH (usually with doses greater than 50 mg/kg), secondary malignancies (e.g., bladder cancers and acute leukemias), and infertility issues.

Ifosfamide

Hemorrhagic cystitis is such a predominant side effect of the alkylator ifosfamide that mesna always must be given with ifosfamide, along with hydration. Dosing regimens of mesna range from an equal milligram dose to the ifosfamide mixed in the same intravenous bag to 20% of the dose prior to ifosfamide and 20% of the dose repeated at 4 and 8 hours after the dose. The pharmacokinetics of ifosfamide are best described by a one-compartment model, with a terminal half-life of 7 to 15 hours. Approximately 50% of a dose is excreted unchanged by the kidney. Ifosfamide has shown clinical activity in the treatment of acute lymphocytic leukemia, lymphomas, and breast, ovary, lung, and head and neck cancers. CNS side effects of confusion, delirium, and somnolence are associated with high doses infused quickly.

Carmustine

Carmustine, a nitrosurea, cross-links DNA strands to inhibit DNA replication. Carmustine, which is reconstituted with ethanol, crosses the blood-brain barrier when given intravenously. It also comes as a wafer formulation that may be implanted surgically for brain tumors. The pharmacokinetics are best described by a two-compartment model, with an α half-life of 6 minutes and a terminal half-life of 21 minutes.[24] Carmustine has shown clinical activity in the treatment of lymphoma, melanoma, and brain tumors. Side effects include myelosuppression, severe nausea and vomiting, and pulmonary fibrosis with long-term therapy.

Lomustine

Lomustine is an orally available nitrosurea alkylating agent. Lomustine is converted rapidly to the *cis*- and *trans*-4-hydroxy metabolites; the range of half-lives of these two metabolites is 2 to 4 hours.[25] Lomustine has shown clinical activity in the treatment of Hodgkin's lymphoma and melanoma. Side effects are similar to those of carmustine. Patients should receive only enough drug for one cycle at a time to prevent confusion and accidental overdose.

Dacarbazine

While the exact mechanism of action remains unclear, dacarbazine appears to inhibit DNA, RNA, and protein synthesis. Dacarbazine disappears rapidly from the plasma, with a terminal half-life of about 40 minutes. Dacarbazine has shown clinical benefit in the treatment of melanoma, Hodgkin's lymphoma, and soft tissue sarcomas. Side effects include myelosuppression, severe nausea and vomiting, and a flulike syndrome that starts about 7 days after treatment and lasts 1 to 3 weeks.

Temozolomide

Temozolomide is an orally active agent with the same mechanism of action as dacarbazine. It is well absorbed and crosses the blood-brain barrier. Temozolamide is converted enzymatically to the active metabolite 5-(3-methyltriazeno)-imidazole-4-carboxamide. Temozolamide has a terminal half-life of 1.8 hours, with a mean time to peak concentrations of 1.4 hours, and a small amount of the drug is excreted unchanged by the kidney.[26] The active metabolite has a terminal half-life of 1.5 hours and is metabolized primarily. Temozolamide may be used in the treatment of melanoma, refractory anaplastic astrocytoma, and glioblastoma multiforme. Nausea may be minimized by dosing the drug at bedtime. Since patients receiving temozolomide may have confusion secondary to their brain tumor, and because dosing can consist of multiple capsule sizes, care must be taken by all providers to simplify regimens to prevent chemotherapy overdose.

Procarbazine

While the exact mechanism of action of procarbazine is unknown, it does inhibit DNA, RNA, and protein synthesis. The pharmacokinetics have never been fully characterized, but it is known that the drug is metabolized extensively. Procarbazine is used most often in the treatment of lymphoma.

Myelosuppression is the major side effect. Nausea, vomiting, and a flulike syndrome occur initially with therapy. Patients must be counseled to avoid tyramine-rich foods because procarbazine is a monoamine oxidase inhibitor. Patients should be provided a list of foods and beverages to avoid to prevent a hypertensive crisis. A disulfiramlike reaction can occur with the ingestion of alcohol.

Thiotepa

Thiotepa is an alkylating agent that reacts with DNA phosphate groups to produce chromosomal cross-linkage. The pharmacokinetics of thiotepa are best described by a two-compartment model, with an α half-life of 6 to 24 minutes and a terminal half-life of 78 to 160 minutes. Thiotepa has shown clinical activity in the treatment of breast, bladder, and ovarian cancer, along with carcinomatous meningitis and malignant effusions, and usually is administered intravenously or as an intravesicular infusion. It also may be used intrathecally. Side effects include myelosuppression, nausea and vomiting, and venous irritation.

Heavy-Metal Compounds

Platinum drugs form reactive platinum complexes that bind to cells, so the pharmacokinetics of the individual drug may be of the platinum, both free and bound, rather than of the parent drug.

Cisplatin

Cisplatin forms inter- and intrastrand DNA cross-links to inhibit DNA synthesis. The pharmacokinetics are best described by a three-compartment model, with an α half-life of 20 minutes, a β half-life of 48 to 70 minutes, and a terminal half-life of 24 hours. Ninety percent of the drug is removed by the kidney by glomerular filtration and tubular secretion. Cisplatin has shown clinical activity in the treatment of numerous tumor types, from head and neck cancers to anal cancer, including many types of lymphoma and carcinoma of unknown primary. Cisplatin is highly emetogenic, even when low doses are given daily for 5 days, and causes delayed nausea and vomiting as well; patients require aggressive antiemetic regimens for both delayed and acute emesis. Significant nephrotoxicity and electrolyte abnormalities can occur if inadequate hydration occurs. Ototoxicity, which manifests as a high-frequency hearing loss, and a glove-and-stocking neuropathy may limit therapy.

Carboplatin

While carboplatin has the same mechanism of action as cisplatin, it has a much less toxic side-effect profile than cisplatin. The pharmacokinetics of carboplatin are best described by a two-compartment model, with an α half-life of 90 minutes and a terminal half-life of 180 minutes. Carboplatin is eliminated almost entirely by the kidney by glomerular filtration and tubular secretion. Many chemotherapy regimens dose carboplatin based on an area under the curve (*AUC*), which is referred to as the *Calvert equation*. According to the Calvert equation, the dose in milligrams = (CrCl + 25) $\times$ *AUC* desired.[27] Carboplatin has shown clinical activity in the treatment of ovarian, lung, breast, testicular, esophageal, and head and neck cancers, as well as lymphomas. Thrombocytopenia, nausea and vomiting, and hypersensitivity reactions are side effects.

Oxaliplatin

The pharmacokinetics of oxaliplatin are best described by a three-compartment model, with an α half-life of 0.28 hours, a β half-life of 16.3 hours, and a terminal half-life of 273 hours.[28] Oxaliplatin has shown clinical activity in the treatment of colorectal cancer. Oxaliplatin, while similar in action to cisplatin and carboplatin, causes a cold-induced neuropathy. Patients should be counseled to avoid cold beverages, to use gloves to remove items from the freezer, and to wear protective clothing in cold climates for the first week after treatment. A glove-and-stocking neuropathy also occur with long-term dosing. Hypersensitivity reactions and moderate nausea and vomiting are also side effects.

Miscellaneous Agents

Altretamine

Altretamine, formerly known as *hexamethylmelamine*, is similar in structure to alkylating agents but is known to have anticancer activity in cancer cells resistant to alkylating agents. Altretamine is well absorbed after oral administration and undergoes rapid and extensive demethylation in the liver. Peak plasma concentrations were observed 0.5 to 3 hours after administration. The terminal half-life is 4.7 to 10.2 hours.



Patient Encounter 1

AB is a 40-year-old white woman who went to urgent care because she hasn't been feeling well for a couple of days and has a fever. Her white blood cell (WBC) count results are greater than 100×10^9/L (100×10^3/μL) with greater than 85% blast cells, which is indicative of acute leukemia. AB is admitted directly to the hospital to start chemotherapy.

The oncologist prescribes the normal doses of idarubicin 12 mg/m^2 IV daily for 3 days and cytarabine 100 mg/m^2 per day by continuous infusion for 7 days to treat her acute myelogenous leukemia. Her baseline laboratory measurements are significant for an elevated WBC count, a creatinine concentration of 2.5 mg/dL (221 μmol/L), and a bilirubin level of 1.6 mg/dL (27 μmol/L).

- Should her chemotherapy dosages be adjusted? If so, how would you adjust the dosages?
- What should be monitored while she is receiving her chemotherapy?

Altretamine has shown activity in the treatment of ovarian and lung cancer. This orally administered drug has the dose-limiting side effects of anorexia, nausea, vomiting, diarrhea, and abdominal cramping. Other side effects include neuropathy, agitation, confusion, and depression.

Bleomycin

Bleomycin is a mixture of peptides with drug activity expressed in units, where 1 unit equals 1 mg. Bleomcyin causes DNA strand breakage. The pharmacokinetics of bleomycin are best described by a two-compartment model, where the α half-life is 10 to 20 minutes and a terminal elimination half-life of 2 to 3 hours, which can be prolonged to 21 hours in patients with renal impairment.[29] Bleomycin has shown clinical activity in the treatment of testicular cancer and malignant effusions, squamous cell carcinomas of the skin, and Kaposi's sarcoma. Hypersensitivity reactions and fever may occur, so premedication with acetaminophen may be required. The most serious side effect is the pulmonary toxicity that presents as a pneumonitis with a dry cough, dyspnea, rales, and infiltrates. Pulmonary function studies will show decreased carbon monoxide diffusing capacity and restrictive ventilatory changes. "Bleomycin lung" is associated with cumulative dosing greater than 400 units and occurs rarely with a total dose of 150 units. The pulmonary toxicity is potentiated by thoracic radiation and by hyperoxia. Additional side effects include fever with or without chills, mild to moderate alopecia, and nausea and vomiting. Bleomycin has been used to manage malignant effusions at doses of 15 to 60 units through installation into the affected area. The drainage tube of the effusion is clamped off for some period of time after administration of the bleomycin (time varies based on the location of the effusion), and then the amount of drainage is monitored to determine efficacy of the bleomycin treatment.

Hydroxyurea

Hydroxyurea is an oral drug that inhibits ribonucleotide reductase, which converts ribonucleotides into the deoxyribuoncleotides used in DNA synthesis and repair. The time to peak concentrations of hydroxyurea is 1 to 2 hours after oral administration. Approximately 50% is degraded by the liver to form urea and respiratory carbon dioxide. The remainder is excreted by the kidney. The half-life ranges from 3.5 to 4.5 hours. Hydroxyurea has shown clinical activity in the treatment of chronic myelocytic leukemia, polycythemia vera, and thrombocytosis. The major side effects are myelosuppression, nausea and vomiting, diarrhea, and constipation. Rash, mucositis, and renal tubular dysfunction occur rarely.

L-Asparaginase

L-Asparaginase is an enzyme that may be produced by *Escherichia coli*. Asparaginase hydrolyzes the reaction of asparagines to aspartic acid and ammonia to deplete lymphoid cells of asparagine, which inhibits protein synthesis. The pharmacokinetics of L-asparaginase are best described by a two-compartment model, with an initial half-life of 4 to 9 hours and a terminal half-life of 1.4 to 1.8 days. L-Asparaginase has shown clinical activity in the treatment of acute lymphocytic leukemia and childhood acute myeloid leukemia. Severe allergic reactions may occur when the interval between doses is 7 days or greater, so while a skin test may be negative, patients should be observed closely after asparaginase administration. Pancreatitis and fibrinogen depletion also may occur during therapy. Repletion of fibrinogen should be done to prevent disseminated intravascular coagulation and fatal bleeding. If the patient suffers an allergic reaction to L-asparaginase, pegaspargase, which is L-asparaginase modified through a linkage with polyethylene glycol, which extends the half-life and allows for lower doses and less frequent administration, may be given. Cost and limited availability are the reasons why pegaspargase is not used first.

Arsenic Trioxide

Arsenic trioxide, which was approved recently for the treatment of acute promyelocytic leukemia, induces the growth of cancer cells into mature, more normal cells, as well as induces programmed cell death, or apoptosis. The pharmacokinetics of arsenic trioxide are best described by a two-compartment model, with an α half-life of 0.89 hours and a β half-life of 12.1 hours. Less than 10% of a dose is excreted by the kidney.[30] Arsenic trioxide causes QT-interval prolongation, so daily electrocardiograms (ECGs) need to be done prior to each dose, and other drugs that may prolong the QT interval need to be avoided during therapy. Other side effects include dry skin with itching, nausea and vomiting, loss of appetite, and elevations of serum hepatic enzymes.

Mitomycin C

Mitomycin C is an alkylating agent that forms cross-links with DNA to inhibit DNA and RNA synthesis. The pharmacokinetics of mitomycin C are best described by a two-compartment model, with an α half-life of 8 minutes and a terminal half-life of 48 minutes.[31] Liver metabolism is the primary route of elimination. Mitomycin C has shown clinical activity in the treatment of anal, bladder, cervix, gallbladder, esophageal, and stomach cancer. Side effects consist of myelosuppression and mucositis, and it is a vesicant.

Tretinoin

Tretinoin, also referred to *ATRA*, which stands for all-trans-retinoic acid, is a retinoic acid that is not cytotoxic but promotes the maturation of early promyelocytic cells and is specific to the t(15;17) cytogenetic marker. The time to peak concentrations is 1 to 2 hours after an oral dose. The elimination half-life is 21 to 51 minutes.[32] These maroon-and-gold capsules are dosed at 45 mg/m^2 per day divided into two doses. The most significant side effect is the retinoic acid syndrome, which may occur anywhere from the first couple of days of therapy until the end of therapy and consists of symptoms of

fever, respiratory distress, and hypotension. Chest radiographs are consistent with a pneumonia-like process. The syndrome can be confused easily with pneumonia in a patient with possible neutropenia. The treatment for retinoic acid syndrome is dexamethasone 10 mg intravenously every 12 hours; the syndrome may resolve within 24 hours of the start of dexamethasone therapy. However, the use of steroids in a febrile neutropenic patient may further compromise the treatment of infection.

Thalidomide

Thalidomide was introduced into the market on October 1, 1957, as a sedative-hypnotic, and when it was taken by pregnant women, it resulted in severe limb deformities (phocomelia). Thalidomide is used for the treatment of leprosy but now is part of the treatment of multiple myeloma. While thalidomide is believed to be an angiogenesis inhibitor, the mechanism of action is still unknown. Possible mechanisms of action include free-radical oxidative damage to DNA, inhibiting tumor necrosis factor α production, altering the adhesion of cancer cells, and altering cytokines that affect the growth of cancer cells. The pharmacokinetics of thalidomide demonstrate a time to peak concentration of 2 to 3 hours and a terminal half-life of 4 to 7 hours.[30] Thalidomide has shown clinical activity in the treatment of multiple myeloma and is still being studied for the treatment of several other cancers. Because of thalidomide's potential to cause phocomelia, each patient must be counseled on the risks of thalidomide not only for the patient but also the patient's reproductive partner. Physicians must be registered to prescribe thalidomide. Pharmacists can fill prescriptions only where both the patient and the physician have completed surveys on a monthly basis.

Lenalidomide

Lenalidomide was approved recently for the indication of myelodysplastic syndrome where the 5q deletion is present. Since lenalidomide is an analog of thalidomide, all the same precautions must be taken to prevent phocomelia. The time to maximum lenalidomide concentrations occurs 0.5 to 4 hours after the dose. The terminal half-life ranges from 3 to 9 hours. Approximately 65% of lenalidomide is eliminated unchanged in the urine, with clearance exceeding the glomerular filtration rate. To date, no pharmacokinetic studies have been done in patients with renal dysfunction. Lenalidomide is used in the treatment of myelodysplastic syndrome and multiple myeloma. Other side effects are neutropenia, thrombocytopenia, deep vein thrombosis, and pulmonary embolus.

Immune Therapies

Interferons

The categories of α, β, and γ interferons exist; the α interferons are used in the treatment of cancer. Interferon enhances the immune system's attack on cancer cells, can decrease new blood vessel formation, and can augment expression of antigen on tumor cell surfaces. Interferon has an elimination half-life of 3.7 to 8.5 hours. Interferon is filtered through the glomeruli and then degraded during tubular reabsorption. Interferon has shown clinical activity in the treatment of melanoma, kidney cancer, Kaposi's sarcoma, and chronic myelocytic and lymphocytic leukemia. Unfortunately, interferon is not well tolerated by patients because it causes a flulike syndrome that consists of fevers and chills; depression, malaise, and fatigue are other side effects. Premedication with acetaminophen will help alleviate the flulike symptoms, which will decrease with chronic administration.

Aldesleukin

Aldesleukin, commonly referred to as *interleukin 2*, is a lymphokine that promotes B- and T-cell proliferation and triggers a cytokine cascade to attack the tumor. The pharmacokinetics are best described by a two-compartment model, with an α half-life of 13 minutes and a terminal half-life of 85 minutes. Aldesleukin is eliminated by both glomerular filatration and peritubular extraction in the kidney. Aldesleukin has shown clinical activity in the treatment of kidney cancer and melanoma. Side effects of interleukin 2 vary by dose and route. Intravenous high-dose interleukin 2 causes a drug-induced shock-like picture. Patients may develop hypotension despite aggressive intravenous hydration. Patients develop a red, itching skin; liver and kidney function tests change; fluid and electrolyte imbalances occur; and high fevers occur while receiving scheduled acetaminophen and nonsteroidal anti-inflammatory agents. Severe rigors and chills may require intravenous meperidine for symptom control. All the side effects reverse within 24 hours of stopping the drug. The toxicity profile is much less with subcutaneous administration. However, with subcutaneous administration, little nodules form at the injection site and may take months to resolve. Corticosteroids should not be administered to patients while receiving aldesleukin unless a life-threatening emergency should occur. Steroids will reverse all the symptoms and the antitumor effect, even with topical administration. The itching, red skin may be treated with topical creams and antihistamines.

Denileukin Diftitox

Denileukin diftitox is a combination of the active sections of interleukin 2 and diphtheria toxin. It binds to high-affinity interleukin 2 receptors on the cancer cell (and other cells), and the toxin portion of the molecule inhibits protein synthesis to result in cell death. The pharmacokinetics of denileukin diftitox are best described by a two-compartment model, with an α half-life of 2 to 5 minutes and a terminal half-life of 70 to 80 minutes. Denileukin diftitox is used for the treatment of persistent or recurrent cutaneous T-cell lymphoma whose cells express the CD25 receptor. Side effects include vascular leak syndrome, fevers/chills, hypersensitivity reactions, hypotension, anorexia, diarrhea, and nausea and vomiting.

TABLE 85–4. Syllable Source Indicators for Monoclonal Antibodies

U	Human
O	Mouse
A	Rat
E	hamster
I	primate
Xi	A cross between humanized and an animal source

Here, mab stands for monoclonal antibody. These letters appear before -mab. Programme on International Nonproprietary Names (INN) Division of Drug Management and Policies, World Health Organization, Geneva. 1997. Web address: whalibdoc.who.int/hg/1997/WHO_Pharm_S_NOM_1570.pdf

Monoclonal Antibodies

The cell surface contains antigens, which are referred to as *CD*, which stands for "cluster of differentiation." The antibodies are produced against a specific antigen. When administered, usually by an intravenous injection, the antibody binds to the antigen, which may trigger the immune system to result in cell death through complement-mediated cellular toxicity, or the antigen-antibody cell complex may be internalized to the cancer cell, which results in cell death. Monoclonal antibodies also may carry radioactivity, sometimes referred to as *hot antibodies*, and may be referred to as *radioimmunotherapy*, so the radioactivity is delivered to the cancer cell. Antibodies that contain no radioactivity are referred to as *cold antibodies*.

All monoclonal antibodies end in the suffix *-mab*. The syllable before *-mab* indicates the source of the monoclonal antibody (see Table 85–4). When administering an antibody for the first time, one should consider the source. The less humanized an antibody, the greater is the chance for the patient to have an allergic-type reaction to the antibody. The more humanized the antibody, the lower is the risk of a reaction. The severity of the reactions may range from fever and chills to life-threatening allergic reactions (which have resulted in death). Premedication with acetaminophen and diphenhydramine is common before the first dose of any antibody. If a severe reaction occurs, the infusion should be stopped and the patient treated with antihistamines, corticosteroids, or other supportive measures.

Alemtuzumab

Alemtuzumab is the antibody to the CD52 receptor present on B and T lymphocytes. The pharmacokinetics of alemtuzumab demonstrate a terminal half-life of 7 days. Alemtuzumab has shown clinical activity in the treatment of chronic lymphocytic leukemia. Severe and prolonged (6 months) immunosuppression may result, which necessitates prophylaxis with cotrimoxazole and antivirals to prevent opportunistic infections.

Bevacizumab

Bevacizumab is a humanized monoclonal antibody that binds to vascular endothelial growth factor, which prevents it from binding to its receptors, ultimately resulting in angiogenesis. The pharmacokinetics of bevacizumab demonstrate a terminal half-life of 21 days, with a volume of distribution consistent with limited extravascular distribution.[34] Bevacizumab has shown clinical activity in the treatment of colorectal, kidney, lung, breast, and head and neck cancer. Patients may develop hypertension requiring chronic medication during therapy. Impaired wound healing, thrombolembolic events, proteinuria, bleeding, and perforation are serious side effects.

Cetuximab

Cetuximab is a human/mouse antibody that binds to the epidermal growth factor receptor to block its stimulation. The pharmacokinetics of cetuximab demonstrate a volume of distribution that approximates the vascular space and a terminal half-life of 70 to 100 hours. Cetuximab has shown clinical activity in the treatment of colorectal cancer. An acnelike rash may appear on the face and upper torso 1 to 3 weeks after the start of therapy. Other side effects include hypersensitivity reactions, interstitial lung disease, fever, malaise, diarrhea, abdominal pain, and nausea and vomiting.

Gemtuzumab Ozogamicin

Gemtuzumab ozogamicin is a humanized antibody to the CD33 receptor present on about 80% of acute myelogenous leukemia cells. The antibody is linked to calicheamicin, a cellular toxin that is released intracellularly after the antigen-antibody complex is internalized. The pharmacokinetics of gemtuzumab ozogamicin show a terminal half-life of 67 to 78 hours of the antibody portion of the drug and a terminal half-life of about 45 hours of the calicheamicin.[35] Gemtuzumab ozogamicin has shown clinical activity in the treatment of acute myeloid leukemia. Severe rigors and chills, which may occur after the infusion is completed, respond to meperidine intravenously. Premedications should include acetaminophen, diphenhydramine, and methylprednisolone to prevent rigors and chills.

Ibrotumomab Tiuxetan

This "hot antibody" is linked to yttrium and binds to the CD20 receptor of B lymphocytes (see "Rituximab" below). Hematologic toxicity may occur several weeks after administration and may take weeks to resolve.

Rituximab

Rituximab is a monoclonal antibody to the CD20 receptor expressed on the surface of B lymphocytes; the presence of the antibody is determined during flow cytometry of the tumor cells. Cell death results from antibody-dependent cellular cytotoxicity. The pharmacokinetics of rituximab are best described by a two-compartment model, with a terminal half-life of 76 hours after the first infusion and a terminal half-life of 205 hours after the fourth dose.[36] Rituximab has shown clinical activity in the treatment of B-cell lymphomas that are CD20+. Side effects include hypersensitivity reactions, hypotension, fevers, chills, rash, headache, and mild nausea and vomiting.

Tositumomab

This "hot antibody" is linked to radioactive iodine and binds to the CD20 receptor present on B lymphocytes (see "Rituximab" above). Tositumomab has shown activity in non-Hodgkin's lymphoma. Hematologic toxicity occurs several weeks after administration and may persist for months. Since radioactive iodine may have adverse effects on the thyroid, all patients must receive thyroid-blocking agents.

Trastuzumab

Trastuzumab is the antibody directed against human epidermal receptor 2 (HER2), which is overexpressed by 25% to 30% of breast cancers and is associated with aggressive disease and decreased survival. Breast cancer tissue must be tested for the presence of HER2. The pharmacokinetics of trastuzumab are best described by a two-compartment model, with a terminal half-life of 19 to 28 days.[34] Severe congestive heart failure may occur with concurrent anthracycline administration. Cardiac toxicity may be seen when the drug is administered months after anthracycline administration, so patients must be counseled on the signs and symptoms of heart failure. Other side effects include hypersensitivity reactions, fever, diarrhea, infections, chills, cough, headache, rash, and insomnia.

Tyrosine Kinase Inhibitors

There are more than 100 different types of tyrosine kinases present in the body. Sometimes tyrosine kinase inhibitors are referred to as small-molecule inhibitors. Each of the following drugs was developed to block either several or a specific tyrosine kinase.

Imatinib

Imatinib was the first FDA-approved tyrosine kinase inhibitor. The drug was designed to block the breakpoint cluster region tyrosine kinase (BCR:ABL) produced by the Philadelphia chromosome associated with chronic myelogenous leukemia and acute lymphocytic leukemia. The pharmacokinetics of imatinib demonstrate a mean time to maximum concentration of 2 to 4 hours, with a terminal half-life of 15 hours.[37] Imatinib also has shown activity against gastrointestinal stroma tumors (GIST). Numerous drug interactions have been reported for imatinib. CYP450 3A4 inducers, such as rifampicin and St. John's wort, increase the clearance of imatinib.[39,40] Ketoconazole, a CYP450 3A4 inhibitor, has been shown to decrease imatinib clearance by almost 30%.[41] Imatinib also may increase the exposure of simvastatin, a CYP450 3A4 substrate.[42]

Erlotinib

Erlotinib, whose pharmacology is not entirely understood, is believed to inhibit the intracellular phosphorylation of the epidermal growth factor receptor. Erlotonib is about 60% absorbed after oral administration; food increases bioavailability to almost 100%. The time to peak concentrations is approximately 4 hours after a dose. The half-life of erlotinib is about 36 hours, and it is eliminated predominately by CYP450 3A4. Smoking increases the clearance of erlotinib by 24%, which may result in treatment failure.[43] Erlotinib is used in the treatment of non–small cell lung cancer and cancer of the pancreas. Side effects include interstitial lung disease, rash, diarrhea, anorexia, pruritus, conjunctivitis, and drug skin. Again, significant drug interactions have been documented with CYP450 3A4 inducers and inhibitors.

Sorafenib

Sorafenib is a multikinase inhibitor that inhibits both intracellular and extracellular kinases to decrease renal cell cancer proliferation. The half-life of sorafenib is 25 to 48 hours, with a bioavailability of 38% to 49% and a time to peak concentration of 3 hours. Sorafenib is metabolized primarily by the liver by CYP450 3A4. Sorafenib is used for the treatment of renal cell cancer. The primary side effects of sorafenib include rash, hand-foot skin reaction, diarrhea, pruritus, and elevations in serum lipase.

Sunitinib

Sunitinib blocks several tyrosine kinases, so it inhibits platelet-derived growth factor, vascular endothelial growth factor receptor, stem cell factor receptor, fms-like receptor growth factor, colony-stimulating growth factor receptor type 1, and glial-cell-line-derived neurotrophic factor receptor. The active metabolite of sunitinib blocks these same enzymes with similar potency. The pharmacokinetics of sunitinib demonstrate a time of peak concentration of about 5 hours, with a half-life of 41 to 86 hours.[44] It is indicated for the treatment of gastrointestinal stromal tumors (GISTs) after disease progression or intolerance to imatinib. It is also indicated for the treatment of advanced renal cell cancer. Significant side effects include left ventricular dysfunction, hemorrhage, asthenia, hypertension, nausea and vomiting, and diarrhea. Approximately one-third of patients may develop a yellow color of the skin, along with dryness and cracking of the skin. Also, hair may become depigmented with doses of 50 mg/day or more, and the depigmentation is reversible when therapy is stopped. Clinically significant drug interactions exist with drugs metabolized via the CYP450 3A4 system; ketoconazole has been shown to increase concentrations of sunitinib, whereas rifampin has been shown to decrease concentrations of sunitinib.

Hormonal Therapies

Hormonal therapies have shown activity in the treatment of cancers whose growth is affected by gonadal hormonal control. Hormonal treatments either block or decrease the production of endogenous hormones.

Antiandrogens: Bicalutamide, Flutamide, and Nilutamide

The antiandrogens block androgen receptors to inhibit the action of testosterone and dihydrotestosterone in prostate

cancer cells. Unfortunately, prostate cancer cells may become hormone refractory.

Flutamide is an androgen receptor antagonist that achieves peak concentrations approximately 2 to 4 hours after an oral dose. Flutamide is metabolized extensively, with a terminal half-life of about 8 hours. Bicalutamide achieves peak concentrations approximately 6 hours after the dose, with a terminal half-life of 6 to 10 days. Bicalutamide undergoes stereospecific metabolism, where the *S*-enantiomer is cleared more rapidly by the liver than the *R*-enantiomer. Nilutamide achieves peak serum concentrations between 1 to 4 hours after an oral dose and has a terminal half-life of 38 to 60 hours. Nilutamide is metabolized extensively, with less than 2% excreted as unchanged drug by the kidney. Side effects common to these agents are hot flashes, gynecomastia, and decreased libido. Flutamide tends to be associated with more diarrhea and requires three-times-daily administration, whereas bicalutamide is dosed once daily. Nilutamide may cause interstitial pneumonia and is associated with the visual disturbance of delayed adaptation to darkness.

Luteinizing Hormone–Releasing Hormone (LHRH) Agonists: Goserelin and Leuprolide

Initially, LHRH agonists increase levels of leutinizing hormone and follicle-stimulating hormone, but testosterone and estrogen levels are decreased because of continuous negative-feedback inhibition. Major side effects are testicular atrophy, decreased libido, gynecomastia, and hot flashes. Leuprolide is well absorbed, with a terminal half-life of 2.9 hours, whereas goserelin has a terminal half-life of 4.9 hours. Goserelin is injected as a pellet under the skin, so subcutaneous injection of lidocaine prior to administration helps to decrease the pain associated with goserelin administration. Numerous dosage forms are available for leuprolide with varying strengths and dosing intervals. Antiandrogens may be administered during initial therapy to decrease symptoms of tumor flare (e.g., bone pain and urinary tract obstruction).

Ketoconazole

While ketoconazole is an antifungal agent, it has been used for treatment of prostate cancer. In high doses of 400 mg three times daily, ketoconazole blocks the production of testosterone.

LHRH Antagonist: Abarelix

Abarelix is a gonadotropin-releasing hormone antagonist that is associated with life-threatening hypersensitivity reactions. Patients must be observed for 30 minutes after administration. The drug is limited to men who cannot risk tumor flare and refuse orchiectomy.

Aminoglutethimide

Aminoglutethimide blocks the conversion of androgens to estrogens and decreases the synthesis of glucocorticoids. Adrenocorticoid suppression may occur, so replacement therapy with hydrocortisone may be required. Other side effects include rash (which usually resolves in 5–8 days), lethargy, and anorexia.

Anastrozole

Anastrozole is a selective nonsteroidal aromatase inhibitor that lowers estrogen levels. The pharmacokinetics of anastrozole demonstrate good absorption, with hepatic metabolism the primary route of elimination and only 10% excreted unchanged by the kidney. The elimination half-life is approximately 50 hours. Anastrozole is used for the adjuvant treatment of postmenopausal women with hormone-positive breast cancer and in breast cancer patients who have had disease progression following tamoxifen. Side effects include hot flashes, arthralgias, osteoporosis/bone fractures, and thrombophlebitis.

Exemestane

Exemestane is an irreversible aromatase inactivator that binds to the aromatase enzyme to block the production of estrogen from androgens. Exemestane is absorbed rapidly after oral administration, with a terminal half-life of 24 hours. The drug is eliminated primarily by the liver and feces, with less than 1% of the dose excreted unchanged in the urine. Exemestane is indicated for the treatment of advanced breast cancer in postmenopausal women who have had disease progression following tamoxifen therapy. Side effects include hot flashes, fatigue, osteoporosis/bone fractures, and flulike symptoms.

Fulvestrant

Fulvestrant is an estrogen receptor antagonist that binds to the estrogen receptor and is given as a monthly intramuscular injection. Fulvestrant has a terminal half-life of 40 days and a large volume of distribution of 3 to 5 L/kg. Fulvestrant is metabolized primarily, with excretion primarily via feces. Fulvestrant is used for the treatment of hormone-receptor-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. Side effects are hot flashes, abdominal pain, depression, and myalgias.

Letrozole

Letrozole is another selective aromatase that inhibits the conversion of androgens to estrogen. Maximum plasma concentrations occur 1 hour after oral dosing; concomitant food has not been shown to have an effect on the extent of absorption of letrazole. The terminal half-life is approximately 2 days. Letrozole is used in the treatment of postmenopausal women with hormone-receptor-positive or unknown advanced breast cancer. Side effects include bone pain, hot flushes, back pain, nausea, arthralgia, osteoporosis/bone fractures, and dyspnea.

Megestrol Acetate

Megestrol is a synthetic progestin with antiestrogen properties that is used for breast cancer and in higher doses for weight

gain. Side effects include fluid retention, hot flashes, vaginal bleeding and spotting, breast tenderness, and thrombosis.

Tamoxifen

Tamoxifen is an estrogen receptor antagonist. Most of a dose of tamoxifen is eliminated primarily by metabolism, with significant enterohepatic recirculation. The time to a peak concentration is 6 hours after an oral dose, and the terminal half-life is 7 days. Tamoxifen is used primarily for the treatment of postmenopausal hormone-receptor-positive breast cancer patients and the prevention of breast cancer in postmenopausal women. Side effects include hot flashes, fluid retention, mood swings, thrombosis, endometrial and uterine cancer, and corneal changes and cataracts. Since tamoxifen is a substrate of CYP450 3A4, decreased tamoxifen levels have occurred with use of St. John's wort, and decreased tamoxifen levels have observed with use of rifampin. Tamoxifen is also a substrate for CYP450 2D6, and recent evidence suggests that those who are *CYP2D6*4/*4* may have a poorer response and more toxicity with tamoxifen.

Toremifene

Toremifene is an estrogen receptor antagonist. The pharmacokinetics of toremifene are best described by a two-compartment model, with an α half-life of 4 hours and an elimination half-life of 5 days. Peak plasma concentrations are achieved approximately 3 hours after an oral dose. Toremifene is metabolized extensively, with metabolites found primarily in the feces. Toremifene is used for the treatment of metastatic breast cancer in postmenopausal women with estrogen-receptor-positive or unknown tumors. Toremifene causes hot flashes, vaginal bleeding, thromboembolism, and visual acuity changes.

Supportive Care

Many of the older chemotherapy treatments of cancer cause severe, even life-threatening toxicities. Toxicities range from nausea and vomiting, pain, myelosuppression, mucositis, decreased nutrition, and alopecia to secondary malignancies from the treatments themselves. This section will focus on the side-effect management of myelosuppression, mucositis, and secondary malignancies. While not a direct toxicity of chemotherapy, medication safety in oncology is of the utmost importance owing to the life-threatening side effects that can occur with inappropriate dosing.

Myelosuppression

Myelosuppression is one of the most common dose-limiting side effects of cancer drugs that cause myelosuppression. Myelosuppression may occur several days to several weeks after treatment and varies with the chemotherapy drugs used. WBCs, in particular, neutrophils, are the first cell line that is decreased because of their rapid proliferation and short life span of 6 to 12 hours. Platelets, with a life span of 9 to 11 days are the next cell line affected by myelosuppressive therapy. The last cell line to be affected by myelosuppressive therapy is red blood cells (RBCs), which have a life span of approximately 120 days. After the first dose of chemotherapy, subsequent doses may need to be held until WBC recovery so that the patient is not at an increased risk of infection. If WBC counts are persistently low owing to numerous myelosuppressive chemotherapy treatments, chemotherapy doses will need to be decreased to prevent febrile neutropenia for palliative chemotherapy regimens, or hematopoietic growth factors will need to be administered in order to deliver full doses of chemotherapy for cancers that are curable.

Neutropenia occurs when the percent of mature neutrophils plus the percent of bands (or immature neutrophils) times the WBC count is less than 500/mm^3 (0.5×10^9/L). The risk of infection increases as the extent of neutropenia becomes severe and the duration increases. The assessment of infection is different in the neutropenic cancer patient. First, WBC counts may be profoundly low, so no left shift is available to evaluate. Second, there is no pus without WBCs. Some bacterial pneumonias may not be readily apparent by chest x-ray. Third, if patients are receiving steroids as part of the cancer treatment, fever curves may be blunted or absent. When a patient does have a fever and is neutropenic, prompt initiation of anti-infectives is necessary.

The colony-stimulating factors sargramostim, filgrastim, and pegfilgrastim are growth factors that shorten the duration and decrease the magnitude of neutropenia by stimulating the production of neutrophils. These drugs usually are administered by subcutaneous injection starting at least 24 hours after the end of chemotherapy and are continued until a WBC count of 2000 to 10,000/mm^3 ($2–10 \times 10^9$/L) is obtained. Pegfilgrastim is the pegylated version of filgrastim that allows a single injection to replace 10 to 14 daily injections of filgrastim or sargramostim. The agents tend to be well tolerated, with the main side effect being bone pain that usually can be relieved with acetaminophen. These agents are relatively expensive, so evidence-based guidelines have been established by the American Society of Clinical Oncology and are updated every few years.[45] These drugs may be used for primary prevention where the incidence of febrile neutropenia with the chemotherapy is approximately 20% and no other equally effective and less myelosuppresive regimen is available or for secondary prevention where the patient already has experienced febrile neutropenia with the previous cycle of chemotherapy. The colony-stimulating growth factors also may be used to stimulate stem cell production, which later can be used for a bone marrow transplant. Colony-stimulating factors have been used in other diseases such as AIDS, congenital neutropenia, and aplastic anemia.

Thrombocytopenia is another dose-limiting side effect of chemotherapy. The primary treatment for thrombocytopenia is platelet transfusions. The risk of bleeding is significant when platelet counts are less than 10,000/mm^3 (10×10^9/L);



Patient Encounter 2

JP is receiving a highly myelosuppressive chemotherapy regimen for the next 3 days for his lymphoma. The chemotherapy orders specify ifosfamide, carboplatin, and etoposide. The goal of this cycle of chemotherapy is to put the cancer into remission so that his lymphoma can be cured with a bone marrow transplant.

- What drug is missing from his ifosfamide orders?
- What instructions should the patient receive about ifosfamide?
- Should JP receive a growth factor after chemotherapy?

the risk of fatal intracranial bleeding occurs when platelet counts are less than 1000 to 2000/mm^3 (1–2 × 10^9/L). Oprelvekin, sometimes referred to as *interleukin 11* (interleukin 11 should be avoided because medication errors have been made with dispensing interleukin 2 instead), is indicated for thrombocytopenia that has occurred after the first cycle of chemotherapy. Unfortunately, oprelvekin has the significant side effect of fluid retention and edema. It also is relatively expensive, and it comes as a powder that has short drug stability when reconstituted, which makes it difficult for home administration. If a patient has bleeding or severe thrombocytopenia, the preferred treatment is still platelet transfusion.

Anemia is a significant side effect of chemotherapy. Products available for the treatment of anemia of cancer include epoetin-α and darbepoietin. The starting dose of epoetin for oncology-associated anemia ranges from 150 units/kg subcutaneously three times weekly to 40,000 units subcutaneously once weekly. Darbepoietin is an analog of epoetin with a sialic acid content that increases the serum half-life to 33 to 50 hours, which allows weekly to every-3-week administration. Clinical practice guidelines for the use of erythropoietic agents are available from the American Society of Hematology/American Society of Clinical Oncology and the National Comprehensive Cancer Network.[46] Medicare also has reimbursement guidelines for these drugs; each state has similar, albeit somewhat different, criteria for reimbursement in the ambulatory clinic. Adverse effects of these agents are nausea, vomiting, fever, hypertension, and increased risk for thrombotic events.

Mucositis and Diarrhea

The rapidly proliferating cells of the GI tract make them susceptible to the effects of chemotherapy. Mucositis is the inflamed, ulcerated mucosa of the mouth, esophagus, and lower GI tract that may result in infection and pain with subsequent decreased fluid and nutritional intake. Methotrexate, 5-FU, etoposide, and doxorubicin are the chemotherapy agents most commonly associated with mucositis. Patients should be instructed on good oral mouth care and use saline rinses several times a day during therapy to prevent mucositis. Oral cryotherapy has demonstrated benefit when used for 30 minutes around the time of bolus 5-FU administration.[47] Nonsmokers benefited more from cryotherapy than did smokers.

The keratinocyte growth factor palifermin was approved by the FDA for the prevention of mucositis in patients receiving high-dose chemotherapy prior to hematopoietic stem cell transplantation. The usual dose is 60 mcg/kg per day as an intravenous bolus for 3 consecutive days before and 3 days after myelotoxic therapy; total number of doses is six. The median number of days with severe mucositis was 3 for the palifermin group versus 9 for the patients on placebo. There also were significant reductions in the incidence of very severe mucositis, opioid doses, and total parenteral nutrition utilization for the patients who received palifermin. Adverse reactions included rash, pruritus, erythema, and taste disorders.[48]

Once mucositis has occurred, supportive care palliates the symptoms of mucositis. During mucositis, patients need to maintain good oral hygiene (saline rinses). Analgesics, ranging from viscous lidocaine to parenteral morphine, may be used for pain control. The mouth needs to be observed for signs of infection from such organisms as herpes viruses and *Candida* species. Topical antifungal therapy, such as nystatin suspension or clotimazole troches, may be sufficient for milder forms of mucositis, whereas systemic azoles or other antifungals may be necessary for severe oral or esophageal fungal infections.[49]

Diarrhea may occur from effects of chemotherapy on the lower portion of the GI tract. Diarrhea can be severe and may need to be treated with intravenous fluids and electrolytes. Infectious causes, such as *C. difficile*, should be ruled out. Pharmacologic therapy of diarrhea can range from loperamide or cholestyramine to octreotide for severe cases of diarrhea that are refractory to usual treatments.

Extravasation

Another issue of chemotherapy safety is extravasation. Antineoplastic agents that cause severe tissue damage when they escape from the vasculature are called *vesicants*. Some examples of vesicants are the anthracyclines and the vinca alkaloids. The tissue damage may be severe, with tissue sloughing and loss of mobility, depending on the area of extravasation. Patients need to be educated to notify the nurse immediately if there is any pain on administration. If extravasation of a vesicant occurs, the injection should be stopped, and any fluid aspirated out of the injection site. If an antidote should be administered, such as with nitrogen mustard extravasation, the pharmacy should be notified immediately so that the sodium thiosulfate can be prepared and delivered quickly. Cold compresses should be applied (heat should be used for vincas) to the affected area. The area of extravasation should be recorded and inked and followed closely to detect early signs of infection and to treat pain. Obviously, prevention of extravasation is very important. Good intravenous access is key, which may include the placement of a central venous catheter, along with free-flowing intravenous fluids. During

administration of a vesicant, blood return should be checked to be sure that the drug is going into the vein. Central venous catheters can be placed for patients needing infusions of vesicants or for patients with small, friable veins to prevent extravasation.

Alopecia

Alopecia, or hair loss, may be very distressing psychologically to some patients. Alopecia varies by patient and by drug but is reversible after therapy stops. Hair loss may extend to areas other than the scalp. Hair loss usually starts about 2 weeks after chemotherapy, and some hair growth may be apparent before the next chemotherapy treatment. Hair may have a different texture when it does regrow. Patients should be encouraged to wear hats, scarfs, or wigs during this period.

Secondary Malignancies

Chemotherapy and radiation therapy treatments may cause cancers later in life; these are referred to as *secondary cancers*. The most common type of secondary cancer is myelodysplastic syndrome, or acute myeloid leukemia. The antineoplastic agents most commonly associated with secondary malignancies are alkylating agents, etoposide, teniposide, and anthracyclines. While the risk for secondary cancers is extremely low, it must outweigh the risk of survival produced by treatment of the primary malignancy. Since secondary malignancies may not occur for several years after treatment, patients with relatively short-term survival owing to the primary malignancy should consider the more immediate benefits of chemotherapy. Radiation therapy rarely may cause solid tumors as secondary cancers decades after treatment. The most common example of radiation therapy–induced secondary malignancy is breast cancer, which rarely occurs after mantle field radiation therapy for Hodgkin's disease.

Reproduction and Fertility

Females

Cancer patients are surviving longer, and issues of reproduction and fertility are becoming important. Radiation therapy can cause progressive and irreversible damage to the ovary that may result in loss of normal menses. Although women younger than 35 years of age may resume normal menses, the risk of infertility and premature menopause increases as the dosage of radiation increases. Radiation therapy also has an effect on the uterus that is associated with infertility, spontaneous pregnancy loss, and intrauterine growth retardation. However, as long as radiation is not done during pregnancy, the risk of teratogenicity is not increased.

The age of the patient duration of chemotherapy and the dose of chemotherapy are the factors affecting amenorrhea. Alkylating agents tend to have a more profound effect on menses and menopause than other chemotherapy agents. Preliminary evidence suggests that gonadotropin-releasing hormone agonists may create an artificial prepubescent state to protect ovarian function. In a small, retrospective study, no protective benefit was observed in patients receiving oral contraceptives. The risk of teratogenicity from chemotherapy occurs if the pregnancy starts following or during chemotherapy treatment. Limited data with limited follow-up suggest that there are no increases in congenital malformations or preterm labor rates in pregnancies following chemotherapy. A minimum period of 6 months is recommended between the time of last chemotherapy and pregnancy, but this is based on animal data. In vitro fertilization, freezing oocytes, and ovarian cyropreservation are options for females.

Treatment of cancer during pregnancy is a challenging situation. Based on limited information, perinatal problems do not appear at a higher rate as long as teratogens are avoided during pregnancy. Careful review of the literature of the chemotherapy drugs used in pregnancy, in conjunction with the weeks of gestation, will guide the clinician to the appropriate treatment. However, all the nonchemotherapy drugs that are used in the supportive care of the patient need to be reviewed for safety.

Males

Male infertility may result from cancer surgery, radiotherapy, hormonal imbalances, or damage of germinal stem cells. Testicular damage from radiotherapy depends on the treatment field, total dose, and fractionation schedule. Depending on the radiation, sperm counts may return to pretreatment levels in 10 to 24 months after therapy or may be permanent in 80% of men after total-body irradiation for transplant.

High dosages of alkylating agents can cause prolonged azoospermia in greater than 90% of men, whereas platinum drugs can cause it in up to 50% of men. Cyropreservation of semen before treatment starts should be discussed with males at risk for treatment-induced infertility.[52]

CHEMOTHERAPY SAFETY

One of the first Institute of Medicine reports starts out with a patient who died from an overdose of chemotherapy; the patient did not have an immediately life-threatening cancer, so her death was hastened by a medication error. Chemotherapy agents may cause harm to patients, health care workers, and the environment if not handled correctly. ❺ *Because of the severe toxicities associated with many of the chemotherapy agents, safety precautions must be in place to prevent chemotherapy errors, accidental chemotherapy exposures, and overdosages.* The Oncology Nursing Society and the American Society of Health-System Pharmacists have information to assist in the safe handling of chemotherapy agents.[51] National, state, and local regulations regarding the safe disposal of chemotherapy agents and the equipment used to administer them need to be followed to protect the environment.

Each organization should have chemotherapy safety checks built into the prescribing, preparation, and administration of chemotherapy.[50] Dosing based on patient-specific body information should be included on every order for chemotherapy, whether it is oral or parenteral. Many chemotherapy regimens

TABLE 85–5. Dosing Adjustment Guidelines for Chemotherapy for Renal Dysfunction

Drug	Dosing Adjustment
Bleomycin	Creatinine 1.5–2.0 mg/dL (133–177 µmol/L): decrease dose by 50% CrCl less than 20 mL/minute (0.19 mL/s × m^2): decrease dose by 60%
Cladribine	No dosing guidelines
Cytarabine	High dose (greater than 2 g/m^2): Creatinine 1.5–1.9 mg/dL (133–177 µmol/L) or increase of 0.5–1.2 mg/dL (44–106 µmol/L): Decrease dose to 1 g/m^2 Creatinine greater than 1.9 mg/dL (168 µmol/L) or an increase greater than 1.2 mg/dL (106 µmol/L): Decrease dose to 0.1 g/m^2 per day continuous infusion
Etoposide	CrCl 15–50 mL/minute (0.001–4.8 mL/s × m^2): decrease dose by 25%
Carboplatin	Dosing adjustment based on Calvert equation
Cisplatin	Proportional to lower creatinine clearance, where normal equal to 70 mL/minute (0.67 mL/s × m^2)
Methotrexate	Proportional to lowered creatinine clearance, where normal equal to 70 mL/minute (0.67 mL/s × m^2)
Melphalan	If BUN greater than 30 mg/dL (10.7 mmol/L) and creatinine greater than 1.5 mg/dL (132 µmol/L): decrease dose by 50%
Pemetrexed	Greater than or equal to 80 mL/minute (0.77 mL/s × m^2): 600 mg/m^2 40–79 mL/minute (0.38–0.76 mL/s × m^2): 500 mg/m^2
Topotecan	20–39 mL/minute (0.2–37 mL/s × m^2): decrease dose by 50% Less than 20 mL/minute (0.2 mL/s × m^2): not established

From DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy a Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: Table 124–10.

are acronyms; these should not be allowed in the prescribing of chemotherapy. Also, abbreviations for the names of chemotherapy agents should be avoided because one abbreviation may stand for two different drug entities. For drugs such as doxorubicin and liposomal doxorubicin, the names should be written out fully, and in this case, the addition of the brand name may help to prevent a mistake.

The measured height and weight, along with the body surface area, if applicable, should be readily available, along with the dosage in milligrams per meter squared or killigram, so that the dosage may be checked. If a chemotherapy regimen is a continuous infusion of 800 mg/m^2 per day for 4 days, an added safety feature would be to include the total dosage of 3200 mg in order to prevent any ambiguity. In cases where the clinician wants to decrease the dosage based on a laboratory value or side effect, it is recommended that the clinician include that information with the order so that everyone understands what the correct dosage is for that patient.

TABLE 85–6. Dosing Adjustment Guidelines for Chemotherapy for Hepatic Impairment

Drug	Dosing Adjustment
Doxorubicin	Bilirubin greater than 1.5 mg/dL (26 µmol/L), reduce dose by 50%
Daunorubicin	Bilirubin greater than 3.0 mg/dL (51 µmol/L), reduce dose by 75%
Vincristine Vinblastine	
Vinorelbine	Bilirubin greater than 2.0 mg/dL (34 µmol/L), reduce dose by 50% Bilirubin greater than 3.0 mg/dL (51 µmol/L), reduce dose by 75%
Gemcitabine	Bilirubin greater than 1.6 mg/dL (27 µmol/L), reduce dose by 20% Bilirubin greater than 7.5 mg/dL (128 µmol/L), should be avoided
Idarubicin	Bilirubin greater than 5 mg/dL (86 µmol/L): avoid use
Docetaxel	Contraindicated with bilirubin greater than 1.5 × ULN or greater than 1.5 × ULN or transaminases greater than 1.5 × ULN or alkaline phosphatases greater than 2.5 × ULN
Irinotecan	Contraindicated with bilirubin greater than 2 mg/dL (34 µmol/L) or transaminases greater than 3 × ULN (without liver metastases), greater than 5 × ULN (with liver metastases)
Paclitaxel	If transaminase levels less than 10 × ULN and bilirubin 1.5–2.4 mg/dL (26–41 µmol/L): reduce dose by 25% Bilirubin 2.5–7.5 mg/dL (43–128 µmol/L): reduce dose by 50% Bilirubin greater than 7.5 mg/dL (128 µmol/L): not recommended

ULN, upper limit of normal.
From DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy a Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: Table 124–10.



Patient Encounter 3

DQ is a 57-year-old man who came to the emergency room because of shortness of breath. A radiographic examination demonstrates a large mass pressing on the bifurcation of the main stem bronchus. A biopsy demonstrates an aggressive lymphoma; a five-drug chemotherapy regimen with both intravenous and intrathecal chemotherapy will start today.

- What steps should be taken to make sure that DQ gets the correct dosages of chemotherapy?

Chemotherapy dosages should be checked for route and dose to determine that the dosages prescribed are correct according to the regimen and do not exceed dosing guidelines. Appropriate laboratory values should be checked to verify that dosages are correct for any organ dysfunction present, and drug interactions should be scrutinized closely. Health care practitioners administering chemotherapy should check the dosage calculation for the body size, along with the five R's of administering medication (i.e., right patient, right medication, right dose, right route, at the right time). If there is any question about the safe dosage or safe administration of a chemotherapy agent, the chemotherapy should not be administered until the question is resolved.

CANCER PREVENTION

Since most cancers are not curable in advanced stages, cancer prevention is an important avenue of exploration. Both lifestyle modifications and chemoprevention agents ultimately may reduce the risk of developing cancer.

Tobacco

Tobacco smoking increases the risk of developing not only lung cancer but also many other types of cancer, including cancer of the bladder, mouth, pharynx, larynx, and esophagus. While the immediate benefit of smoking cessation is minimal for lung cancer, documented benefit has been observed 6 or more years after stopping.

Sun Exposure

Ultraviolet light and increased skin exposure may increase the risk of skin malignancies, especially in individuals who are fair-skinned. Practitioners can counsel patients to minimize skin exposure to the sun and to use to strong sun screens on exposed areas.

TREATMENT OUTCOMES

Once a pathologic diagnosis of cancer is made, the patient may be evaluated by a radiation oncologist, a surgical oncologist, and a medical oncologist. Options for treatment are presented that may include surgery, radiation, chemotherapy, or some combination of these modalities. The goals of treatment will vary by the cancer and the stage of disease. For example, the patient who has metastatic kidney cancer could be cured by high-dose aldesleukin or receive palliative therapy with sorafenib or sunitinib or may decline any therapy because of fears of significant toxicity that would decrease quality of life. In this case, if the patient's performance status is poor, such as an Eastern Cooperative Oncology Group (ECOG) performance status 3, then the patient would not be a candidate for aldesleukin therapy because of significant toxicity or even death from treatment for a patient who has a performance status of 3. The patient with the poor performance status will receive palliative therapy to control symptoms of the disease to improve the quality of life at the end of life. For the patient with a poor performance status and extensive metastatic disease, no treatment of the cancer may be appropriate, and the patient may be enrolled in a hospice program or provided comfort care.



Patient Care and Monitoring

❻ *Clinicians should play a role in chemotherapy safety, patient education, and monitoring patient response to therapy.*

Chemotherapy Administration

1. Evaluate the chemotherapy regimen to ensure the correct dose and route of administration.
2. Check patient laboratory values to ensure that the complete blood count (CBC) and organ function studies are normal prior to administering chemotherapy.
3. If a patient has renal or hepatic impairment or a poor metabolizer genotype, adjust chemotherapy doses if necessary.
4. Ensure appropriate antiemetic therapy for the degree of emetegenicity.
5. Assess the regimen to determine if primary prophylaxis with colony-stimulating factors is needed.
6. Assess the patient's concurrent medications for the possibility of drug interactions, and discontinue potentially interacting medications, if possible.
7. Employ safe handling and disposal methods.

Monitoring

1. *Efficacy:* Monitor CT scans or other imaging studies, and categorize patient with a complete response (CR), partial response (PR), stable disease (SD), or progressive disease.
2. *Toxicity:*
   - Monitor CBC and other lab tests.
   - Monitor patient for other known toxicities of the chemotherapy regimen, and decrease the dose or discontinue the regimen if necessary.

ABBREVIATIONS

2-CDA: 2-chlorodeoxyadenosine
2-FLAA: 2-fluoro-Ara-AMP
5-FU: fluorouracil
6-MP: 6-mercaptopurine
6-TG: 6-thioguanine
Ara-C: cytarabine
ATRA: all-trans-retinoic acid
CD: cluster of differentiation
DNA: deoxyribonucleic acid
FdUMP: fluorodeoxyuridine monophosphate
IL: interleukin
PCR: polymerase chain reaction
RNA: ribonucleic acid
TNM: tumor, nodes, metastases
TPMT: thiopurine S-methyltransferase

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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86 Breast Cancer

Kristine Hahn and Laura Boehnke Michaud



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. List factors associated with an increased risk of breast cancer in the United States.
2. Assess patients for signs and symptoms related to breast cancer in early and late stages of the disease.
3. List all modalities that are appropriate screening tools for breast cancer and determine how they should best be used in the public domain.
4. Discuss available options for breast cancer prevention.
5. Critique available prognostic variables for clinical utility.
6. Determine which patient populations may benefit from adjuvant systemic therapy for breast cancer.
7. Determine the treatment goals for early-stage, locally advanced, and metastatic breast cancer.
8. Determine appropriate indications for endocrine therapy, chemotherapy, and biologic therapy for patients with metastatic breast cancer.
9. Evaluate available chemotherapy options for patients with metastatic breast cancer based on pertinent patient and disease-state characteristics.
10. Discuss the role of trastuzumab in the management of early- and advanced-stage breast cancer.

Key Concepts

❶ Although controversial, the benefits of annual screening mammography in women younger than 50 years of age are apparent, and a large number of national and international studies demonstrate a 20% to 40% reduction in breast cancer mortality from annual or biannual screening mammography in women aged 50 to 70 years.

❷ Breast cancer is diagnosed most commonly in early stages, when it is a highly curable malignancy.

❸ Local therapy of early-stage breast cancer consists of modified radical mastectomy or lumpectomy plus external-beam radiation therapy. The surgical approach to the ipsilateral axilla may consist of a full level I/II axillary lymph node dissection or a lymph node mapping procedure with sentinel lymph node biopsy.

❹ Adjuvant endocrine therapy reduces the rates of relapse and death in patients with hormone-receptor-positive early breast cancer tumors. Adjuvant chemotherapy reduces the rates of relapse and death in all patients with early-stage breast cancer.

❺ The choices of chemotherapy regimen, dose, schedule, and duration of therapy, as well as the choice of endocrine therapy, are controversial and rapidly changing as results from ongoing randomized clinical trials are reported.

❻ Neoadjuvant chemotherapy is appropriate for patients with locally advanced or inflammatory breast cancer, followed by local therapy and further adjuvant systemic therapy.

❼ The goal of adjuvant chemotherapy is curative, whereas the goal of chemotherapy in the metastatic setting is palliative.

❽ Initial therapy of metastatic breast cancer in women with hormone-receptor-positive tumors should consist of hormonal therapy.

❾ Women with metastatic breast cancer who have hormone-receptor-positive tumors and respond to an initial hormonal manipulation usually will respond to a second hormonal manipulation.

❿ Approximately 50% to 60% of women who have not received prior chemotherapy for metastatic disease will respond to chemotherapy regimens; doxorubicin- and taxane-containing regimens are the most active.

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Although the incidence of breast cancer has been increasing in the United States, the mortality rate has been decreasing over the past two decades. This trend reflects the success of early detection and the development of effective treatment regimens. Treatment for most breast cancer patients includes a combination of pharmacologic and nonpharmacologic therapy.

EPIDEMIOLOGY AND ETIOLOGY

Breast cancer is the most common site of cancer and is second only to lung cancer as a cause of cancer death in American women. It is estimated that 214,640 new cases of breast cancer will be diagnosed and that 41,430 women will die of breast cancer in 2006.[1] Whites account for the largest portion of estimated cases (82%) and deaths (80%). In addition to invasive breast cancers, it is estimated that 61,980 cases of in situ cancer will be diagnosed among women in the United States in 2006. The median age for the diagnosis of breast cancer is between the ages of 60 and 65 years.[2]

Most breast cancers diagnosed are small tumors (less than or equal to 2 cm), and disease is localized in all racial and ethnic groups. However, blacks and other minority women have proportionally more cases of disease diagnosed at more advanced stages compared with white women. This is thought to reflect access to and use of screening mammography and timely treatment.

The etiology of breast cancer is unknown, but a number of factors that increase a woman's chances of developing the disease have been identified. These risk factors, as well as information regarding the biology of the disease, suggest that a complex interplay between hormones, genetic factors, and environmental and lifestyle influences all contribute to the etiology of this disease.

The two variables most strongly associated with the occurrence of breast cancer are gender and age. Although one commonly thinks of breast cancer as a disease confined to women, about 1,720 cases of male breast cancer were projected to be diagnosed in the United States in 2006.[1] When stage and other known prognostic factors are controlled for, men do not fare any differently from their female counterparts and receive similar treatment regimens.

The incidence of breast cancer increases with advancing age. Perhaps the most frequently quoted breast cancer statistic is that one in seven women will develop breast cancer during their lifetime. It should be emphasized that this is a cumulative lifetime risk of developing the disease from birth to age 110 and that the estimates are weighted by the probability of surviving through each decade of life.[3] The one in seven women figure is often misinterpreted by women who assume that it translates into one in seven women being diagnosed with breast cancer each year. Feuer and colleagues developed a more useful method of presenting the risk data based on age intervals.[3] As Table 86–1 demonstrates, the risk of a woman developing breast cancer before the age of 40 years is about 1 in 250. It is apparent from this table that although the cumulative probability of developing breast cancer increases with increasing age, more than half the risk occurs after age 60 years.

TABLE 86–1. Risk of Developing Breast Cancer in SEER Areas, Women, All Races, 1998–2000

Age Interval (years)	Probability (%) of Developing Invasive Breast Cancer During the Interval
30–40	0.40 or 1 in 250
40–50	1.45 or 1 in 69
50–60	2.78 or 1 in 36
60–70	3.81 or 1 in 26
From birth to death	13.51 or 1 in 7

From Ries LAG, Eisner MP, Kosary CL, (eds.) SEER Cancer Statistics Review: 1975–2001. Bethesda, MD, http://seer.cancer.gov/csr/1975–2001/, 2004.

As many as 85% of American women have "lumpy breasts" and may have a clinical diagnosis of fibrocystic breast disease or benign breast disease. Data suggest that benign breast disease or fibrocystic disease is most often not associated with proliferation and that these women are not at an increased risk for developing breast cancer.[4] However, it must be noted that "lumpy breasts" may lead to a delay in diagnosis of breast cancer because of an inability of the patient or physician to detect a true malignant lesion.

Endocrine Factors

A number of endocrine factors have been linked to the incidence of breast cancer.[5,6] Many of these relate to the total duration of menstrual life. Early **menarche** (prior to age 12) and late **menopause** (after age 55) increase a women's breast cancer risk. Similarly, investigators have reported that bilateral **oophorectomy** prior to age 35 reduces the relative risk of developing breast cancer. **Nulliparity** and a late age at first birth (greater than or equal to 30 years) have been reported to increase the lifetime risk of developing breast cancer twofold.

Long-term use of hormone-replacement therapy and concurrent use of progestins appear to contribute to breast cancer risk.[7] The use of postmenopausal estrogen-replacement therapy in women with a history of breast cancer generally is considered contraindicated. However, most experts believe that the safety and benefits of low-dose oral contraceptives currently outweigh the potential risks and that changes in the prescribing practice for the use of oral contraceptives are not warranted. Oral contraceptives are known to reduce the risk of ovarian cancer by about 40% and the risk of endometrial cancer by about 60%.

Genetic Factors

Both personal and family histories influence a woman's risk of developing breast cancer. A past medical history for breast cancer is associated with about a fivefold increased risk of

contralateral breast cancer. Cancer of the uterus and ovary also has been associated with an increased risk of the development of breast cancer.

It has been recognized for some time that a family history of breast cancer is associated rather strongly with a woman's own risk for developing the disease. The percentage of all breast cancers in the population that can be attributed to family history range between 6% and 12%.[8] Empirical estimates of the risks associated with particular patterns of family history of breast cancer indicate the following:[8]

1. Having any first-degree relative with breast cancer increases a woman's risk of breast cancer 1.5- to 3-fold, depending on age.
2. The higher relative risk is associated with breast cancer with onset younger than age 45 years in one or more first-degree relatives.
3. Having multiple first-degree relatives affected has been inconsistently associated with elevated risks.
4. Having a second-degree relative affected increases a woman's risk of developing breast cancer by approximately 50% [relative risk (RR) = 1.5].
5. Affected family members on the maternal side and the paternal side contribute similarly to the risk.

In the early 1990s, the *BRCA1* gene on the long arm of chromosome 17 (17q21) was identified as abnormal in a large percentage of hereditary breast and ovarian cancer patients.[9,10] A second breast cancer gene, called *BRCA2*, has been mapped to chromosome 13. Both genes are tumor suppressors. A woman with a strong family history of breast or ovarian cancer, or both, who carries a germ-line mutation of *BRCA1* faces roughly an 85% lifetime risk of breast cancer and a 60% risk of ovarian cancer.[11] Carriers of the *BRCA2* mutation have similar risks for breast cancer but much lower risks for ovarian cancer. Jewish people of eastern European decent (Ashkenazi Jews) have an unusually high (2.5%) carrier rate of germ-line mutations in *BRCA1* and *BRCA2* compared with the rest of the United States population.

There is a commercially available test for screening that should be done under the guidance of a genetic counselor. To date, there are no clear recommendations for carriers of *BRCA1* and *BRCA2* from high-risk families. **Bilateral** total mastectomy does reduce the risk of breast cancer occurrence; however, both breast and ovarian cancer have been reported in patients who have had prophylactic removal of these organs. In *BRCA* carriers who do not opt for surgical prophylaxis, mammography every 6 months is recommended. Because no effective screening for ovarian cancer exists, most experts recommend bilateral oophorectomy at completion of childbearing.

Environmental and Lifestyle Factors

Experimental and epidemiologic evidence suggests an association between breast cancer and the Western diet (high in calories, fat, and cooked meats). Obesity in postmenopausal women and distribution of body fat around the abdominal region also appear to increase the risk of breast cancer. A recent meta-analysis[12] indicates both a modest positive association between alcohol ingestion and breast cancer and a dose-response relationship. Cigarette smoking and augmentation mammoplasty do not appear to increase the risk of breast cancer. Exercise may provide a modest protection against breast cancer.

Radiation is associated with an increased risk of breast cancer in survivors of the atomic bomb, in patients given radiation for postpartum mastitis, in women receiving multiple fluoroscopic examinations during therapy for tuberculosis, and in patients who receive **mediastinal** radiation for malignancies. Interestingly, this risk appears to be confined to exposure to radiation prior to age 40, which suggests that a "window of initiation" for breast cancer occurs at a relatively early age. Exposure to diagnostic x-rays, including annual screening mammography, does not impart a sufficient dose of radiation for clinical concern.

It should be emphasized that more than 60% of women with breast cancer have no identifiable major risk factor, indicating that the search for the etiology of this disease is largely incomplete.

A number of calculators are available on the Internet to estimate a patient's risk of developing breast cancer. The National Cancer Institute (NCI) has an online version of the Breast Cancer Risk Assessment Tool that is considered to be the most authoritative and accurate standard (www.cancer.gov/ bcrisktool). The Breast Cancer Risk Assessment Tool was designed for health professionals to project a women's individualized risk for invasive breast cancer over a 5-year period and over her lifetime.



Patient Encounter, Part 1

BB is a 65-year-old woman who presents with a history of a small, hard lump in the upper outer quadrant of her right breast. This lump has been there for at least 3 months. She reports having mammograms in the past that were normal, but she has not had one in about 3 years. The lump in her breast is not painful. She has no nipple discharge or drainage from that breast, and the skin appears normal. The left breast is normal. She has a history of hypertension and has been postmenopausal for approximately 10 years. She does not smoke and drinks an occasional glass of wine. She has no family history of breast cancer but does have a sister with ovarian cancer at age 58, and her father had prostate cancer at age 85. She began menses at age 10, had two pregnancies (first at age 25) with two healthy daughters, and has taken Prempro since menopause at age 55 (for 10 years).

- What risk factors for breast cancer does this patient have?

PATHOPHYSIOLOGY

The pathologic evaluation of breast lesions serves to establish the histologic diagnosis and to confirm the presence or absence of other factors believed to influence prognosis. These prognostic factors include the presence of necrosis, lymphatic or vascular invasion, nuclear grade, hormone receptor status, proliferative index, amount of **aneuploidy**, and *HER-2/neu* expression.

Invasive Carcinoma

Invasive breast cancers are a histologically heterogeneous group of lesions. Most breast carcinomas are **adenocarcinomas** and are classified on the basis of their microscopic appearance as either ductal or lobular, corresponding to the ducts and lobules of the normal breast. The various histologic types of breast cancer have different prognoses, but it is unknown whether their response to therapy differs because patients in therapeutic trials typically are not stratified according to histologic type. *Infiltrating lobular carcinoma* commonly metastasizes to **meningeal** and **serosal** surfaces and other unusual sites, whereas other types usually metastasize to the bone, brain, or liver.

Noninvasive Carcinoma

As with invasive carcinoma, the noninvasive lesions may be divided broadly into ductal and lobular categories. The widespread use of screening mammography and subsequent biopsy, coupled with recognition of noninvasive breast carcinoma by pathologists, has resulted in a significant increase in the diagnosis of in situ breast cancer during the past decade. A detailed discussion of the biology and appropriate management of noninvasive breast cancer is beyond the scope of this chapter, but some of the more salient characteristics of ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS) are described below, and the reader is referred to a number of excellent reviews for a more comprehensive discussion.[13,14]

DCIS is seen more frequently than LCIS. It is important to note that carcinoma in situ is treated as cancer. *Simple* or *total mastectomy* (without lymph node dissection) has been the standard treatment of DCIS for several decades. Breast conservation, i.e., wide local excision followed by irradiation of breast tissue, may be an effective alternative to mastectomy. Although radiation following lumpectomy does not appear to change the survival of patients with DCIS, it significantly reduces the incidence of local recurrences and enhances the breast preservation rate in these women. Axillary dissection generally is not indicated because there is only a 1% incidence of axillary node involvement. There is currently no proven benefit for the use of cytotoxic chemotherapy in patients who receive local therapy for DCIS. However, there are subgroups of patients with DCIS, such as hormone-receptor-positive patients, who may benefit from the addition of tamoxifen to lumpectomy plus radiation.[15]



Clinical Presentation and Diagnosis

Common early symptoms include:

- Painless lump (90% of cases) that is:
  - Solitary
  - Unilateral
  - Solid
  - Hard
  - Irregular
  - Nontender
- Stabbing or aching pain (10% of cases) as the first symptom

Uncommon early symptoms include:

- Nipple discharge (3% of women and 20% of men), retraction, or dimpling
- Eczema appearance of the nipple (Paget's carcinoma)
- Prominent skin edema, redness, warmth, and induration of the underlying tissue (inflammatory carcinoma)

Metastatic symptoms: Tissues most commonly involved with metastases are lymph nodes (other than axillary or internal mammary), skin, bone, liver, lungs, and brain. The following symptoms of metastases will be present in about 10% of patients when they first seek treatment:

- Bone pain
- Difficulty breathing
- Abdominal enlargement
- Jaundice
- Mental status changes

Prevention and Early Detection

Current efforts at breast cancer prevention are directed toward the identification and removal of risk factors. Unfortunately, a number of risk factors associated with the development of breast cancer, such as family history of breast cancer or personal history of breast or other gynecologic malignancies, cannot be modified. Isolation and cloning of breast cancer susceptibility genes now allows screening of women with histories suggestive of "breast cancer families" and identification of appropriate candidates for prophylactic bilateral mastectomy. There are currently no absolute indications for prophylactic bilateral mastectomy. This surgery is considered for women at very high risk for the development of breast cancer, particularly if the women's breasts are difficult to evaluate by both physical examination and mammography, and the women have persistent disabling fears that they will be diagnosed with the disease.

The agent currently being used clinically as a breast cancer chemoprevention agent is tamoxifen. In randomized trials of tamoxifen as an adjuvant treatment for breast cancer, women who received tamoxifen also were found to have a reduced incidence of contralateral primary breast carcinomas.[16] A

recent meta-analysis of these tamoxifen chemoprevention trials indicates a consistent benefit in reducing the incidence of estrogen receptor (ER)–positive breast cancers (48%).[17] Tamoxifen's estrogenic effects on the uterus and the coagulation system increase the risk of serious adverse effects that may be critical for patients taking this agent in the prevention setting. Other agents being studied for breast cancer chemoprevention are raloxifene (currently approved to prevent bone loss in postmenopausal women), aromatase inhibitors, and retinoids (synthetic derivative of vitamin A).

The rationale for early detection of breast cancer is based on the clear relationship between stage of breast cancer at diagnosis and the probability of cure. Thus, if all breast cancers could be detected at a very early stage of the disease (i.e., small primary tumor and negative lymph nodes), then more patients with the disease could be cured. Screening guidelines for early detection of breast cancer have been put forward by the American Cancer Society, the United States Preventive Services Task Force, and the National Cancer Institute[18–20] (Table 86–2). These all include recommendations for women at average risk, with some general statements regarding screening for high-risk women as well. ❶ *Nearly 75% of all breast cancer occurs in women 50 years of age or older, and it has been demonstrated conclusively that regular use of screening mammography can reduce mortality from breast cancer by 20% to 40% in this age group. Controversy regarding the use of screening mammography is largely confined to women younger than 50 years of age. After many years of debate, the three available guidelines discussed here recommend mammograms in this age group of women every 1 to 2 years.*[18–20]

Diagnosis

Initial work-up for a woman presenting with a lesion or symptoms suggestive of breast cancer should include a careful history, physical examination of the breast, three-dimensional mammography, and possibly other breast imaging techniques such as ultrasound. Most (80% to 85%) breast cancers can be visualized on a mammogram as a mass, a cluster of calcifications, or a combination of both. Breast biopsy is indicated for a mammographic abnormality that suggests malignancy or for a palpable mass on physical examination.

Clinical Staging

Stage (anatomic extent of disease) is defined on the basis of the primary tumor size ($T_{1–4}$), presence and extent of lymph node involvement ($N_{1–3}$ or $pN_{1–3}$ if pathologic examination of lymph nodes is conducted), and presence or absence of distant metastases ($M_{0–1}$) (Table 86–3). For a more complete description of the staging system, the reader is referred to the guidelines.[21] Although many possible combinations of T and N are possible within a given stage, simplistically, stage 0 represents carcinoma in situ (T_{is}) or disease that has not invaded the basement membrane. Stage I represents small primary tumor without lymph node involvement, and the majority of stage II disease involves regional lymph nodes. Stages I and II are often referred to as *early breast cancer.* It is in these early stages that the disease is curable. Stage III, also referred to as *locally advanced disease,* usually represents a large tumor with extensive nodal involvement in which either node or tumor is fixed to the chest wall. Stage IV disease is characterized by the presence of metastases to organs distant from the primary tumor and is often referred to as *advanced* or *metastatic disease,* as described earlier. Most cancer today presents in early stages, where the prognosis is favorable (Table 86–4).

Prognostic Factors

A number of potential prognostic factors have been identified for breast cancer. *Prognostic factors* are measurements available at diagnosis or time of surgery that in the absence of adjuvant therapy are associated with recurrence rate, death rate, or other clinical outcome.

- *Patient age.* Patients diagnosed at age younger than 35 years have a worse prognosis.
- *Tumor size.* In general, patients with a larger tumor have a worse prognosis.

TABLE 86–2. Guidelines for Early Detection of Breast Cancer

	American Cancer Society[18]	United States Preventive Services Task Force[19]	National Cancer Institute[20]
BSE	Age greater than or equal to 20: risk/benefit discussion	All ages: ±	NR
CBE	Age 20–30: every 3 years Age greater than or equal to 40: every year	All ages: ± (recommended with mammogram)	All ages: every year
Mammogram	Age greater than or equal to 40: interval not designated	Age greater than or equal to 40: every 1–2 years (with or without CBE)	Age 40–49: every 1–2 years Age greater than or equal to 50: every 1–2 years

BSE, breast self-examination; CBE, clinical breast examination; NR, not recommended; ±, insufficient data to recommend for or against.

TABLE 86–3. TNM Stage Grouping for Breast Cancer

Stage	Grouping		
0	T_{is}	N_0	M_0
I	T_1[a]	N_0	M_0
IIA	T_0	N_1	M_0
	T_1[a]	N_1	M_0
	T_2	N_0	M_0
IIB	T_2	N_1	M_0
	T_3	N_0	M_0
IIIA	T_0	N_2	M_0
	T_1[a]	N_2	M_0
	T_2	N_2	M_0
	T_3	N_1	M_0
	T_3	N_2	M_0
IIIB	T_2	N_0	M_0
	T_2	N_1	M_0
	T_2	N_2	M_0
IIIC	Any T	N_3	M_0
IV	Any T	Any N	M_1

[a]T_1 includes T_1mic; tumor (T)
- T_0 No evidence of tumor
- T_{is} Carcinoma in situ or Paget's disease of the nipple with no tumor
- T_1 less than or equal to 2 cm
- T_2 greater than 2–5 cm
- T_3 greater than 5 cm
- T_4 Any size; direct extension to chest wall (excluding pectoral muscle) or skin infiltration

Regional lymph nodes (pN)
- pN_x Regional lymph nodes cannot be assessed
- pN_0 No regional lymph node metastasis histologically
- pN_1 Metastasis in one to three axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
- pN_2 Metastasis in four to nine axillary lymph nodes, or in clinically apparent* internal mammary lymph nodes in the *absence* of axillary lymph node metastasis
- pN_3 Metastasis in ten or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent* ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes

* *Clinically apparent* is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.
***Not clinically apparent* is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

Metastasis (M)
- M_0 No distant metastases
- M_1 Distant metastasis

Adapted with permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original source for this material is the AJCC Cancer Staging Manual, 6th edition (2002), published by Springer-Verlag, New York, www.springer-ny.com.

TABLE 86–4. Estimated Stage at Presentation and 5-Year Disease-Free Survival (DFS): Breast Cancer

	Percentage of Total Cases	5-Year DFS[a] (%)
Stage I	40	70–90
Stage II	40	50–70
Stage III	15	20–30
Stage IV	5	0–10[b]

[a]With current conventional local and systemic therapy.
[b]Patients in stage IV are rarely free of disease; however, 10% to 20% of these patients may survive with minimal disease for 5 to 10 years.



Patient Encounter, Part 2: Medical History and Physical Examination

PMH
Hypertension for 15 years, currently controlled.

Endocrine History
Menarche age 10; menopause age 55 (natural); first child age 25; $G_2P_2A_0$. Last Pap smear 10 years ago. HRT with Prempro since age 55 (10 years). No other exogenous hormone exposure.

Meds
- Valsartan 160 mg PO daily
- Prempro 1 tablet PO daily

ROS
(+) lump in right breast; otherwise (–).

PE
- **Gen:** Obese 65 year-old Caucasian woman who appears her stated age in NAD.
- **VS:** BP 135/76, P 78, RR 18, T 38.1°C (100.6°F); ht 5 ft, 4 in, wt 100 kg
- **Breast:** Right: Hard 2.4 × 3.0 cm mass in upper outer quadrant without associated erythema, dimpling, or skin changes, not fixed to skin, no ulceration. No palpable lymph nodes in axilla. Left: Without masses or lymphadenopathy.

Labs
All within normal limits.

CXR: Lungs are clear.

- What information is suggestive of breast cancer?
- What other tests do you need to make a diagnosis and develop a treatment plan?

- *Nuclear grade* describes the size and shape of the nucleus in tumor cells and the percentage of tumor cells that are dividing. A high nuclear grade signifies that a tumor is growing quickly and indicates a worse prognosis.
- *Lymph node involvement*. Patients with node-positive disease have a worse prognosis.
- *Hormone-receptor status*. Patients with negative-estrogen-receptor (ER) and negative-progesterone-receptor (PR) tumors have a worse prognosis.
- *HER-2/neu protein expression*. Patients with *HER-2/neu* overexpression have a worse prognosis.

TREATMENT: EARLY BREAST CANCER

Desired Outcome

❷ *Most patients presenting with breast cancer today have either an in situ tumor, a small tumor with negative lymph nodes (stage I), or a small stage II cancer. The goal of therapy in early breast cancer is curative.* Surgery alone can cure most, if not all, patients with in situ cancers and approximately half of all patients with stage II cancers.

Nonpharmacologic Local-Regional Therapy

The choice of surgical procedures has changed drastically over the past 50 years. ❸ *Current surgical management options for early invasive breast cancer include the modified radical mastectomy (also termed total mastectomy with* ***ipsilateral*** *axillary lymph node dissection) and breast conservation*. In the modified radical mastectomy, the pectoralis minor muscle may be excised, divided, or left intact, and more important, there may be variation in the extent of axillary lymph node dissection, ranging from sampling to full dissection. It is important to note that in the elderly, patients with comorbid conditions, patients with particularly favorable tumors, or patients whose adjuvant therapy likely would not be affected by node status, axillary dissection can be considered optional. Breast conservation consists of lumpectomy, also referred to as *segmental mastectomy* or *partial mastectomy,* and is defined as excision of the primary tumor and adjacent breast tissue, followed by radiation therapy to reduce the risk of local recurrence. Removal of level I/II axillary lymph nodes is recommended for completeness of staging and prognostic information. The National Institutes of Health (NIH) Consensus Conference on the Treatment of Early Stage Breast Cancer addressed the roles of modified radical mastectomy versus breast conservation and concluded that primary therapy for breast cancer stages I and II should be *breast conservation.*[22] The reason given for favoring breast conservation therapy is that it achieved similar results to more extensive surgical procedures and had superior results cosmetically.

In most instances, external-beam radiation therapy used in conjunction with breast-conserving procedures involves 4 to 6 weeks of radiation therapy directed to the breast tissue to eradicate residual disease. Complications associated with radiation therapy to the breast are minor and include reddening and erythema of the breast tissue and subsequent shrinkage of total breast mass beyond that predicted on the basis of breast tissue removal. Some clinical situations also require postmastectomy radiation therapy as well (see section on locally advanced breast cancer).

There are several contraindications to breast conservation that must be considered when selecting patients:

- Multiple sites of cancer within the breast
- Pregnancy (patient cannot receive radiation)
- Inability to attain negative pathologic margins on the excised breast specimen
- Preexisting collagen-vascular diseases (e.g., scleroderma and systemic lupus erythematosus)
- Diffuse malignant-appearing microcalcifications on mammogram
- Prior radiation treatment to the breast or chest wall
- Large tumor volume in a woman with small breasts (better cosmetic results often can be obtained with mastectomy and reconstruction)

The importance of stage I/II axillary dissection is being challenged. Although highly accurate, its morbidity is significant, with an acute complication rate as high as 20% to 30% and rates of chronic lymphedema also on the order of 20% to 30%.[23,24] A new procedure involving lymphatic mapping and sentinel lymph node biopsy is becoming more acceptable at many academic centers across the United States.[25] The sentinel lymph node is the first lymph node that drains a cancer. Injection of a dye around the primary breast tumor results in identification of the sentinel lymph node in the majority of patients, and the status of this lymph node may predict the status of the remaining nodes in the nodal basin. A sentinel lymph node can be identified in 90% of patients and can accurately predict the status of the remaining axillary nodes in 95% of patients.[26]

Pharmacologic Systemic Adjuvant Therapy

Unfortunately, breast cancer cells often spread by contiguity, lymph channels, and through the blood to distant sites. This often occurs early in the breast cancer growth, and deposits of tumor cells form in distant sites that cannot be detected with current diagnostic methods and equipment (micrometastases). *Systemic adjuvant therapy* is defined as the administration of systemic therapy following definitive local therapy (i.e., surgery, radiation, or a combination of these) when there is no evidence of metastatic disease but a high likelihood of disease recurrence. ❹ *Most published results confirm that chemotherapy (in all patients), hormonal therapy (in patients with hormone-receptor-positive disease), or both result in improved disease-free survival (DFS) and/or overall survival (OS) for patients with early-stage brease cancer.*

An NIH Consensus Development Conference Statement[22] advises that adjuvant hormonal therapy should be recommended to women whose tumors contain hormone-receptor protein regardless of age, menopausal status, involvement of axillary lymph nodes, or tumor size. They also support a benefit of adjuvant chemotherapy for most women with lymph node metastases or with primary breast cancers larger than 1 cm in diameter (both node-negative and node-positive).[22]

In 2005, a group of international experts in the treatment of breast cancer met at the ninth St. Gallen meeting in Switzerland.[27] At the conclusion of the conference, a consensus panel of experts reviewed and modified its previous guidelines and recommendations for selection of adjuvant systemic therapies. The panel decided that endocrine responsiveness was the most important patient characteristic to consider. They developed three categories: endocrine responsive, endocrine nonresponsive, and tumors of uncertain endocrine responsiveness. These categories then are divided by menopausal status. Finally, the panel divided patients into low-, intermediate- and high-risk categories.

1. *Low risk:* Node-negative and all the following: pathologic tumor size of 2 cm or less, or grade 1, absence of peritumoral vascular invasion, *HER2/neu* gene neither overexpressed nor amplified, and age 35 years or older

2. *Intermediate risk*
   - Node-negative and at least one of the following: pathologic tumor size greater than 2 cm, or grade 2 to 3, presence of peritumoral vascular invasion, *HER2/neu* gene overexpressed or amplified, and age older than 35 years
   - Node positive (1–3 involved nodes) and *HER2/neu* gene overexpressed or amplified
3. *High risk*
   - Node positive (1–3 involved nodes) and *HER2/neu* gene overexpressed or amplified
   - Node positive (4 or more involved nodes)

In general, the panel recommended

1. Chemotherapy for patients with endocrine-nonresponsive disease.
2. Endocrine therapy is primary therapy for endocrine-responsive disease, with chemotherapy being added for some intermediate- and all high-risk patients
3. Both endocrine therapy and chemotherapy are used in patients with an uncertain endocrine response category unless the patients are low risk, in which case they may just try endocrine therapy alone.

The National Comprehensive Cancer Network (NCCN) also has developed practice guidelines for the treatment of breast cancer.[28] Their most recent guidelines differ a bit from the St. Gallen expert consensus guidelines because they stratify selection of adjuvant therapy based on both hormone responsiveness and *HER2/neu* level of expression. For patients who have *HER2/neu* overexpressed tumors, the NCCN guidelines recommend that biologic therapy with trastuzumab be added to the adjuvant regimen.

The use of preoperative systemic therapy is gaining favor in both early-stage and locally advanced breast cancers. This approach to therapy, referred to as *neoadjuvant* or *primary systemic therapy*, most often consists of chemotherapy but in special circumstances also may include hormonal therapy (e.g., in inoperable patients with significant comorbidities). The advantages of preoperative systemic therapy include (1) decrease in the size of the tumor to minimize surgery and (2) to determine response to chemotherapy/hormone therapy in vivo (an important prognostic indicator). While this approach to therapy generally is reserved for patients with inoperable tumors (locally advanced), early-stage breast cancer patients who meet the criteria for breast-conserving therapy except for the size of the tumor may be considered for preoperative systemic therapy in order to decrease the size of the tumor, allowing for less radical surgery and better cosmetic results.

Adjuvant Chemotherapy

❺ *Cytotoxic drugs that have been used alone and in combination as adjuvant therapy in breast cancer include doxorubicin, epirubicin, cyclophosphamide, methotrexate, fluorouracil, paclitaxel, docetaxel, melphalan, prednisone, vinorelbine, and vincristine.* The most common combination chemotherapy regimens employed in the adjuvant and metastatic setting are listed in Table 86–5. The dose-limiting toxicities and other significant toxicities are listed for each chemotherapeutic agent in Table 86–6.

The basic principle of adjuvant therapy for any cancer type is that the regimen with the highest response rate in advanced disease should be the optimal regimen for use in the adjuvant setting. Early administration of effective combination chemotherapy at a time when the tumor burden is low should increase the likelihood of cure and minimize the emergence of drug-resistant tumor cell clones. Anthracyclines (e.g., doxorubicin and epirubicin) historically have been referred to as the most active class of chemotherapy agents in the treatment of metastatic breast cancer. This has led to the assumption that anthracycline-containing regimens are associated with a higher cure rate than non-anthracycline-containing regimens when used in the adjuvant setting.

The taxanes (e.g., paclitaxel and docetaxel) are a newer class of agents that rival the anthracyclines in their activity in metastatic breast cancer, becoming (arguably) the most active class of chemotherapy for this disease.

Although the optimal duration of adjuvant chemotherapy administration is unknown, it appears to be on the order of 12 to 24 weeks and may depend on the regimen being used. Chemotherapy is usually initiated within 3 weeks of surgical removal of the primary tumor. Dose intensity and dose density appear to be critical factors in achieving optimal outcomes in adjuvant breast cancer therapy. *Dose intensity* is defined as the amount of drug administered per unit of time and typically is reported in milligrams per square meter of body surface area per week (mg/m^2 per week). Increasing dose, decreasing time, or both can increase dose intensity. *Dose density* is equivalent to the concept of increasing dose intensity but not by increasing the amount of drug given, as occurs with dose escalation, but instead by decreasing the time between treatment cycles. Reducing the dose for standard treatment regimens should be avoided unless necessitated by severe toxicity. On the other hand, increasing doses beyond those contained in standard treatment regimens does not appear to add benefit because there is a threshold for dosing adjuvant chemotherapy above which only additional toxicity is seen without any improvement in patient outcomes.

The short-term toxic effects of chemotherapy used in the adjuvant setting generally are well tolerated. Although a number of investigators have demonstrated a reduction in quality of life, most patients are able to maintain a reasonable level of function and emotional and social well-being during treatment.[30] In general, supportive therapy of the patient receiving systemic adjuvant chemotherapy has improved in the past decade. Increased attention to the impact of symptoms on quality of life may account for some of this improvement. In addition, serotonin-antagonist antiemetics have become available to assist in

TABLE 86–5. Common Chemotherapy Regimens for Breast Cancer

Adjuvant Chemotherapy Regimens

AC
Doxorubicin 60 mg/m^2 IV, day 1
Cyclophosphamide 600 mg/m^2 IV, day 1
Repeat cycles every 21 days for 4 cycles[a]

FAC[w]
Fluorouracil 500 mg/m^2 IV, days 1 and 4
Doxorubicin 50 mg/m^2 IV continuous infusion over 72 hours[w]
Cyclophosphamide 500 mg/m^2 IV, day 1
Repeat cycles every 21–28 days for 6 cycles[c]

CAF
Cyclophosphamide 600 mg/m^2 IV, day 1
Doxorubicin 60 mg/m^2 IV bolus, day 1
Fluorouracil 600 mg/m^2 IV, days 1 and 8
Repeat cycles every 28 days for 6 cycles[e]

FEC
Fluorouracil 500 mg/m^2 IV, day 1
Epirubicin 100 mg/m^2 IV bolus, day 1
Cyclophosphamide 500 mg/m^2 IV, day 1
Repeat cycle every 21 days for 6 cycles[g]

CEF
Cyclophosphamide 75 mg/m^2 orally on days 1–14
Epirubicin 60 mg/m^2 IV, days 1 and 8
Fluorouracil 600 mg/m^2 IV, days 1 and 8
Repeat cycles every 21 days for 6 cycles (requires prophylactic antibiotics or growth factor support)[i]

AC → paclitaxel (CALGB 9344)
Doxorubicin 60 mg/m^2 IV, day 1
Cyclophosphamide 600 mg/m^2 IV, day 1
Repeat cycles every 21 days for 4 cycles
Followed by:
Paclitaxel 175 mg/m^2 IV over 3 hours
Repeat cycles every 21 days for 4 cycles[b]

TAC (BCIRG 001)
Docetaxel 75 mg/m^2 IV, day 1
Doxorubicin 50 mg/m^2 IV bolus, day 1
Cyclophosphamide 500 mg/m^2 IV, day 1
(Doxorubicin should be given first)
Repeat cycles every 21–28 days for 6 cycles[d]

Paclitaxel → FAC[w]
Paclitaxel 80 mg/m^2 per week IV over 1 hour every week for 12 weeks
Followed by:
Fluorouracil 500 mg/m^2 IV, days 1 and 4
Doxorubicin 50 mg/m^2 IV continuous infusion over 72 hours
Cyclophosphamide 500 mg/m^2 IV, day 1
Repeat cycles every 21–28 days for 4 cycles[n]

CMF
Cyclophosphamide 100 mg/m^2 per day orally, days 1–14
Methotrexate 40 mg/m^2 IV, days 1 and 8
Fluorouracil 600 mg/m^2 IV, days 1 and 8
Repeat cycles every 28 days for 6 cycles[h]
or
Cyclophosphamide 600 mg/m^2 IV, day 1
Methotrexate 40 mg/m^2 IV, day 1
Fluorouracil 600 mg/m^2 IV, days 1 and 8
Repeat cycles every 28 days for 6 cycles[i]

Dose-dense AC → paclitaxel
Doxorubicin 60 mg/m^2 IV bolus, day 1
Cyclophosphamide 600 mg/m^2 IV, day 1
Repeat cycles every 14 days for 4 cycles (must be given with growth factor support)
Followed by:
Paclitaxel 175 mg/m^2 IV over 3 hours
Repeat cycles every 14 days for 4 cycles (must be given with growth factor support)[k]

Metastatic Single-Agent Chemotherapy

Paclitaxel
Paclitaxel 175 mg/m^2 IV over 3 hours
Repeat cycles every 21 days[l]
or
Paclitaxel 80 mg/m^2 per week IV over 1 hour
Repeat dose every 7 days[m]

Docetaxel
Docetaxel 60–100 mg/m^2 IV over 1 hour
Repeat cycles every 21 days[o]
or
Docetaxel 30–35 mg/m^2 per week IV over 30 minutes
Repeat dose every 7 days[p]

Vinorelbine
Vinorelbine 30 mg/m^2 IV, days 1 and 8
Repeat cycles every 21 days
or
Vinorelbine 25–30 mg/m^2 per week IV
Repeat cycles every 7 days (adjust dose based on absolute neutrophil count; see product information)[n]

Gemcitabine
Gemcitabine 600–1000 mg/m^2 per week IV, days 1, 8, and 15
Repeat cycles every 28 days (may need to hold day 15 dose based on blood counts)[q]

(*Continued*)

TABLE 86–5. Common Chemotherapy Regimens for Breast Cancer *(Continued)*

Metastatic Single-Agent Chemotherapy (*continued*)

Capecitabine
Capecitabine 2000–2500 mg/m^2 per day orally, divided twice daily for 14 days
Repeat cycles every 21 days[q,r]

Liposomal doxorubicin
Liposomal doxorubicin 30–50 mg/m^2 IV over 90 minutes
Repeat cycles every 21–28 days[s]

Metastatic Combination Chemotherapy Regimens

Docetaxel + capecitabine
Docetaxel 75 mg/m^2 IV over 1 hour, day 1
Capecitabine 2000–2500 mg/m^2 per day orally divided twice daily for 14 days
Repeat cycles every 21 days[t]

Epirubicin + docetaxel[x]
Epirubicin 70–90 mg/m^2 IV bolus
Followed by:
Docetaxel 70–90 mg/m^2 IV over 1 hour
Repeat cycles every 21 days[v]

Doxorubicin + docetaxel[x]
Doxorubicin 50 mg/m^2 IV bolus, day 1
Followed by:
Docetaxel 75 mg/m^2 IV over 1 hour, day 1
Repeat cycles every 21 days[u]

[a]From Fisher B et al. J Clin Oncol 1990; 8:1483.
[b]From Henderson CI et al. J Clin Oncol 2003; 21:976.
[c]From Buzdar AU et al. In: Salmon S, ed. Adjuvant Therapy of Cancer, VIII. Philadelphia: Lippincott-Raven, 1997: 93–100.
[d]From Martin et al. San Antonio Breast cancer Symposium 2003; A43.
[e]From Wood WC et al. New Engl J Med 1994; 330:1253.
[f]From Green et al. Proc Am Soc Clin Oncol 2002; A135.
[g]French Adjuvant Study Group. J Clin Oncol 2001; 19:602.
[h]From Bonadonna G et al. New Engl J Med 1976; 294:405.
[i]From Fisher B et al. New Engl J Med 1989; 32:473.
[j]From Levine MN et al. J Clin Oncol 1998;16:2651.
[k]From Citron et al. J Clin Oncol 2003; 21;1431.
[l]From Taxol (paclitaxel) product information, Bristol-Myers Squibb, April 2003.
[m]From Perez EA et al. Clin Oncol 2001; 19:4216.
[n]From Zelek L. Cancer 2001; 92:2267.
[o]From Taxotere (docetaxel) product information, Aventis Pharmaceuticals, Inc., April 2003.
[p]From Hainsworth JD et al. J Clin Oncol 1998; 16:2164.
[q]From Carmichael J et al. J Clin Oncol 1995; 13:2731.
[p]From Xeloda product information.[58]
[r]From Michaud et al. Proc Am Soc Clin Oncol 2000; A402.
[s]From Ranson MR et al. J Clin Oncol 1997; 15: 3185.
[t]From O'Shaughnessy et al. J Clin Oncol 2002; 20: 2812
[u]From Nabholtz JM et al. J Clin Oncol 2003; 21: 968.
[v]From Levin MN et al. J Clin Oncol 1998; 16: 2651.
[w]FAC also may be given with bolus doxorubicin administration, and the fluorouracil dose is then given on days 1 and 8.
[x]Paclitaxel also may be given concurrently with doxorubicin ***or*** epirubicin as a combination regimen. Pharmacokinetic interactions make these regimens more difficult to give.

managing chemotherapy-induced nausea and vomiting, and colony-stimulating factors often are helpful in preventing febrile neutropenia, particularly in elderly patients or patients receiving high-dose and dose-dense chemotherapy regimens. A number of side effects are common with the regimens employed, and patients should be counseled appropriately regarding the likelihood of alopecia, weight gain, and fatigue. Patients who are menstruating usually experience a cessation of menses that may or may not return. Along with cessation of menses are accompanying signs and symptoms of menopause. Deep vein thrombosis has been reported in women receiving combination chemotherapy regimens.[31] A recent study estimated that 1 to 10 of 10,000 patients treated for 6 months with cyclophosphamide-based regimens might be expected to have leukemia within 10 years of diagnosis of breast cancer.[32] Cardiomyopathy induced by doxorubicin occurs less than 1% of the time in women whose total dose of doxorubicin is less than 320 mg/m^2.[33] It should be noted that epirubicin in the adjuvant setting is given at a dose of 100 to 120 mg/m^2.[34] At this dose, epirubicin has an equal chance of causing cardiomyopathy as standard doxorubicin doses when both agents are given as bolus or short infusions. Taxanes often are associated with hypersensitivity reactions, peripheral neuropathy, and/or myalgias and arthralgias for a few days following the infusion.

It is important to note that the magnitude of survival benefit for chemotherapy appears to be small, with an absolute reduction in mortality of only 5% at 10 years for patients with negative axillary lymph nodes and 10% for patients with positive axillary lymph nodes. In addition, there is currently no means to identify patients who will attain this survival benefit. However,

TABLE 86–6. Toxicities of Common Chemotherapies Used for Breast Cancer

Class	Drug	Dose-Limiting Toxicities	Other Toxicities
Anthracyclines	Doxorubicin, epirubicin	Myelosuppression, cardiomyopathy	Alopecia, nausea, vomiting, stomatitis, ulceration & necrosis with extravasation, red-colored urine, radiation-recall effect
	Liposomal doxorubicin	Myelosuppression, palmar-plantar erythrodysesthesia (hand-foot syndrome)	Alopecia, infusion reactions, stomatitis, fatigue, nausea, vomiting
Taxanes	Paclitaxel	Neutropenia, peripheral neuropathy	Alopecia, fluid retention, myalgia, skin reactions, ulceration & necrosis with extravasation, bradycardia, stomatitis, hypersensitivity reactions
	Docetaxel	Myelosuppression, severe fluid retention	Alopecia, fatigue, stomatitis, nausea, vomiting, diarrhea, peripheral neuropathy, nail disorder, skin reactions, hypersensitivity reactions
Antimetabolites	Capecitabine	Diarrhea, palmar-plantar erythrodysesthesias (hand-foot syndrome)	Myelosuppression, stomatitis, nausea, vomiting
	Gemcitabine	Myelosuppression (especially thrombocytopenia)	Flulike syndrome (fever, chills, myalgias, & arthralgias), nausea
	Fluorouracil	Myelosuppression	Stomatitis, diarrhea, alopecia
	Methotrexate	Myelosuppression, stomatitis	Diarrhea, nausea, vomiting, renal toxicity
Vinca alkaloids	Vinorelbine	Myelosuppression	Fatigue, nausea, vomiting, ulceration & necrosis with extravasation
Alkylating agents	Cyclophosphamide	Myelosuppression, hemorrhagic cystitis	Alopecia, stomatitis, amenorrhea, aspermia, secondary leukemias

two investigators report that most patients with breast cancer would accept severe toxicity from treatment to achieve as little as a 1% to 5% improvement in survival.[35,36] Therefore, in the absence of the ability to predict who will benefit, it is likely that most patients with stage I and stage II breast cancer will choose an adjuvant chemotherapy treatment. The optimal chemotherapy regimen for use in the adjuvant setting has yet to be identified and depends on many patient and tumor characteristics.

Adjuvant Biologic Therapy

Trastuzumab is a monoclonal antibody directed against the *HER-2/neu* receptor. *HER-2/neu* is a member of the erbB (or HER) growth factor receptor family and is expressed at low levels in the epithelial cells of normal breast tissue. The overexpression of *HER-2/neu* is associated with increased transmission of growth signals that control aspects of cell growth and division. Most experts would agree that women whose tumors overexpress *HER-2/neu* appear to be relatively resistant to alkylating agent–based adjuvant therapy, and they might derive greater benefit from an anthracycline-based adjuvant therapy regimen.[29] *HER-2/neu* positively predicts response to trastuzumab therapy but is also considered a negative prognostic factor. Currently, the use of trastuzumab is indicated for treatment of adjuvant and metastatic breast cancer in patients who have tumors that overexpress *HER-2/neu*.[28] It is important to note that trastuzumab therapy should not be given concurrently with the anthracyclines because of an increased risk of cardiotoxicity (see section on metastatic breast cancer). Doses and common toxicities for trastuzumab are listed in Table 86–7.

TABLE 86–7. Biologic Therapy Used for Breast Cancer

Drug	Dose	Side Effects
Trastuzumab	4 mg/kg IV over 90 minutes on day 1 followed by 2 mg/kg over 90 minutes (30 minutes if no infusion-related reactions) once weekly ***or*** 8 mg/kg IV over 90 minutes on day 1 followed by 6 mg/kg IV over 90 minutes every 3 weeks	Infusion reactions (fever, chills, rigors), nausea, vomiting, pain at tumor sites, headaches, dizziness, dyspnea, hypotension, heart failure
Bevacizumab	10 mg/kg IV on days 1 and 15, cycled every 28 days (paclitaxel 90 mg/m^2 IV on days 1, 8 and 15)	Hypertension, gastrointestinal perforation, impaired wound healing, bleeding, thromboembolic events, proteinuria

Adjuvant Endocrine Therapy

❺ *Hormonal therapies that have been studied in the treatment of primary or early breast cancer include antiestrogens, oophorectomy, ovarian irradiation, luteinizing hormone–releasing hormone (LHRH) agonists, and aromatase inhibitors.*

Hormone receptors are used clinically as indicators of prognosis and to predict response to hormone therapy. Hormone receptors are cytoplasmic proteins that transmit signals to the nucleus of the cell for growth and proliferation. The hormone receptors clinically useful in discussions of breast cancer include the estrogen receptor (ER) and the progesterone receptor (PR). The presence of these proteins in the primary tumor (or less often metastases) is measured routinely by enzyme-linked immunochemical assays and radioassays (enzyme-linked immunosorbent assay). About 50% to 70% of patients with primary or metastatic breast cancer have hormone-receptor-positive tumors. Hormone-receptor positivity is associated with a superior response to hormone therapy and a longer disease-free interval between primary and subsequent metastatic disease and overall a more favorable prognosis. Hormone-receptor-positive tumors are more common in postmenopausal patients than in premenopausal patients. Many experts suggest that breast cancer in postmenopausal women is substantively different from that occurring in premenopausal women.

Tamoxifen traditionally was the "gold standard" adjuvant hormonal therapy and has been used in the adjuvant setting for three decades. Tamoxifen is antiestrogenic in breast cancer cells, but it appears to have estrogenic properties in other tissues and organs.[37,38] Newer information confirms that tamoxifen and other similar drugs have many estrogenic and antiestrogenic effects that depend on the tissue and the gene in question, and they are more appropriately called *selective estrogen receptor modulators* (SERMs). Women receiving adjuvant tamoxifen therapy have a reduction in recurrence and mortality compared with women not receiving adjuvant tamoxifen therapy.[16] This observation, coupled with evidence of tamoxifen's tolerability, including beneficial estrogenic effects on the lipid profile and bone density, led to tamoxifen being the hormonal agent of choice.

Adjuvant tamoxifen therapy generally is initiated shortly after surgery or as soon as pathology results are known and the decision to administer tamoxifen as adjuvant therapy is made. The administration of tamoxifen should be limited to administration after completion of chemotherapy based on results from a study that randomized patients to receive chemotherapy for six cycles with concurrent tamoxifen, followed by continued tamoxifen for a total of 5 years, or chemotherapy with sequential tamoxifen for 5 years.[39] After a median follow-up of 8.5 years, the administration of sequential tamoxifen resulted in an estimated DFS advantage of 18% [hazard ratio (HR) = 1.18] compared with the concurrent use of tamoxifen with chemotherapy.[39] It is believed the growth-inhibitory effect of tamoxifen therefore may diminish the cytotoxic effect of chemotherapy, resulting in subsequent recurrence of disease in women who received the two agents concurrently.

The optimal duration of tamoxifen therapy (20 mg/day) in the adjuvant setting is currently defined as 5 years. Studies examining prolonged administration (e.g., 10 years) have failed to demonstrate any advantage and may, in fact, be associated with a slightly worse survival.[40] Owing to the potential serious side effects of tamoxifen, all patients must be counseled properly about warning signs of endometrial cancer (i.e., vaginal bleeding or groin pain/pressure) and thromboembolism (i.e., chest pain, trouble breathing, changes in vision, one-sided weakness, or pain/swelling in the legs).

Toremifene is a recently marketed antiestrogen whose primary advantage is a lower estrogenic:antiestrogenic ratio than tamoxifen (based on laboratory data).[41] Toremifene (60 mg orally daily) has been found to have efficacy similar to that of tamoxifen in metastatic disease and a generally similar side-effect profile.[42] Currently, toremifene is indicated as an alternative to tamoxifen in patients with metastatic breast cancer, but studies are ongoing that evaluate its safety and efficacy in the adjuvant setting.

In premenopausal women, the use of LHRH agonists or other means of ovarian ablation have been shown to provide benefit in the adjuvant setting.[43] The use of goserelin (an LHRH agonist), alone or with tamoxifen, has been compared with standard chemotherapy (CMF) for six cycles. As a single agent, goserelin appears to provide similar benefit to CMF for six cycles for node-positive, ER-positive premenopausal breast cancer patients.[44] In another trial, the combination of goserelin and tamoxifen was compared with CMF for six cycles.[45] After a median follow-up of 6 years, this trial demonstrated a significant advantage of endocrine therapy in terms of DFS over chemotherapy alone. Retrospective reviews have found that premenopausal women who cease to menstruate with chemotherapy may have a better survival than women who continue to menstruate.[46] Therefore, the role of an LHRH agonist after chemotherapy in women who continue to menstruate is being investigated.

In postmenopausal women, recently reported evidence supporting the use of aromatase inhibitors in the adjuvant setting is intriguing and may usurp the role of tamoxifen. Three different approaches to therapy have been undertaken with these new agents: (1) direct comparison with tamoxifen for adjuvant hormonal therapy, (2) sequential use after 5 years of adjuvant tamoxifen therapy, and (3) sequential use after 2 to 3 years of adjuvant tamoxifen. Based on results of several studies, it has been concluded that therapy for postmenopausal women with ER-positive breast cancer should include an aromatase inhibitor.[27,47] It is still unclear if the aromatase inhibitor should be used instead of tamoxifen or sequentially after receiving tamoxifen for 2 to 5 years.[27] Concerns surrounding loss of bone density, changes in blood lipids, and cardiac and vascular disease require further study.[27]

Successful coadministration of bisphosphonates with the aromatase inhibitors has been accomplished in many patients in the metastatic setting. The three available aromatase inhibitors are exemestane, anastrozole, and letrozole.

TREATMENT: LOCALLY ADVANCED BREAST CANCER (STAGE III)

Desired Outcome

Locally advanced cancer breast cancer generally refers to breast carcinomas with significant primary tumor and nodal disease but in which distant metastases cannot be documented. A wide variety of clinical scenarios can be seen within this group of patients, including neglected tumors that have spread locally and inflammatory breast cancers that are a unique clinical entity. Many locally advanced breast cancers are diagnosed in patients who have had symptoms for months to years and have neglected to seek medical attention. Patients with inflammatory breast cancer often are treated inappropriately for cellulitis with antibiotics for several weeks to months.

Treatment of stage III breast cancer generally consists of a combination of surgery, radiation, and chemotherapy administered in an aggressive approach. The natural history of locally advanced breast cancer suggested that even when local-regional control was accomplished, systemic relapse and death from breast cancer occurred eventually in most patients.[48] This led to interest in the use of neoadjuvant or primary chemotherapy in locally advanced breast cancer, as discussed previously. This approach to therapy renders inoperable tumors resectable and can increase rates of breast-conserving therapy. Theoretical advantages also include potential benefits related to early initiation of systemic therapy, delivery of drugs through an intact vasculature, in vivo assessment of response to therapy, and the opportunity to study the biologic effects of the systemic treatment. However, this approach to therapy also results in a loss of standard, well-validated pathologic prognostic markers, such as initial tumor size and the number of axillary lymph nodes involved. Also, as discussed earlier, OS with adjuvant compared with neoadjuvant chemotherapy is similar, making either approach reasonable for a patient with operable breast cancer.

Pharmacologic Therapy

❻ *For patients with inoperable breast cancer, including inflammatory breast cancer, the initial approach to therapy should be chemotherapy with the goal of achieving resectability.* After neoadjuvant chemotherapy, most tumors respond with more than a 50% decrease in tumor size; about 70% of patients experience downstaging. Chemotherapy regimens used in this setting are similar to those used in the adjuvant setting. Supporting evidence for each individual regimen differs, but most of the available data support the use of anthracycline-containing regimens, incorporation of the taxanes in some manner, and other approaches to improve dose density or dose intensity. For more details regarding the specific regimens, the reader is referred to a recently published review.[48] Neoadjuvant endocrine therapy may be an option for patients who have unresectable hormone-receptor-positive tumors who are unable to receive chemotherapy (e.g., multiple comorbid conditions). In terms of local therapy, this usually follows chemotherapy, and the extent of surgery will be determined by response to chemotherapy, the wishes of the patient, and the cosmetic results likely to be achieved. Many patients may be able to have breast-conserving surgery if an acceptable response to chemotherapy is achieved. Adjuvant radiation therapy should be administered to all locally advanced breast cancer patients to minimize local recurrences regardless of the type of surgery used for that individual patient (e.g., mastectomy or segmental mastectomy). Inoperable tumors that are unresponsive to systemic chemotherapy may require radiation therapy for local management and may or may not be eligible for surgical resection after that radiation. Such patients are not seen commonly, but they have a very poor prognosis. For most patients in this category, cure is still the primary goal of therapy and can be achieved in a large number of patients when all treatment modalities are employed.

TREATMENT: METASTATIC BREAST CANCER (STAGE IV)

Desired Outcome

The goal of therapy with early and locally advanced breast cancer is to cure the disease. ❼ *Breast cancer is currently incurable after it has advanced beyond local-regional disease. The goal of treatment of metastatic breast cancer is to improve symptoms, maintain quality of life, and extend survival.* Thus it is important to choose therapy with good activity while minimizing toxicities. Treatment of metastatic breast cancer with either cytotoxic or endocrine therapy often results in regression of disease and improvements in quality of life.

General Approach to Treatment

The choice of therapy for metastatic disease is based on the site of disease involvement and presence or absence of certain characteristics (i.e., hormonal status of the primary tumor and disease location). For example, patients who experience a long DFS following local-regional therapy or have disease that is located primarily in the bone or soft tissue likely will respond to endocrine therapy. Patients with asymptomatic visceral involvement (e.g., liver or lung) may be candidates for hormonal therapy depending on the clinical circumstance (generally

hormones work more slowly than chemotherapy). ❽ *Patients who are hormone-receptor-positive generally will receive initial endocrine therapy followed by combination chemotherapy when endocrine therapy fails.* ❾ *Patients who respond to initial endocrine therapy often respond to a second (or even third) hormonal manipulation.* Response rate is lower and duration of response is shorter with second (and third) hormonal manipulations. Patients are treated sequentially with endocrine therapy until their tumors cease to respond, at which time cytotoxic chemotherapy can be given. Between 50% and 60% of ER-positive patients and 75% and 80% of ER- and PR-positive patients will respond to hormonal therapy, whereas those with ER- and PR-negative tumors have a less than 10% response rate. Thus the largest factor determining choice of endocrine versus cytotoxic chemotherapy is the presence of hormone receptors in the primary breast tumor.

Patients who are hormone-receptor-negative with rapidly progressive or symptomatic disease involving the liver, lung, or central nervous system or those having progressed on initial endocrine therapy usually are treated initially with cytotoxic chemotherapy. ❿ *Chemotherapy will result in an objective response in about 50% to 60% of patients previously unexposed to chemotherapy.* Most patients have partial response, and complete disappearance of disease occurs in fewer than 20% of patients treated. Median duration of response is 5 to 12 months, although some patients will have an excellent response to an initial course of chemotherapy and may live 5 to 10 years without evidence of disease. In general, survival of patients after treatment with commonly used drug combinations for metastatic breast cancer is a median of 14 to 33 months. The response rate to second- and third-line combination chemotherapy varies from 20% to 40% depending on the previous chemotherapy regimens the patient has received. Combinations of different hormonal therapies or chemotherapy plus hormones are not employed in the setting of metastatic breast cancer owing to the lack of increased efficacy and evidence of increased toxicity. *Patients with tumors that have HER2/neu overexpression should be considered for treatment with trastuzumab, alone or with chemotherapy.*

Pharmacologic Systemic Therapy

Endocrine Therapy

The pharmacologic goals of endocrine therapy for breast cancer are either to decrease circulating levels of estrogen and/or to prevent the effects of estrogen at the breast cancer cell (targeted therapy) through blocking the hormone receptors or downregulating the presence of those receptors. Achievement of the first goal depends on the menopausal status of the patient, but achievement of the second goal is independent of menopausal status. Many endocrine therapies are available to target either goal of therapy, and combination studies also have been conducted in an attempt to combine differing mechanisms of action and improve outcomes. Unfortunately, combinations have not demonstrated any efficacy benefits but have increased toxicity. Therefore, combinations of endocrine agents for breast cancer are not recommended outside the context of a clinical trial. Patients often are treated with a series of endocrine agents, frequently over several years, before chemotherapy is considered.

Until recently, there was little evidence that the response or survival benefit from one endocrine therapy was clearly superior to that achieved with other therapies. Given this equality in efficacy, the choice of a particular endocrine therapy was based primarily on toxicity (Table 86–8). Based on these criteria, tamoxifen is the preferred initial agent when metastases are present. An exception to this occurs when the patient is receiving adjuvant tamoxifen at the time or within 1 year of occurrence of metastatic disease.

Over the past decade, new information has been published regarding the use of a new generation of aromatase inhibitors. These data have changed the way we treat metastatic breast cancer, as well as early-stage breast cancer (as noted previously). In postmenopausal and castrated women, the main source of estrogen is derived from the peripheral conversion of androstenedione, produced by the adrenal gland, into estrone and estradiol. This conversion requires the enzyme aromatase. Aromatase also catalyzes the conversion of androgens to estrogens in the ovary in premenopausal women and in extraglandular tissue, including the breast itself, in postmenopausal women. Therefore, aromatase inhibitors (e.g., anastrozole, letrozole, and exemestane) effectively reduce the level of circulating estrogens, as well as estrogens in the target organ. Their toxicity profile consists mainly of nausea, hot flashes, arthralgias/myalgias, and mild fatigue. Anastrozole and letrozole are nonsteroidal compounds that exhibit reversible, competitive inhibition of aromatase. Exemestane is a steroidal compound that binds irreversibly to aromatase, forming a covalent bond. There is no clinical evidence that exemestane produces superior results over the other agents in this class.

Aromatase inhibitors are used for first-line therapy for advanced breast cancer in postmenopausal women. Large trials have compared these agents with tamoxifen and have found similar response rates and a longer median time to progression for patients receiving the selective aromatase inhibitor.[49] A consistent finding in these trials was a lower incidence of thromboembolic events and vaginal bleeding in patients who received selective aromatase inhibitors, which, together with the advantage in terms of time to progression, led to the conclusion that the new aromatase inhibitors are superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women. Use of a steroidal aromatase inhibitor (exemestane) after a patient progresses on a nonsteroidal inhibitor (anastrozole or letrozole) may provide some benefit and is a common practice based on small clinical trials investigating this sequential approach to therapy.[49] The opposite sequence also has shown some benefit. Therefore, patients may receive two aromatase inhibitors (first and second line sequentially), especially patients who progress while on adjuvant tamoxifen therapy.

TABLE 86–8. Endocrine Therapies Used for Metastatic Breast Cancer

Class	Drug	Dose	Side Effects
Aromatase Inhibitors			
Nonsteroidal	Anastrozole	1 mg orally daily	Hot flashes, arthralgias, myalgias, headaches, diarrhea, mild nausea, osteoporosis (boneloss)
	Letrozole	2.5 mg orally daily	
Steroidal	Exemestane	25 mg orally daily	
Antiestrogens			
SERMs	Tamoxifen	20 mg orally daily	Hot flashes, vaginal discharge, mild nausea, thromboembolism, endometrial cancer
	Toremifene	60 mg orally daily	
SERDs	Fulvestrant	250 mg IM every 28 days	Hot flashes, injection site reactions, possibly thromboembolism
LHRH Analogs	Goserelin	3.6 mg SC every 28 days	Hot flashes, amenorrhea, menopausal symptoms, injection site reactions
	Leuprolide	7.5 mg IM every 28 days	
	Triptorelin	3.75 mg IM every 28 days	
Progestins	Megestrol acetate	40 mg orally four times daily	Weight gain, hot flashes, vaginal bleeding, edema, thromboembolism
	Medroxyprogesterone	400–1000 mg IM every week	
Androgens	Fluoxymesterone	10 mg orally twice a day	Deepening voice, alopecia, hirsutism, facial/truncal acne, fluid retention, menstrual irregularities, cholestatic jaundice
Estrogens	Diethylstilbestrol	5 mg orally three times daily	Nausea/vomiting, fluid retention, anorexia, thromboembolism, hepatic dysfunction
	Ethinyl estradiol	1 mg orally three times daily	
	Conjugated estrogens	2.5 mg orally three times daily	

SERM, selective estrogen receptor modulator; SERD, selective estrogen receptor downregulator; LHRH, luteinizing hormone–releasing hormone.

As mentioned several times so far, the aromatase inhibitors are only used appropriately in women who are postmenopausal. Pre- or perimenopausal women, whose ovaries are functioning, are not appropriate candidates for these therapies, at least based on the available evidence. Use of the aromatase inhibitors in addition to ovarian ablation (e.g., oophorectomy or LHRH agonists) is currently being investigated. Also, the use of aromatase inhibitors in men with advanced breast cancer should be avoided. Available evidence suggests that use of these agents in men increases circulating levels of testosterone, which may negate the therapeutic effects of the drug.[50]

Antiestrogens bind to estrogen receptors, preventing receptor-mediated gene transcription, and therefore are used to block the effect of estrogen on the end target. This class of agents now is subdivided into two pharmacologic categories, SERMs and pure antiestrogens. SERMs include tamoxifen and toremifene and demonstrate tissue-specific activity, both estrogenic and antiestrogenic, as described previously. The agonistic activity is thought to be responsible for many of the adverse reactions seen with these agents, including the increased risk of endometrial cancer. Research into how to minimize this agonistic activity has lead to the production of pure estrogen-receptor antagonists that lack estrogen agonist activity. Pure antiestrogens are a new class of agents that are also referred to as *selective estrogen receptor downregulators* (SERDs). These molecules bind to the ER, inhibiting estrogen binding, and cause a degradation of the drug-ER complex, decreasing the amount of ER on the tumor cell surface. There is currently only one pure antiestrogen available commercially in the United States, namely, fulvestrant.

Tamoxifen can be used in both premenopausal and postmenopausal women with metastatic breast cancer who have tumors that are hormone-receptor-positive. The toxicities of tamoxifen are described in the section on adjuvant endocrine therapy. The only additional toxicity that one might expect to find in the setting of metastatic breast cancer (specifically bone metastases) is a tumor flare or hypercalcemia, which occurs in approximately 5% of patients following the initiation of any SERM therapy and is not an indication to discontinue SERM therapy. It is generally accepted that this is a positive indication that the patient will respond to endocrine therapy.

Toremifene is another commercially available SERM for the treatment of breast cancer. It exhibits similar efficacy and tolerability to tamoxifen in the metastatic setting. Cross-resistance to toremifene has been demonstrated in patients with tamoxifen-refractory disease.[51] Therefore, toremifene appears to be an alternative to tamoxifen in postmenopausal patients with positive or unknown hormone-receptor status with metastatic breast cancer.

Fulvestrant is a new agent approved for the second-line therapy of postmenopausal metastatic breast cancer patients who have tumors that are hormone-receptor-positive. Studies examining the role of fulvestrant in the treatment of metastatic breast cancer have compared this agent with anastrozole. Given anastrozole's mechanism of action, only postmenopausal women were eligible for these trials. There is no biologic reason why fulvestrant should not produce similar outcomes in premenopausal

women, but no data exist to confirm the safety or efficacy in premenopausal women. In the comparative trials with fulvestrant and anastrozole, similar efficacy and safety were demonstrated with both agents when given after patients progressed on tamoxifen therapy.[52,53] Adverse events related to fulvestrant include injection-site reactions, hot flashes, asthenia, and headaches. This agent is a good option for patients who are unable to take an oral medication because it is given as a intramuscular injection ever 28 days.

Another goal of antitumor treatment is to reduce estrogen production in premenopausal women with surgery, irradiation, or medication. No difference has been found in two randomized trials of the overall response rate between tamoxifen and oophorectomy in premenopausal women. However, the secondary response rate to oophorectomy after tamoxifen treatment was somewhat higher than the response to tamoxifen after primary oophorectomy (33% versus 11%).[54] Some experts interpret this as suggesting that tamoxifen does not completely antagonize available estrogen, particularly in premenopausal women. Ovarian ablation (surgically or chemically) is still used commonly in some parts of the United States and is considered by many specialists to be the endocrine therapy of choice in premenopausal women. The mortality rate with surgical oophorectomy is low, usually less than 2% to 3% in appropriately selected patients. Irradiation of the ovaries was a means of castration many years ago but was associated with multiple complications and is no longer performed for these purposes. Medical castration with LHRH analogs is used increasingly in lieu of oophorectomy in premenopausal women.

Medical castration with LHRH analogs has been used in premenopausal metastatic breast cancer patients and induces remission in about one-third of unselected patients. The mechanism of action of LHRH analogs in breast cancer is thought to result from down-regulation of LHRH receptors in the pituitary. Decreased levels of luteinizing hormone (LH) subsequently lead to a decrease in estrogen to castrated levels. The three agents available in the United States are leuprolide, goserelin, and triptorelin, but only goserelin is approved for the treatment of metastatic breast cancer. These agents are administered as an injection and are associated with minimal side effects, including amenorrhea, hot flashes, and occasionally nausea. A recent meta-analysis was reported on combined tamoxifen and LHRH agonists versus LHRH agonists alone in premenopausal patients with metastatic breast cancer.[55] With a median follow-up of 6.8 years, there was a significant survival benefit and progression-free survival benefit in favor of the combined treatment. The overall response rate was significantly higher on combined endocrine treatment. However, this analysis did not compare tamoxifen alone with the combination of an LHRH agonist with tamoxifen. LHRH agonists also may produce a flare response owing to an initial surge in LH and estrogen production for the first 2 to 4 weeks. This flare response is similar to that seen with tamoxifen, and patients should be monitored for increasing pain and/or hypercalcemia during the initiation period.

Progestins such as megestrol acetate and medroxyprogesterone acetate have been compared with tamoxifen in randomized trials and have been found to yield equal response rates. Although there were no direct comparisons of these two forms of progestational therapy, they appear to be equally effective. Medroxyprogesterone acetate is used more frequently in Europe, and megestrol acetate is used more frequently in the United States. Based on efficacy and tolerability, these agents generally are reserved as third-line therapy after patients have received an aromatase inhibitor and a SERM (i.e., tamoxifen or toremifene). The most common side effect is weight gain, occurring in 20% to 50% of patients. Patients experiencing weight gain may have fluid retention, but fluid retention is not totally responsible for the weight gain. In **cachectic** cancer patients, the weight gain may be desirable, but this is not uniformly true of all patients with metastatic breast cancer. Additional side effects associated with progestins include vaginal bleeding in 5% to 10% of patients, either while patients are taking the progestational agent or when it is discontinued, and somewhat less than a 10% incidence of hot flashes. Thromboembolic complications are also significant with these agents.

High-dose estrogens and androgens are used rarely today because these agents are more toxic than the other hormonal agents discussed thus far. About one-third of patients placed on high-dose estrogens will discontinue them because of side effects, the most important of which are thromboembolic events, vomiting, and fluid retention. Given the recent availability of the aromatase inhibitors, use of androgens and estrogens has become rare.

Cytotoxic Chemotherapy

Cytotoxic chemotherapy is eventually required in most patients with metastatic breast cancer. Patients with hormone-receptor-negative tumors require chemotherapy as initial therapy of symptomatic metastases. Patients who respond initially to hormonal manipulations eventually cease to respond and go on to require chemotherapy. The median duration of response is 5 to 12 months, but some patients will have an excellent response to an initial course of chemotherapy and may live 5 to 10 years or longer without evidence of disease. In general, median survival of patients after treatment with commonly used drug combinations for metastatic breast cancer is 14 to 33 months. The median time to response has ranged from 2 to 3 months in most studies, but this period depends in large part on the site of measurable disease. The median time to appearance of response is between 3 and 6 weeks in patients whose disease is primarily in the skin and lymph nodes, 6 to 9 weeks in patients with metastatic lung involvement, 15 weeks in patients with hepatic involvement, and nearly 18 weeks in patients with bone involvement. Thus it is often the case that an immediate response to therapy is not

apparent, and in general, once a chemotherapy regimen has been initiated, it is continued until there is unequivocal evidence of progressive disease.

There are no well-defined clinical characteristics or established tests to identify patients likely to benefit from chemotherapy. Factors associated with an increased probability of response that have been identified include a good performance status, a limited number (one to two) of disease sites, and patients who respond to chemotherapy or hormonal therapy with a long disease-free interval. Patients who have progressive disease during chemotherapy have a lower probability of response to a different type of chemotherapy. However, this is not necessarily true for patients who are given chemotherapy after some interval during which they have received no chemotherapy. Patients who do not respond to endocrine therapy are as likely to respond to chemotherapy as patients who are treated with chemotherapy as their initial treatment modality. Age, menopausal status, and receptor status have not been associated with favorable or unfavorable response to chemotherapy.

A number of chemotherapeutic agents have demonstrated activity in the treatment of breast cancer, including doxorubicin, epirubicin, paclitaxel, docetaxel, capecitabine, fluorouracil, cyclophosphamide, methotrexate, vinblastine, vinorelbine, gemcitabine, mitoxantrone, mitomycin-C, thiotepa, and melphalan. ❿ *The most active classes of chemotherapy in metastatic breast cancer are the anthracyclines and the taxanes, producing response rates as high as 50% to 60% in patients who have not received prior chemotherapy for metastatic disease.*[56] The most useful weekly dose of paclitaxel in the metastatic setting appears to be 80 mg/m^2 per week with no breaks in therapy. With this approach, the toxicity profile of paclitaxel changes with less myelosuppression and delayed onset of peripheral neuropathy but slightly more fluid retention and skin and nail changes. Patients should be premedicated with a steroid (dexamethasone), H_1 antagonist (diphenhydramine), and H_2 antagonist (ranitidine or famotidine) prior to treatment to minimize hypersensitivity reactions. A randomized study comparing doses of 60, 75, and 100 mg/m^2 docetaxel was published recently and demonstrates a dose-response relationship with regard to response rates only.[57] Time to progression and overall survival were similar among all three dose levels. Therefore, dose remains important for symptomatic patients who require a rapid response to therapy. In asymptomatic patients requiring docetaxel chemotherapy, lower doses may be appropriate. Results from a single randomized trial appear to indicate that docetaxel is associated with less neuropathy, myalgia, and hypersensitivity than paclitaxel given every 3 weeks, but febrile neutropenia, fluid retention, and skin reactions appear to occur more frequently with the newer taxane.[58] The median cumulative docetaxel dose to the onset of fluid retention is 400 mg/m^2 in nonpremedicated patients. Premedication with a steroid (dexamethasone) prior to beginning docetaxel and continued for three days helps to prevent hypersensitivity reactions and fluid retention.

Capecitabine is a novel oral agent approved in the mid-1990s with significant activity in metastatic breast cancer patients who have progressed on an anthracycline-containing regimen as well as a taxane regimen. This agent is a prodrug for fluorouracil with somewhat targeted activity toward malignant cells. The parent compound undergoes a three-step enzymatic conversion to become fluorouracil at the target cell. The third and final step in this conversion is more likely to occur in malignant cells than normal cells owing to the presence of higher levels of the responsible enzyme in malignant tissues. In patients who have been exposed to an anthracycline and a taxane, capecitabine produces response rates of about 25%, which is impressive compared with other tested chemotherapy agents.[59]

Vinorelbine, a microtubule interactive agent, also has shown impressive response rates in metastatic breast cancer.[60] Vinorelbine was approved by the FDA in 1994 for the treatment of non–small cell lung cancer. It is not approved for breast cancer, but response rates to vinorelbine range from 30% to 50%, with an overall 5% complete response rate in phase I and phase II studies in patients with advanced breast cancer. Importantly, paclitaxel, docetaxel, and vinorelbine do not appear to be cross-resistant with anthracyclines, which are arguably considered first-line treatment of metastatic breast cancer.

Gemcitabine is another agent that is used quite frequently in patients who have received the aforementioned chemotherapy regimens, who still have a good performance status, and who may benefit from additional chemotherapy. This is a nucleotide analog that inhibits DNA synthesis. Response rates ranging from 13% to 42% have been reported in a number of phase II trials.[60] In patients who have been exposed to an anthracycline and a taxane, gemcitabine appears to provide similar benefit to capecitabine. This agent appears to affect platelets more frequently than other chemotherapy previously mentioned, and close monitoring is required for patients receiving this agent.

Combination chemotherapy regimens are associated with higher response rates than are single-agent therapies in the treatment of metastatic breast cancer, but the higher response rates usually have not translated into significant differences in time to progression and OS. The use of sequential single-agent chemotherapies versus the combination regimens has been debated widely for metastatic breast cancer. Current consensus is that first-line chemotherapy includes sequential single agents or combination chemotherapy.[28] In the palliative metastatic setting, using the least toxic approach is preferred when efficacy is considered equal. In clinical practice, patients who require a rapid response to chemotherapy (e.g., those with symptomatic bulky metastases) often receive combination therapy despite the added toxicity. This decision is complex and should be made on an individual patient basis.

Because most patients are given adjuvant chemotherapy, regimens chosen for first-line use in the metastatic setting often are

different from those used in the adjuvant setting. If a patient's cancer recurs within 1 year of finishing adjuvant chemotherapy, those chemotherapy agents are not considered effective for treatment of the metastatic disease. However, if the patient recurs more than 1 year after the end of her adjuvant chemotherapy, the same agents also may be helpful in the metastatic setting.

Biologic Therapy

Trastuzumab is a humanized monoclonal antibody that binds with a specific epitope of the *HER-2/neu* protein. Single-agent treatment with trastuzumab has a response rate of 15% to 20% and a clinical benefit rate of nearly 40% in patients with *HER-2/neu*-overexpressing cancers.[61] Trastuzumab has additive and perhaps synergistic activity with other chemotherapeutic agents.[62] In the pivotal trial, patients who received the doxorubicin-trastuzumab combination had a very high incidence of cardiotoxicity (27%), leading to a black-box warning regarding this combination in the product information for trastuzumab. Many investigators are attempting to circumvent this toxicity while giving these two classes of agents together (e.g., liposomal doxorubicin or continuous-infusion doxorubicin). Until further information regarding the safety of these approaches becomes available, this combination should not be given outside the context of a clinical trial. Other chemotherapy agents that are being evaluated in combination with trastuzumab include docetaxel, vinorelbine, gemcitabine, capecitabine, and the platinum agents (e.g., cisplatin and carboplatin).[63]

Trastuzumab is reasonably well tolerated. The most common adverse effects are infusion-related, primarily fever and chills, and occur in about 40% of patients during the initial infusion. Acetaminophen and diphenhydramine may be given and/or the infusion rate reduced to help alleviate the symptoms related to these reactions. A more severe adverse effect consisting of severe hypersensitivity and/or pulmonary reactions has been reported but is rare. It is important to educate patients regarding the pulmonary reactions because these may occur up to 24 hours after the infusion and can be fatal if not treated promptly. Trastuzumab may increase the incidence of infection, diarrhea, and/or other adverse events when given with chemotherapy. As mentioned previously, when given with an anthracycline, the rates of heart failure are unacceptably high, but even when given as a single agent, there is about a 5% incidence of heart failure. Fortunately, the heart failure seen with trastuzumab is somewhat reversible with pharmacologic management, and some patients have continued therapy with trastuzumab after their left ventricular ejection fraction has returned to normal. Close monitoring for clinical signs and symptoms of heart failure is important in order to intervene with appropriate cardiac treatments.

It should be noted that only 20% to 30% of patients with metastatic breast cancer overexpress *HER-2/neu*, and



Patient Encounter, Part 3: Diagnostic Tests

Diagnostic Bilateral Mammogram

- American College of Radiology Category V report highly suspicious for malignancy in right breast. Spiculated mass measuring approximately 2 × 1.8 cm. Recommend biopsy.
- Left breast shows no abnormality.

Unilateral Ultrasound Right Breast and Right Axilla with Biopsy

- Solid-appearing mass favoring malignancy in right upper outer quadrant. This mass measures 1.7 × 1.8 cm in dimension. There is no associated skin thickening or edema. Fine-needle aspiration (FNA) was performed with two passes with preliminary evaluation suggestive of malignancy.
- Abnormal axillary adenopathy. Within the left axillar is a single lymph node that is abnormal in appearance. The node measures 0.8 × 0.9 cm and was sampled with FNA using a 20-gauge needle with two passes without complication. Preliminary cytologic evaluation suggested malignancy.

Fine-Needle Aspiration of Right Breast Mass and Right Axillary Mass

- *Right breast 10 o'clock:* Breast carcinoma, ductal type, modified Black's nuclear grade III (poorly differentiated), ER 50%, PR 30%.
- *Right axillary lymph node:* Metastatic adenocarcinoma; the cytomorphology of the malignant cells in the lymph node aspiration is similar to that seen in the breast aspiration material.

Core Needle Biopsy of Right Breast Mass

Infiltrating ductal carcinoma, modified Black's nuclear grade III (poorly differentiated), *HER2/neu* overexpression 2+ by IHC; *HER2/neu* amplification negative by FISH.

Ultrasound Liver

No lesions suggestive of malignancy.

Bone Scan

No evidence of active osseous metastases.

Echocardiogram

- Left ventricular systolic function is normal. Left ventricular ejection fraction by visual inspection is estimated at 55% to 60%. The left ventricle is grossly normal size.
- The right ventricle is normal in size and function.
- There is mild tricuspid regurgitation.
- Right ventricular systolic pressure is elevated at 30 to 40 mm Hg.
- There is no pericardial effusion.

- Given this information, what is your assessment of the patient's stage and prognosis?
- Identify your treatment goals for the patient.
- What nonpharmacologic and pharmacologic alternatives are available for this patient?

commercially available immunohistochemistry (IHC) tests that are reported back as 2+ for *HER-2/neu* are often negative by the more sensitive and specific fluorescence in situ hybridization (FISH) technique. To date, there is no benefit associated with the administration of trastuzumab to the subset of patients who are *HER-2/neu*-negative and a very questionable benefit associated with administration of trastuzumab to women who are 2+ for *HER-2/neu* by IHC staining alone. The patients who benefit most from trastuzumab therapy include those whose tumors express *HER2* protein at the 3+ level and/or demonstrate gene amplification by FISH testing.

Another monoclonal antibody, bevacizumab, was combined with paclitaxel in a clinical trial for first-line chemotherapy in women with metastic breast cancer. The DFS was improved for the combination regimen over paclitaxel alone.[28] Bevacizumab targets vascular endothelial growth factor (VEGF), thereby preventing angiogenesis, which is a necessary process to support tumor growth and metastasis. Bevacizumab was first approved by the FDA for the treatment of colorectal cancer. Additional studies are being conducted to elucidate bevacizumab's role in the treatment of beast cancer, including combination with trastuzumab.

Bisphosphonates

For women whose breast cancer has metastasized to bone, bisphosphonates are recommended, in addition to chemotherapy or endocrine therapy, to reduce bone pain and fractures.[28,64] Pamidronate (90 mg) and zoledronate (4 mg) can be given intravenously once each month. These bisphosphonates are given in combination with calcium and vitamin D.

Local-Regional Control

Radiation Therapy

Radiation is an important modality in the treatment of symptomatic metastatic disease. The most common indication for treatment with radiation therapy is painful bone metastases or other localized sites of disease refractory to systemic therapy. Radiation therapy gives significant pain relief to approximately 90% of patients who are treated for painful bone metastases. Radiation is also an important modality in the palliative treatment of metastatic brain lesions and spinal cord lesions, which respond poorly to systemic therapy, as well as eye or orbit lesions and other sites where significant accumulation of tumor cells occurs. Skin and/or lymph node metastases confined to the chest wall area also may be treated with radiation therapy for palliation (e.g., open wounds or painful lesions).



Patient Encounter, Part 4: Creating a Care Plan

Based on the information presented, create a care plan for this patient's breast cancer. Your plan should include (1) a statement of the drug-related and non-drug-related needs and/or problems, (2) the goals of therapy, (3) a patient-specific detailed therapeutic plan (including options for local control), and (4) a plan for follow-up to determine whether the goals have been achieved and adverse effects managed adequately.

OUTCOME EVALUATION

Early breast cancer is resected completely with curative intent, and adjuvant chemotherapy and hormonal therapy are initiated to prevent recurrence. During adjuvant chemotherapy, laboratory values to monitor chemotherapy toxicity are obtained prior to each cycle of chemotherapy. After completion of adjuvant therapy, patients are monitored every 3 months for the first few years after diagnosis, with intervals between exams extended as time from diagnosis lengthens.

- Physical examination to detect breast cancer recurrence
- Annual mammography
- Symptom-directed work-up

Locally advanced breast cancer often is treated with neoadjuvant therapy to make the tumor surgically respectable. During neoadjuvant chemotherapy, laboratory values to monitor chemotherapy toxicity are obtained prior to each cycle of chemotherapy, and a physical examination and ultrasound exams to detect size of tumor are performed after the cycles of neoadjuvant therapy are completed. After a complete surgical resection, monitoring proceeds as described earlier for early breast cancer.

Metastatic breast cancer is not curable, and therapy is intended to palliate symptoms. In most cases, hormonal therapy is the mainstay. While on therapy, patients are monitored monthly for signs of disease progression or metastasis to common sites, such as the bones, brain, or liver.

- Pain
- Mental status or other neurological findings
- Laboratory tests
  - Liver function tests
  - Complete blood count
  - Calcium, electrolytes



Patient Care and Monitoring

1. Review the patient's diagnostic information to determine the stage of disease, overall prognosis, and goals of therapy.
2. Obtain a thorough history of prescription, nonprescription, and natural drug product use. Is the patient taking any medications that may contribute to breast cancer and require discontinuation?
3. Review the patient's past medical history to determine the risks associated with any potential therapies and/or surgery and/or radiation therapy.
4. Educate the patient on the chemotherapy or endocrine therapy regimen chosen for the patient, focusing on what adverse events to expect, when to expect them, and how to manage them if they do occur. Also include in the initial education an overall plan of care, including the duration of therapy, other treatment modalities that will follow (e.g., radiation therapy, surgery, endocrine therapy), and when the patient will receive them.
5. Develop a pre- and postmedication plan for the chemotherapy or endocrine therapy regimen chosen based on the patient's risk factors for adverse events, chemotherapy/endocrine therapy drugs chosen, and dose, route, and timing of administration chosen.
6. Develop a plan to assess the effectiveness of the overall treatment plan, focusing on educating the patient on ways to monitor and track adverse events and/or disease-related symptoms throughout therapy.
7. Determine success of the overall treatment plan by obtaining a thorough history of adverse events experienced with the previous chemotherapy/endocrine therapy treatment and objective measures of response to therapy. Assess effects on quality-of-life measures such as physical, psychological, and social function and well-being.
8. Address any adverse events the patient experienced, and alter the pre- and postmedication plan for the next treatment accordingly.
9. Provide follow-up patient education regarding the new plan for side-effect management.
10. Stress the importance of reporting adverse events and adherence with the prescribed medication regimen. Attempt to develop a therapeutic regimen that is easy for the patient to accomplish.

ABBREVIATIONS

BSE:	breast self-examination
CBE:	clinical breast examination
CMF:	cyclophosphamide, methotrexate, fluorouracil (regimen)
DCIS:	ductal carcinoma in situ
DFS:	disease-free survival
ER:	estrogen receptor
FISH:	fluorescence in situ hybridization
IHC:	immunohistochemistry
LCIS:	lobular carcinoma in situ
LHRH:	luteinizing hormone–releasing hormone
NCI:	National Cancer Institute
NIH:	National Institutes of Health
NCCN:	National Comprehensive Cancer Network
OS:	overall survival
PR:	progesterone receptor
SERD:	selective estrogen-receptor downregulator
SERM:	selective estrogen-receptor modulators
TNM:	tumor-node-metastasis staging system
VEGF:	vascular endothelial-derived growth factor

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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87 Lung Cancer

Val Adams and Justin Balko



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Identify major risk factors for the development of lung cancer.
2. Explain the pathologic progression of lung cancer and its relationship with signs and symptoms of the disease.
3. Make appropriate recommendations for screening or preventative measures in high-risk patients.
4. Understand staging of lung cancer patients and how it influences treatment decisions.
5. List the rationale, advantages, disadvantages, and place in therapy for adjuvant and neoadjuvant chemotherapy
6. Identify the chemotherapeutic regimens of choice for limited and extensive small cell lung carcinoma, as well as local, locally advanced, and advanced non–small cell lung carcinoma.
7. Monitor patients for chemotherapy-associated toxicity, and recommend appropriate management.
8. Distinguish the treatment goals of palliative care versus those of first-line treatment.

Key Concepts

❶ The single most important risk factor for the development of lung cancer is smoking, and the most effective way for high-risk patients to reduce their risk is to stop smoking. Additional recommendations should include an increase in dietary intake of fruits and vegetables.

❷ The signs and symptoms of lung cancer can be classified as pulmonary, extrapulmonary, and paraneoplastic. These classifications relate to disease progression.

❸ Surgical resection of the tumor is the mainstay of treatment in early-stage non–small cell lung cancer and produces the longest survival rates.

❹ The performance status of the patient represents an important aspect of chemotherapy treatment decisions. Patients with a performance status of 0 to 1 may be treated with chemotherapy. Patients with a performance status of 2 may be treated with less aggressive regimens that have a decreased risk of major toxicities, whereas performance status 3 and 4 patients should be treated with supportive care only.

❺ Doublet chemotherapy regimens are superior in response to single-agent regimens and should be used when the patient can tolerate the associated toxicity. Platinum-containing doublets are first-line treatment in most cases.

❻ The treatment goals in lung cancer are cure (early-stage disease), prolongation of survival, and maintenance or improvement of quality of life through alleviation of symptoms.

❼ Knowing how to prevent and treat adverse events from chemotherapy is an important aspect of patient care. Unmanaged events may result in excess morbidity and cause delays in chemotherapy administration and reduced chemotherapy doses and contribute to treatment failure.

Lung cancer has a major health impact both in the United States and worldwide. Prior to 1930, lung cancer was a relatively rare disease, but a sharp incline in industrialization and smoking in the early 1900s has bred an epidemic. Lung cancer has a high mortality rate, and although treatment can cure selected patients, most therapies prolong survival for only months. Recent advances in lung cancer research provide good reason for optimism, although antismoking campaigns still appear to offer the best opportunity to reduce lung cancer incidence and mortality.

EPIDEMIOLOGY AND ETIOLOGY

Incidence and Mortality

Cancer is the second leading cause of death in the United States, and cancers of the lung and bronchus rank first in mortality,

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comprising over 28% of cancer-related deaths.[1] In 2007, over 213,380 new cases of lung cancer were reported. A close correlation exists between incidence and mortality of lung cancer, reflecting the reality that approximately 85% of lung cancer patients ultimately die of their disease.

Gender

Lung cancer incidence and mortality are slightly higher in males, but the rate in females is expected to match that of males in future years[2] owing to changes in smoking patterns. Typically, women with lung cancer are diagnosed at an earlier age, which has raised the question that there may be inherent genetic differences between males and females in susceptibility to lung cancer. Furthermore, there are differences in the prevalence of histologic types of tumors. Interestingly, historically studies have shown improved prognosis and survival times for women diagnosed with lung cancer.[3]

Race

While no significant difference is noted in incidence or mortality between black and white females, black males have a markedly higher incidence and mortality rate than white males. Smoking habits, including cigarette type (i.e., increased menthol cigarette use) have a proposed contribution to this gap.[2] Black Americans also show a significantly lower 5-year survival rate than white Americans regardless of gender. They present with more advanced disease and are less likely to be treated, which suggests that genetic, psychosocial, and socioeconomic components contribute to this disparity.[4] People of other races, such as Asians, Hispanics, and Native Americans, have lower rates of lung cancer than both Caucasians and African Americans, although it remains a significant health care issue.[5]

Clinical Risk Factors

Smoking

❶ *The single most important risk factor for the development of lung cancer is smoking.* Furthermore, one of the most predictive factors on lung cancer epidemiology is trends in population cigarette smoking. Since lung cancer is a fatal disease in most cases, both incidence and mortality strongly reflect the smoking trends of the population on a 20- to 30-year lag. In other words, decreases in tobacco use now would not be expected to affect lung cancer incidence until approximately 2030. With this knowledge, the current expectation is that lung cancer incidence and mortality will decrease steadily until 2020, reflecting decreases in cigarette smoking between 1970 and 1990. Since smoking has continued at a steady rate since 1990, lung cancer incidence is expect to plateau.[2] Correlation between smoking and lung cancer continues to drive antismoking campaigns and should be considered an investment in the future health care of the nation.[6] Furthermore, smoking cessation plays a important role in reducing lung cancer risk on a patient-to-patient basis, and appropriately guiding such therapy is a crucial part of treating at-risk patients.[7] Total smoke exposure, as well as current use, correlates with the individual's risk of developing malignancy. The risk of lung cancer decreases to near-normal levels 10 to 15 years following successful smoking cessation. Total smoke exposure is reported as pack-years. One pack-year is the equivalent of smoking 1 pack per day for 1 year. A patient who smokes 40 cigarettes per day (2 packs) for 5 years would have a 10 pack-year history (2 packs/day × 5 years).

Other Air-Related Risks

In addition to direct inhalation of cigarette smoke, other environmental factors have been identified as risks for the development of primary lung tumors. Environmental tobacco smoke (ETS) presents a significant occupational hazard for nonsmokers working in environments that have a high smoking population, such as bars or restaurants. Some states have instituted laws banning public smoking in order to protect individuals working in these locations. It is estimated that approximately 3000 cases of lung cancer each year in nonsmokers are due to ETS.[8] Other environmental factors linked to lung cancer include radon, arsenic, nickel, and chloromethyl ethers. Those who live in an urban environment are also at an increased risk for lung cancer owing to exposure to high concentrations of combustion fumes.[5] Asbestos causes a distinct type of lung cancer called **mesothelioma,** which is rare and not discussed in this chapter.

Nutrition

Diet and nutrition have long been suspected to play a role in cancer susceptibility, and many studies have sought to define specific foods or nutrients that influence cancer risk. Since not all heavy smokers develop lung cancer, it is thought that nutritional factors may explain in part this variation. Epidemiologic studies focusing on diet and nutrition in lung cancer have shown reduced rates of lung cancer in individuals who report higher fruit and vegetable consumption. However, studies attempting to identify specific chemical components of fruits and vegetables that are responsible for this effect have not been successful.[9] ❶ *Recommendations to patients who are at risk owing to smoking or other factors or those who are simply interested in reducing their risk of cancer should include an increase in dietary intake of fruits and vegetables.*

Hereditary or Genetic Risk Factors

The majority of people who smoke never develop lung cancer. Genetic risk factors may predispose certain smokers to lung cancer. After adjustments for age, smoke exposure, occupation, and gender, relatives of a lung cancer patient have approximately a twofold risk of developing lung cancer. The



Patient Encounter, Part 1

A 53-year-old African-American man presents at your clinic complaining of new-onset cough. He has had several upper respiratory infections in the last 2 months, with occasional hemoptysis. He has consistently smoked 1.5 packs per day for the last 20 years. He has worked as a bartender at a local restaurant downtown for most of his life.

- What risk factors for lung cancer are present?
- Calculate this patient's pack-year history.

degree of inherited risk correlates with the age of the relative at the time of diagnosis. The relative risk is approximately six-fold higher for first-degree relatives of a lung cancer patient diagnosed between the ages of 40 and 59 years. Familial lung cancer that develops at an early age in nonsmokers fits a Mendelian codominant inheritance model. However, a lung cancer gene has not been identified.[10]

Other genetic links to lung cancer involve metabolic enzymes that process carcinogens. The damaging effects of tobacco smoke are thought be a result of bulky aromatic hydrocarbons that damage DNA. These chemicals are activated by certain phase I metabolic enzymes and are deactivated by phase II conjugating enzymes such as the glutathione-*S*-transferases. People with elevated cytochrome CYP450 2D6, 1A1, or 1A2 have greater risk of DNA damage and subsequent cancer owing to higher formation rates of active carcinogens. Those with deficient phase II metabolism (*GSTM1* or *GSTT1*) similarly may have increased risk owing to lower clearance of these carcinogens.[11–13]

PATHOPHYSIOLOGY

Most lung cancers are derived from the epithelium of the airways and therefore are classified as **carcinomas.** There are four major and several rare histologic types of lung cancer that appear to form through different mutagenic pathways. However, they all appear to transition through a premalignant state. The presence of a transition state from normal tissue to cancerous tissue is important because the premalignant cells contain damage that generally is thought to be reversible. Researchers currently are trying to develop methods to identify people with premalignant lesions as well as drugs that can reverse the damage.

Continued damage to premalignant cells can lead to cancer. The first appearance of cancer cells that have not yet become invasive is referred to as *carcinoma in situ.* Patients are rarely diagnosed with this early stage of cancer owing to a lack of symptoms and relatively rapid progression to larger invasive tumors. As the tumor grows, cells may become dislodged from the tumor bulk and enter the hematologic or lymphatic circulatory systems, where they can travel to either local or distant parts of the body. Hematologic spread usually results in metastatic sites in the bones, liver, and central nervous system.[11] Lymphatic spread is more orderly in nature, with the hilar and mediastinal lymph nodes in the pleural cavity commonly being involved. Once the tumor has spread to multiple locations, curative treatment is rare because surgical excision and radiotherapy cannot remove all or nearly all the cancer cells.

Histologic Classification

Histologic classification of lung cancer involves determining the cellular origin of the tumor. Knowing the histology of the tumor influences treatment decisions as well as prognosis. In order for histologic classification to be carried out, the pathologist must obtain a tissue sample. Methods of tissue sampling are discussed in the section on diagnostic principles.

There are four major histologic types of lung cancer that are divided into two classes based on response to treatment and prognosis: small cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC). However, it is important to note that certain other rare malignancies can be seen as well as mixed-type carcinomas. The four major types of lung cancer are outlined in Table 87–1.

TABLE 87–1. Lung Tumor Histopathology[11]

Tumor Type	Percent of Tumors	Approximate Cell Doubling Time	Sensitivity to Chemotherapy and Radiotherapy	Relative Risk of Metastasis
Small cell	10–15%	30 days	High	High
Non–small cell				
Adenocarcinoma	30–35%	180 days	Low	Medium
Large cell (giant)	9%	100 days	Low	Low
Squamous (epidermoid)	30–35%	180 days	Low	Low

CLINICAL PRESENTATION AND DIAGNOSIS



❷ Clinical Presentation

Signs and symptoms of lung cancer can be classified into three subdivisions: pulmonary, extrapulmonary, and paraneoplastic syndromes. Distinguishing between these classes of symptoms is important because it can aid in determining the severity of the disease, guide treatment options, and affect prognosis.

Pulmonary Symptoms

Symptoms owing to the direct effects of the primary tumor are often the first to appear and are the most common. These include

- Cough
- Chest pain
- SVC obstruction
- Shortness of breath
- Dysphagia
- Hemoptysis
- Pleural effusion

Extrapulmonary Symptoms

Once the tumor invades tissues outside the pleural cavity, it can produce a wide array of symptoms, including

- General bone pain
- Adrenal insufficiency
- Confusion
- Personality changes
- Enlarged lymph nodes
- Weight loss
- Seizures
- Nausea
- Focal neurologic symptoms
- **Horner's syndrome**
- Fatigue
- Headache
- Vomiting
- Subcutaneous skin nodules

Paraneoplastic Syndromes

Symptoms that are not a result of the direct effects of the tumor are termed **paraneoplastic syndromes.** They may be caused by substances secreted by the tumor or in response to the tumor and often occur in tissues far from the site of malignancy. Paraneoplastic syndromes are numerous and affect a wide variety of systems, including the endocrine, neurologic, skeletal, renal, metabolic, vascular, and hematologic systems.

Clinical symptoms are seen not commonly until lung cancer tumors become large and/or have metastasized. This is a key factor in the poor prognosis associated with lung cancer. Patients who are diagnosed at an earlier clinical stage are more likely to respond to treatment than those at later stages. Therefore, diagnosing lung cancer earlier through screening and identification of initial signs and symptoms is important. Since screening techniques have not been refined sufficiently to demonstrate high rates of both sensitivity and specificity, identifying lung cancer patients on symptomatic presentation is of utmost importance.

Chemoprevention

The term **chemoprevention** refers to the use of prophylactic medications to prevent the development of cancer. Many studies of potential chemopreventatives, including nonsteroidal anti-inflammatory drugs (NSAIDs), retinoids (β-carotene), inhaled glucocorticoids, vitamin E, selenium, and green tea extracts, have been conducted, but none has been successful. Large randomized clinical trials have evaluated β-carotene as a lung cancer chemopreventative agent in high-risk patients (older smokers). The trials clearly show that older people who smoke have a higher risk of developing and dying of lung cancer if they take a β-carotene supplement. Nonsmokers do not appear to have an altered risk of lung cancer with β-carotene consumption.[14]

Currently, one of the most promising agents for the prevention of lung cancer is selenium, which appeared to prevent the development of lung tumors in patients with skin cancer.[15] This has not yet been shown in patients without preexisting skin cancer, although studies are underway.

Diagnosis

Diagnosis of lung cancer requires both visualization of the cancerous lesion and tissue sampling for pathologic assessment. Visualization of the suspected tumor provides the clinician with the information necessary to choose the most appropriate sampling technique. While some lung tumors may be very apparent using relatively simple techniques such as a chest x-ray (CXR), many can be either too small to detect or located in an anatomically difficult area to visualize. Therefore, multiple methods of visualization are used often. Once the tumor has been located, sampling provides tissue to confirm malignancy and to determine the histology (i.e., squamous cell, adenocarcinoma, large cell, or small cell). The advantages and disadvantages of various sampling methods must be weighed carefully so that the least invasive procedure can be performed that has a high likelihood of resulting in an accurate diagnosis. Tools used in the diagnosis of lung cancer are outlined in Table 87–2.

TABLE 87–2. Diagnostic Tools

	Technique	Description
Visualization	Chest x-ray	The least expensive visualization method in the diagnosis of lung cancer. Readily accessible and does not require systemic administration of contrast dye. However, it often detects lesions that are not cancerous and is not capable of assessing lymph node status.
	Computed tomography	More accurate when providing information on size, location, and invasion than CXR. It is recommended as part of the standard work-up in most cases.
	PET scanning	Uses a substance called 5-fluorodeoxyglucose (5-FDG) to produce a functional image of the lungs. Cells that are actively growing and dividing use greater amounts of glucose and therefore take up more 5-FDG. Focal regions of fluorescence can be visualized in cancerous lesions. PET scanning combined with a CT scan is more accurate than CT scan alone; however, the exact role of PET scanning in staging and monitoring is unclear. The apparent benefit and common role in staging is to evaluate mediastinal disease when it can influence the tumor resectability.
Tumor Sampling	Fine-needle aspiration	A method of aspirating cells from the tumor via insertion of a small-bore needle into the lesion and aspirating. Commonly used to evaluate lymph nodes or other poorly accessible sites, it has the advantage of being faster and less invasive than other biopsy methods; however, it does not preserve the architecture of the tumor and may return cells that are undergoing cell death, which negates histologic analysis.
	Bronchoscopy	A fiberoptic camera is inserted through the airways to examine the site of the suspected lesion. Once the lesion. Once the lesion is visualized, a tool attached to the camera allows for a tissue biospy.
	Core needle biopsy	A method of obtaining tissue and preserving the tumor architecture. A large-bore needle is inserted into a lesion, where it cuts a core of tissue out that then can be evaluated
	Thoracentesis	Involves removal of fluid in the pleural cavity via a needle. The fluid then is assayed for presence cancerous cells. This procedure has low sensitivity and depends on the presence of a pleural effusion
	Sputum cytology	Detects cancerous cells that become disloged from the airways into the sputum. Sputum cytology is useful because it is not invasive, although it has much lower sensitivity for detecting cancer.

Clinical Staging

Once the diagnosis of lung cancer is confirmed through visualization and biopsy, the extent of disease must be determined. For NSCLC, tumor growth and spread are staged using the American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) staging system. Small cell lung cancer typically is staged with the Veterans Administration Lung Cancer Study Group method. Clinical staging serves two primary purposes: predicting prognosis and guiding therapy.

Non–Small Cell Lung Cancer

Clinical staging of NSCLC with the TNM system evaluates the size of the tumor, extent of nodal involvement, and presence of metastatic sites. The combination of these three evaluations determines the stage. Clinical stages and associated survival rates are outlined in Table 87–3. Local disease includes tumors that are confined to a single hemithorax and those cancers which have spread to the ipsalateral hilar lymph nodes. Once malignancy invades the mediastinal lymph nodes or contralateral hilar nodes, the disease becomes locally advanced. When signs of cancer are detected outside the pleural cavity, it is classified as advanced disease. Local disease is associated with the highest cure and survival rates, whereas those with advanced disease have less than a 10% 5-year survival rate.

Small Cell Lung Cancer

The most commonly used system of staging SCLC was developed originally by the Veterans Administration Lung Cancer Study Group. This system categorizes SCLC into two classifications: limited and extensive disease.[16]

TABLE 87–3. Clinical Stage and Prognosis[61, 62]

Clinical Stage	TNM staging			Survival Rate	
	Tumor	Node	Metastasis	1 Year	5 Year
Local					
IA	1	0	0	94%	67%
IB	2	0	0	87%	53%
IIA	1	1	0	89%	40%
Locally Advanced					
IIB	2	1	0	73%	30%
	3	0	0		
IIIA	1	2	0	58%	15%
	2	2	0		
	3	1	0		
	3	2	0		
IIIB	Any	3	0	37%	10%
Advanced					
IIIB	4	Any	0	37%	10%
IV	Any	Any	1	18%	Less than 5%



Patient Encounter, Part 2: Medical History, Physical Examination, and Diagnosis

PMH
Significant for COPD (poorly controlled), GERD (controlled with PPIs), and moderate hypertension

FH
Father died of MI, mother living.

Meds
- Lisinopril 20 mg daily
- Lansoprazole 30 mg daily
- Albuterol/ipratropium MDI 2 puffs bid

ROS
(+) light chest pain, shortness of breath, hemoptysis; (–) recent weight loss

PE
VS: BP 135/69, RR 26, P 80, T 99°F (37.2°C)
CV: RRR

Labs
- Slightly elevated ionized calcium and LFTs; all others WNL.
- CXR reveals a solitary nodule in right lower lobe.
- Fine-needle aspiration confirms adenocarcinoma.
- Further evaluation with CT and PET scans reveal a $T_2N_0M_0$ tumor.

- What clinical stage is this patient's disease?
- What is the estimated survival time for this stage of NSCLC?

- When evidence of the tumor is confined to a single hemithorax and can be encompassed by a single radiation port, the disease is considered limited.
- Any progression beyond this point is extensive disease.

TREATMENT

Desired Outcome and General Approach to Patient

The treatment of lung cancer depends on tumor histology, stage of disease, and patient characteristics such as age, gender, history, and performance status. All these aspects must be assessed before appropriate treatment can be recommended. The general approach to treatment of lung cancer is outlined in Fig. 87–1. In the development of a patient care plan, keep in mind the ultimate goals of therapy. ❻ *In patients with early-stage disease, a definitive cure is the primary goal of treatment, although this end point is not always met. Additional goals of treating lung cancer patients include prolongation of survival and improvement of quality of life through alleviation of symptoms.* The goals of treatment must be considered when selecting a therapeutic plan. Some treatments may show prolonged survival by a few months but at the expense of significant decreases in patient quality of life. Treatment decisions must include both the health care team and an informed and well-counseled patient.

Nonpharmacological Therapy

Surgery

❸ *Of all treatment modalities, surgical resection of the affected lobe or lung leads to the greatest improvement in survival for NSCLC patients. If at all possible, surgery should be considered the mainstay of treatment for all patients with early-stage NSCLC (clinical stage IA, IB, or IIA) and locally advanced tumors.*[17] The resectability of the tumor should only be determined by an experienced thoracic surgeon who routinely works with cancer patients.[18] During surgery, peripheral lymph nodes may be removed if they are thought to be involved, and mediastinal nodes often are dissected for biopsy to determine their involvement. Surgery is not curative and as a general approach does not prolong survival in patients with advanced disease; however, it is an important palliative treatment that can improve some patients' quality of life. In this respect, surgery is limited to local sites where the tumor is causing significant morbidity (e.g., spinal cord compression). Patients with small cell carcinomas are treated rarely with surgery because the results of a randomized trial published in 1969 showed that surgery did not result in any 5- or 10-year survivors, whereas radiation produced a 4% survival rate at 5 and 10 years.[19,20] With improved imaging and surgical techniques and the use of effective adjuvant therapy, some clinicians believe that surgery does have a role in early-stage disease; however, this has yet to be proven in a clinical trial.

Radiation

As mentioned earlier, radiation is the treatment of choice for limited-stage small cell lung cancer. It is synergistic with chemotherapy, and optimal patient outcomes are realized when radiation is administered concurrently with chemotherapy. In patients with advanced small cell lung cancer, radiation is limited to palliation of symptoms caused by a local tumor. Patients with localized NSCLC are best treated with surgery; however, many of these patients are inoperable because of comorbidities (e.g., lung disease from smoking). In these situations, radiation therapy can be used in place of surgery with curative intent, although at a success rate approximately 50% that of surgery.[21] Similar to small cell lung cancer, patients with late-stage NSCLC can receive radiation therapy to palliate symptomatic metastases. Although radiation is less invasive than surgery, it can have marked toxicity on normal tissue, and patients may experience esophagitis, pneumonitis, cardiac abnormalities, myelopathies, and skin irritation. These adverse events can be decreased by using stereotactic radiation and/or hyperfractionated administration.[17]

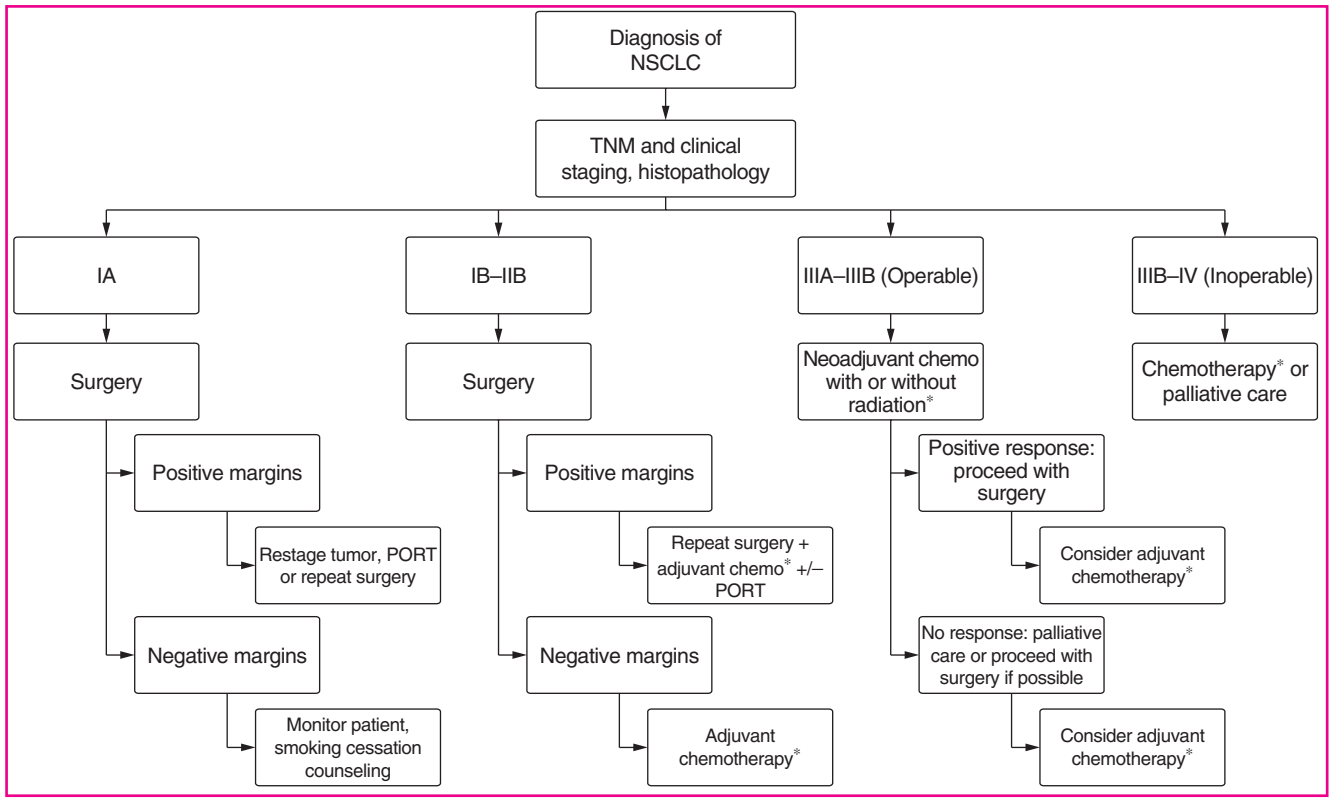


FIGURE 87–1. Clinical pathway for non–small cell lung cancer. *See text for specific treatment recommendations. Chemo, chemotherapy; NSCLC, non–small cell lung cancer; PORT, post operative radiotherapy; TNM, tumor node metastasis.

Pharmacologic Therapy

Chemotherapy

Traditional chemotherapeutic agents interfere with processes during cell division or DNA replication in nondividing cells that result in cell death. Unfortunately, these agents are not specific for cancer cells, and other tissues in the body often are affected as well. Rapidly cycling cells, both tumor and normal tissue such as bone marrow, the epithelial cells of the gastrointestinal tract, and hair follicles, are most susceptible to chemotherapy toxicity. Since the dose of traditional chemotherapy agents is determined in phase I studies where the maximum tolerated dose is considered the best dose, toxicity is seen with all these agents. Preventing and managing chemotherapy toxicity are crucial to optimizing patient outcomes (i.e., curing, prolonging life, or palliating symptoms). Making the decision to start chemotherapy depends greatly on the overall patient picture, with emphasis on performance status (see below) and comorbid conditions. Knowledge of the major adverse effects of individual regimens is important for anticipation and prophylaxis of such toxicities. Many regimens require appropriate premedications and hydration. Furthermore, decisions to start chemotherapy must include the full consent and understanding of risks by the patient. Counseling on the chemotherapy and risk of toxicity is imperative before dosing. Lung cancer regimens and their associated toxicities are shown in Table 87–4.

Performance Status

The performance status of an individual patient predicts response and likelihood of toxicity to chemotherapy as well as overall survival.[22] The performance status scaling system used most frequently was developed by the Eastern Cooperative Oncology Group (ECOG)[23] (Table 87–5). ❹ *Categorizing patients on their ECOG performance status (PS) allows for an objective measure of capability to tolerate systemic therapies that may severely compromise the patient's health. Patients who score well (0–1) are more likely to tolerate intense therapy, whereas patients who score highly (3–4) are considered unfit for chemotherapy or surgery. There is some controversy over whether to treat patients with a PS of 2. At this point, treatment is aimed at treating comorbidities to improve the performance status or the use of palliative symptomatic therapy.* Patients with less advanced disease may be treated more aggressively in this scenario.

Adjuvant Therapy

The term *adjuvant therapy* refers to the use of chemotherapy or radiotherapy following surgical resection of a tumor mass. The rationale behind adjuvant chemotherapy is to eradicate micrometastases or other tumor cells that may have been missed during removal of the primary tumor. The recent results of five relatively large prospective trials (n = 344–1867) suggest that there is benefit from adjuvant chemotherapy. The largest study, the International Adjuvant Lung Trial (IALT),[24] has led to the

TABLE 87–4. Chemotherapy Regimens in Lung Cancer and Associated Toxicities[23,39,44,63–75]

	Dose	Cycle Length	Neutropenia	
			Grade III	Grade IV
Non-Small Cell				
Paclitaxel-carboplatin-bevacizumab	Carboplatin, dose targeted to *AUC* of 6 IV (day 1), paclitaxel 200 mg/m^2 IVover 3 hours (day 1), bevacizumab 15 mg/kg IV (day 1)	21 days	N/A	24%
Cisplatin-paclitaxel	Paclitaxel 135 mg/m^2 IV over 24 hours (day 1) and cisplatin 75 mg/m^2 IV (day 2)	21 days	18%	57%
Cisplatin-docetaxel	Cisplatin 75 mg/m^2 IV (day 1) and docetaxel 75 mg/m^2 IV (day 1)	21 days	21%	48%
Cisplatin-gemcitabine	Cisplatin 100 mg/m^2 IV (day 1) and gemcitabine 1000 mg/m^2 IV (days 1, 8, 15)	28 days	24%	39%
Carboplatin-paclitaxel	Carboplatin, dose targeted to *AUC* of 6 IV (day 1), and paclitaxel 225 mg/m^2 IV over 3 hours (day 1)	21 days	20%	43%
Gemcitabine-paclitaxel	Paclitaxel 200 mg/m^2 IV (day 1) and gemcitabine 1000 mg/m^2 (day 1 and 8)	21 days	10%	5%
Gemcitabine-docetaxel	Gemcitabine 1100 mg/m^2 IV (days 1 and 8) and docetaxel 100 mg/m^2 IV (day 8)	21 days	11%	11%
Gemcitabine	Gemcitabine 1125 mg/m^2 (days 1 and 8)	21 days	19%	
Pemetrexed	Pemetrexed 500 mg/m^2 (day 1), vitamin B_{12} 1 mg IM 1–2 weeks before treatment initiation and every 9 weeks thereafter, folic acid 1 mg daily beginning 3 weeks before treatment initiation	21 days	5–6%	
Paclitaxel	Paclitaxel 200 mg/m^2 IV over 3 hours (day 1)	21 days	34%	3%
Docetaxel	Docetaxel 35 mg/m^2 IV over 1 hour (days 1, 8, 15)	28 days	5%	
Small Cell				
EP	Etoposide 100 mg/m^2 IV (days 1–3) and cisplatin 100 mg/m^2 IV (day 2)	28 days	85%	18%
CAV	Cyclophosphamide 800 mg/m^2 IV (day 1), doxorubicin 50 mg/m^2 (day 1), and vincristine 1.4 mg/m^2 (maximum of 2 mg) IV (day 1)	21–28 days	15%	72%
EC	Etoposide 100 mg/m^2 IV (days 1–3) and carboplatin *AUC* 5–6 IV (day 1)	21 days	10–20%	5–15%
IC	Irinotecan 60 mg/m^2 (days 1, 8, 15) and cisplatin 60 mg/m^2 (day 1)	28 days	40%	25%
Topotecan	Topotecan 1.5 mg/m^2 IV over 30 minutes (days 1–5)	21 days	18%	70%

	Other Significant Toxicities	Nausea and Vomiting Potential
Non–Small Cell		
Paclitaxel-carboplatin-bevacizumab	Diarrhea, fever, headache, hypertension, hemoptysis, infection, leucopenia, nausea, neuropathy, peripheral neuritis, vomiting, thromobocytopenia, thrombotic events	High (day 1 only)
Cisplatin-paclitaxel	Febrile neutropenia, infection, thrombocytopenia, nausea, vomiting, diarrhea, cardiac toxicity, renal toxicity, neuropathy, weakness, hypersensitivity reactions, anemia	High (day 2 only)
Cisplatin-docetaxel	Infection, thromocytopenia, nausea, vomiting, diarrhea, cardiac, renal, neuropathy, weakness, hypersensitivity, anemia	High (day 1 only)
Cisplatin-gemcitabine	Febrile neutropenia, infection, thrombocytopenia, nausea, vomiting, diarrhea, cardiac, renal, neuropathy, weakness, anemia	High (day 1) Mild (days 8 and 15)
Carboplatin-paclitaxel	Infection, thrombocytopenia, nausea, vomiting, diarrhea, cardiac, renal, neuropathy, weakness, hypersensitivity, anemia	High (day 1 only)
Gemcitabine-paclitaxel	Alopecia, nausea and vomiting, neurotoxicity, thrombocytopenia	Moderate
Gemcitabine-docetaxel	Nausea and vomiting, diarrhea, thrombocytopenia, asthenia, neurotoxicity	Moderate
Gemcitabine	Thrombocytopenia	Mild
Pemetrexed	Anemia	Mild
Paclitaxel	Infection, nausea, vomiting, diarrhea, mucositis, arthralgia, asthenia, peripheral neuropathy, alopecia, cardiovascular	Mild (day 1 only)
Docetaxel	Fatigue, nausea, vomiting, skin toxicity, neuropathy, anemia, hypersensitivity, alopecia	Mild (on administration days only)

(Continued)

TABLE 87–4. Chemotherapy Regimens in Lung Cancer and Associated Toxicities[23,39,44,63–75] (*Continued*)

	Other Significant Toxicities	Nausea and Vomiting Potential
Small Cell		
EP	Infection, fever, nausea, vomiting, thrombocytopenia, anemia	High (day 2 only)
CAV	Nausea, vomiting, thrombocytopenia, neuropathy, hepatic, renal, alopecia	High
EC	Infection, thrombocytopenia, alopecia	High (day 1 only)
IC	Fever, infection, thrombocytopenia, anemia, diarrhea, nausea and vomiting, liver enzymes	High (day 1), moderate (days 8 and 15)
Topotecan	Neutropenic fever, neutropenic sepsis, anemia, thrombocytopenia, nausea, fatigue, vomiting, stomatitis, anorexia, diarrhea, fever	Mild (days 1–5)

CAV, cyclophosphamide, doxorubicin, vincristine; EC, etoposide carboplatin; EP, etoposide cisplatin; IC, irinotecan, cisplatin. See Table 87–4 for doses and schedules.

conclusion that adjuvant chemotherapy following surgical resection of non–small cell tumors leads to a 4% improvement in survival. Interestingly, the majority of patients in the IALT trial were treated with a cisplatin and an older agent, which have been proven inferior to combinations of cisplatin and a newer agent in the advanced disease setting. Two studies (Intergroup JBR-10 and CALGB 9633) evaluated cisplatin-vinorelbine and carboplatin-paclitaxel (current standards for advanced-stage disease) and found a survival advantage of 12% to 15%.[25] Consequently, adjuvant therapy has become the standard of care and should be offered to patients after resection,[26] and although the regimen of choice is unclear, carboplatin-paclitaxel and cisplatin-vinorelbine appear to be the regimens with the most evidence.

Adjuvant radiotherapy, or postoperative radiotherapy (PORT), is thought to eliminate remnants of the resected tumor that might be deposited in nearby tissue. Clinical trials have clearly shown that PORT decreases local recurrence; however, a survival benefit has never been shown. A meta-analysis of PORT when used alone suggest that PORT actually may be detrimental to patients with early-stage disease (stage I or II).[27,28] The meta-analysis evaluated older studies that used outdated radiation techniques, and consequently, some argue that the meta-analysis does not apply to current practice.[29] Nonetheless, no studies to date have demonstrated a survival advantage with PORT. In cases where local recurrence is a significant risk, PORT still may be a viable option. In fact, current guidelines recommend that patients with positive surgical margins (i.e., cancerous cells are detected on the surface of the excised tissue) undergo reresection or systemic chemotherapy or PORT.[18] Outside this indication, adjuvant radiotherapy without concurrent chemotherapy is not considered beneficial, especially in early-stage disease.

TABLE 87–5. ECOG Performance Status[33–35]

ECOG Score	Patient Status
0	Unrestricted, asymptomatic
1	Able to complete light work activities but restricted from strenuous tasks. Otherwise ambulatory.
2	Ambulatory for more than 50% of waking hours. Able to care for self completely but unable to complete even light work.
3	Able to care for self on a limited basis, confined to bed or chair more than 50% of time awake. Unable to carry out work activities
4	Completely disabled, confined to bed or chair
5	Deceased

Neoadjuvant Therapy

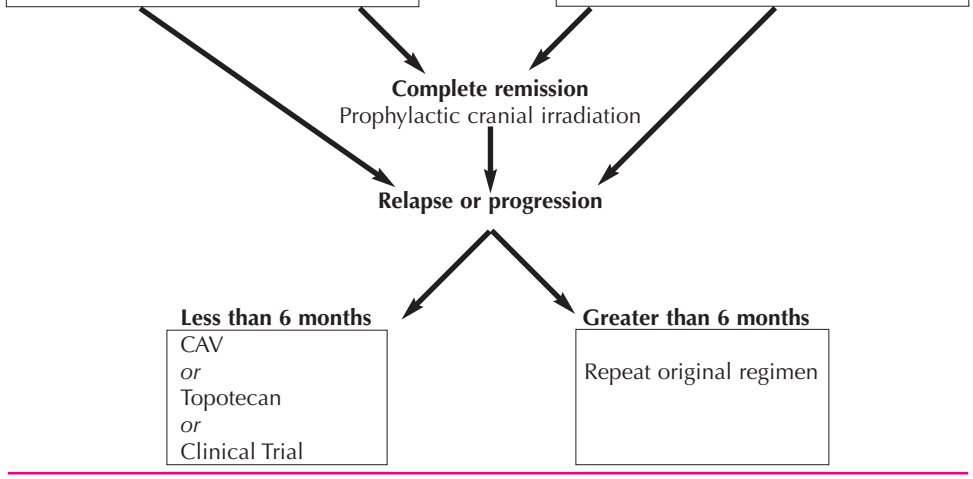
Neoadjuvant, or *induction*, *therapy* refers to the use of chemotherapy regimens or radiotherapy prior to surgery. The rationale behind neoadjuvant therapy is to decrease the size of the tumor so that it can be extracted more easily with clean margins, as well as to eliminate distant micrometastases before invasive local treatment. Furthermore, patients with marginally resectable or nonresectable tumors may respond sufficiently to induction therapy that surgery becomes an option. Neoadjuvant chemotherapy has been shown to yield benefits in NSCLC (i.e., increase in median survival and disease-free survival and decreased risk of metastasis) for both local and locally advanced disease.[30] However, the toxicity of induction regimens may delay surgery, and if the tumor does not respond to the treatment, there is a risk of disease progression. Nonetheless, current data suggest that over 90% of patients who are treated with neoadjuvant therapy maintain their scheduled surgery.[31] This approach is most common in patients with locally advanced tumors (stage III).[32] Current studies are aimed at comparing neoadjuvant with adjuvant therapy in earlier-stage NSCLC patients.

Small Cell Lung Cancer

Small cell lung cancer typically presents as extensive disease (approximately 60% to 70% of new cases) and progresses very quickly. Small cell carcinomas are very responsive to chemotherapy and radiation. Radiotherapy became the standard in 1969, when a randomized trial showed that it offered the potential for cure, whereas surgery did not.[20] For the vast majority of patients, chemotherapy with or without radiotherapy is the treatment of choice. Even after a complete response to therapy, the cancer usually recurs within 6 to 8 months, and survival time following recurrence is typically short (~4 months). This yields a typical survival rate of 14 to 20 months for limited disease and 8 to 13 months for extensive disease.[33] Table 87–6 illustrates the general treatment path of SCLC.

TABLE 87–6. Small Cell Lung Cancer Treatment Overview[60]

Stage	First Line
Limited	EP × 4 cycles *or* EC × 4 cycles *plus* Concurrent radiation
Extensive	EP × 4–6 cycles *or* EC × 4 cycles *or* IC × 4 cycles



CAV, cyclophosphamide, doxorubicin, vincristine; EC, etoposide carboplatin; EP, etoposide cisplatin; IC, irinotecan, cisplatin. See Table 87–4 for doses and schedules.

Limited Disease

The regimen of choice for limited-disease SCLC is etoposide-cisplatin (EP). Carboplatin may be substituted for cisplatin to reduce nausea and vomiting, nephrotoxicity, or neurotoxicity,[34] although increased myelosuppression in the form of thrombocytopenia may result.[35] In patients who are able to tolerate combined therapy, concomitant chemoradiotherapy offers the most substantial survival benefit. In European countries, a three-drug combination containing an anthracycline has been the mainstay of therapy; however, mounting clinical evidence shows that these regimens are inferior to EP plus concurrent radiation and have more toxicity.[36] Consequently, the guidelines recommend that the EP regimen be used with concurrent radiotherapy.[33] Since patients with small cell lung cancer commonly have a recurrence in the central nervous system (CNS), trials have been performed to evaluate the benefit of prophylactic cranial irradiation (PCI). A pivotal study showed that PCI reduces the incidence of brain metastasis and increases 3-year survival from 15% to 21%.[37,38] Consequently, patients who achieve a complete response with treatment should be offered PCI.

Extensive Disease

Platinum regimens are also the treatment of choice in extensive disease, and many studies have failed to show superiority to the EP regimen as first-line treatment. A combination of irinotecan and cisplatin in one Japanese study demonstrated an increased median survival time by approximately 3 months over the EP regimen. This regimen showed a lower incidence of severe neutropenic side effects but exhibited higher rates of middle- to high-grade diarrhea.[39] However, this study was repeated in the United States and did not show a similar improvement over the EP regimen.[40] Therefore, EP remains the regimen of choice for treating extensive SCLC in the United States. Concurrent radiotherapy is not used routinely in extensive disease.[39]

Recurrent Disease

The treatment of recurrent disease depends on the time to recurrence. If the time to recurrence is less than 6 months, second-line therapy should be considered if the patient has an acceptable performance status (see "Patient Care and Monitoring"). The most widely accepted second-line therapies in SCLC are topotecan alone or CAV [cyclophosphamide, doxorubicin (Adriamycin), vincristine]. Relapses occurring more than 6 months after treatment warrant a repeat of the initial regimen. Poor performance status patients (3–4) typically are treated with palliative care therapies.

Non–Small Cell Lung Cancer

The first step in treatment of NSCLC involves confirmation of the clinical stage and determination of resectability of the tumor. This decision always should be made by a thoracic surgeon who routinely performs lung cancer surgery. Treatment options depend on the advancement of disease (i.e., local, locally advanced, or metastatic).

Local Disease

Local disease encompasses stages IA through IIA and is associated with a favorable prognosis because approximately 40% to 60% of patients are expected to live more than 5 years from diagnosis. Goals of therapy are curative in local disease, and surgery is the mainstay of treatment. Stage IA tumors are seen rarely clinically but may be treated with surgery alone. In this case, neoadjuvant or adjuvant therapy has not been studied adequately to know if it conveys a benefit. If surgical margins are positive, radiotherapy or reresection is recommended.[18] Stage IB, IIA, and IIB disease is treated with adjuvant chemotherapy. Patients who have positive or questionable margins may receive radiation therapy, which typically is administered with the adjuvant chemotherapy. The regimen of choice in this setting is not clear; however, the most benefit seen in clinical trials used carboplatin-paclitaxel or cisplatin-vinorelbine.[18,25]

Locally Advanced Disease

Patients with locally advanced disease (stages IIB and IIIA) still may be considered for surgery. Neoadjuvant chemotherapy with concurrent radiotherapy can be used prior to surgery, although this practice varies from institution to institution. Progression of disease during induction therapy may preclude surgery, and the regimen should be altered if disease progresses in this time. If there is a response, surgery may proceed, preferably with additional adjuvant chemotherapy. Nonresectable locally advanced disease may be treated with both an active platinum-containing regimen and radiotherapy.

Advanced or Metastatic Disease (Stages IIIB and IV)

Advanced disease is treated with chemotherapy if the patient has an acceptable ECOG PS score (0–1). Platinum-containing doublets have produced the highest overall response rates (25% to 35%) and survival times (30% to 40% 1-year survival) in well-performing patients with advanced disease. A platinum agent and one of the newer agents (see below) are superior to a platinum agent and an older agent (e.g., etoposide or vindesine). A number of different platinum doublet treatment regimens which have used in this setting, and no agent appears to be clearly superior to the others. There has been some debate about the equivalence of cisplatin and carboplatin. To address this question, a recent meta-analysis[41] was performed that found that cisplatin is superior to carboplatin when combined with a newer agent in advanced-stage NSCLC. This analysis had some limitations, which leaves clinicians to make their own decision. Additionally, two non-platinum-containing regimens have been shown to have similar response and survival benefits. Both gemcitabine-paclitaxel and gemcitabine-docetaxel have been shown to produce similar response durations and survival times as platinum-containing regimens[42,43] and may be substituted when patients are unlikely to tolerate the toxicity of platinum regimens owing to comorbidities or other factors. NSCLC chemotherapy doublets that are considered generally equivalent include

- Paclitaxel-cisplatin
- Paclitaxel-carboplatin
- Cisplatin-gemcitabine
- Cisplatin-docetaxel
- Carboplatin-docetaxel
- Cisplatin-vinorelbine
- Gemcitabine-paclitaxel
- Gemcitabine-docetaxel

A large randomized trial comparing the first four regimens reported similar response rates and survival with all treatments, although there was less life-threatening toxicity and treatment-related death associated with the administration of paclitaxel-carboplatin. Consequently, one may argue that paclitaxel-carboplatin is the treatment of choice. However, the carboplatin- paclitaxel regimen used in the trial[44] infused paclitaxel over 24 hours, which is uncommon in clinical practice. The most common carboplatin-paclitaxel regimen infuses a higher dose of paclitaxel over 3 hours in the clinic rather than admit patients to the hospital for a 24-hour infusion. It is unfair to extrapolate the toxicity advantage from this trial to the commonly used 3-hour paclitaxel infusion, and consequently, there is truly not a single best regimen.

While it is unclear exactly which platinum combination is the best, new research is being aimed at adding nontraditional agents to platinum regimens. Adding the EGFR tyrosine kinase inhibitors to chemotherapy provides no benefit; however, adding bevacizumab to the carboplatin-paclitaxel (3-hour infusion) regimen increases response rates and prolongs progression-free and overall survival.[45] Consequently, carboplatin-paclitaxel and bevacizumab are arguably the new standard of care. Based on the inclusion/exclusion criteria for this study, bevacizumab is recommended when the patient meets the following criteria:[18]

- Non–squamous cell histology (NSCLC only)
- History negative for hemoptysis
- History negative for CNS metastasis
- No concurrent anticoagulation therapy (i.e., enoxaparin, heparin, or warfarin)
- Chemotherapy regimen that does not have significant (greater than 10%) risk of thrombocytopenia

Treating patients with a PS of 2 is a subject of much debate. While PS 2 patients typically show inferior survival rates and higher toxicity to platinum chemotherapy than higher-performing patients, low-toxicity single-agent regimens may offer a survival advantage in this subset. Use of these regimens also presents a method of providing symptomatic care for advanced-stage patients.[46] Newer third-generation agents such as pemetrexed, gemcitabine, and docetaxel may be used in this scenario. In PS 3 or 4 patients, chemotherapy typically results in high rates of toxicity and fails to convey a survival benefit. Consequently, treatment should be aimed at relief of symptoms instead of a definitive cure.



Patient Encounter, Part 3

The patient's condition has not interfered with his ability to work, and he is able to complete most daily activities. Therefore his ECOG PS score in 0.

- Are there any nonpharmacologic interventions you would suggest?

Recurrent (Progressive) Disease

Although patients may experience a response to initial therapy, disease recurs in many cases. If the recurrence is localized, surgery options may be assessed. If the patient's PS remains acceptable (0–1), second-line systemic chemotherapy has been shown to improve survival. A single-agent therapy with docetaxel, pemetrexed, or erlotinib is recommended at this stage.[47] Recurrences in poorly performing patients (3–4) usually are not treated with chemotherapy and are instead treated with supportive care. Additional recurrences (i.e., third-line therapy) may be treated with erlotinib if not used previously. Otherwise, repeat single-agent therapy or administer best supportive care.

Single-Agent Therapy

First-line therapy for advanced-stage NSCLC and small cell lung cancer is best done with a two-drug regimen. However, patients who have a recurrence after the initial regimen are best treated with a single chemotherapy agent. Single-agent therapy is also acceptable for poor health patients with advanced disease because toxicities tend to be lower with one-drug regimens.[48] Typical agents used in monotherapy in lung cancer include pemetrexed, erlotinib, docetaxel, gemcitabine, paclitaxel, topotecan, and vinorelbine.[10,47–49]

Combination Therapy

❺ *Doublet chemotherapy regimens clearly are superior in response to single-agent regimens and should be used when the patient can tolerate the increased toxicity. Platinum-containing regimens are the mainstay of multidrug regimens.* There are several regimens that contain either cisplatin or carboplatin, and some clinicians feel that they can be substituted for each other; however, it is unclear if cisplatin and carboplatin are equally efficacious. When combined with newer agents (e.g., paclitaxel), both improve survival in patients with advanced-stage NSCLC compared with combinations with older agents (e.g., etoposide). Because of differences in toxicity, many clinicians favor carboplatin over cisplatin.[49] There is also interest in developing non-platinum-containing doublets. Recent studies suggest that gemcitabine combined with paclitaxel or docetaxel is just as effective in advanced-stage NSCLC as a platinum doublet; however, guidelines still suggest that a platinum-containing doublet should be used when feasible.[18] In small cell lung cancer, a platinum agent combined with an older agent (e.g., etoposide) is the treatment of choice. However, there are a number of non-platinum-containing three-drug anthracycline-containing regimens that are equally effective as a platinum doublet, at least in extensive-stage disease. However, the three-drug regimens are more toxic and therefore used rarely in the United States. In limited-stage disease, cisplatin and etoposide are superior to the three-drug anthracycline-containing regimens, and when combined with concurrent radiation, they provide optimal outcomes.[36] A direct comparison of cisplatin and carboplatin combined with etoposide found similar results, and many clinicians consider the agents interchangeable; however, this trial enrolled primarily patients with extensive-stage disease. A direct comparison in patients with limited-stage disease has not been performed, and most clinicians consider cisplatin and etoposide to be the treatment of choice because they have been used in nearly all the large comparative trials.

Monoclonal Antibodies

Bevacizumab and cetuximab are IgG monoclonal antibodies that have activity in NSCLC. Bevacizumab targets vascular endothelial-derived growth factor (VEGF), which is thought to facilitate angiogenesis, a process contributing to growth and maintenance of the tumor environment.[50] Cetuximab targets epidermal growth factor receptor (EGFR), a cytokine receptor on tumor cells that is frequently involved with tumor survival and proliferation. These monoclonal antibodies have different and less extensive toxicity profiles than traditional chemotherapy agents and appear to be synergistic with chemotherapy; hence they have been studied with the most active chemotherapy regimens for lung cancer. At this relatively early point in testing, bevacizumab has been shown to improve survival of advanced-stage NSCLC patients in a large phase III trial[45] and has been incorporated into current guidelines.[18,51,52] Cetuximab appears promising, but no large phase III trials have been completed at this time. Consequently, it is not recommended for use in lung cancer outside a clinical trial.

Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors (TKIs) work by targeting specific intracellular messenger proteins that transmit growth and survival signals. Two TKIs are currently available for treatment of lung cancer: erlotinib and gefitinib. These agents, like cetuximab, target the EGFR, which has been shown to be mutated or overexpressed in some lung tumors.[53] Both these medications are structurally related and presumably have the same mechanism of action; however, recent data show that erlotinib prolongs survival, whereas gefitinib does not. Consequently, gefitinib availability is restricted until the FDA and the company determine if there is a predictable way to identify patients who will respond to therapy. It appears that certain clinical factors are able to aid in prediction of response to both EGFR inhibitors, such as female gender, Asian ancestry, adenocarcinoma histology, and lack of significant smoking history.[54] However, the fate of gefitinib is undetermined at this time. Currently, several TKIs

that target the EGFR and other cell-signaling cascades are in clinical trials and show promise for the treatment of lung cancer.

PATIENT CARE AND MONITORING

Screening and Early Detection

Overall 5-year survival in lung cancer is only 15%, whereas those who are diagnosed at a localized stage exhibit a 5-year survival rate of 50%. Currently, over three-quarters of newly diagnosed lung cancers present with locally advanced or metastatic disease, and therefore, very few patients are able to undergo surgical resection.[1] In an attempt to identify tumors when they are localized and have higher cure rates, many investigators are evaluating different screening modalities. Effective screening methods have the potential to save thousands of lives. To date, no screening study has demonstrated a benefit in overall survival; however, the use of spiral computed tomographic (CT) scanning has been shown to be sensitive in detecting small nodules. Unfortunately, spiral CT scanning alone is not likely to be of benefit owing to the high rate of false-positive results (i.e., lack of specificity) leading to excessive patient anxiety and work-up, which can have a negative effect on morbidity and mortality. Since lung cancer tumors are hypermetabolic, they typically can be visualized with 5-FDG positron-emission tomographic (PET) scanning. The combination of spiral CT scanning and follow-up PET scanning for positive lesions is currently the most promising method. In a recent study, this combination resulted in 90% specificity and 100% sensitivity for detection of cancer when a 3-month follow-up CT was used after a negative PET scan. Furthermore, 92% of non–small cell tumors were diagnosed at stage IA or IB.[55] Additional studies evaluating the benefits on mortality of this approach are underway. ❼ *Identification and screening of high-risk patients with spiral CT scanning and PET scanning are currently the most promising, and high-risk individuals should be encouraged to enter randomized, controlled trials aimed at demonstrating a survival benefit from screening.*

Management of Toxicity

❽ *Knowing when and how to treat adverse events from chemotherapy is an important aspect of patient care. Unmanaged events may cause delays in chemotherapy administration and reduced chemotherapy doses and may contribute to treatment failure.* Given the fatal nature of untreated lung cancer, patients and health care professionals are willing to tolerate high risks of severe and life-threatening side effects, provided that the therapy has been shown to benefit the patient. There are multiple methods of preventing or reducing toxicity to chemotherapeutic agents. These methods usually are agent-specific but commonly include maintenance of adequate hydration, use of appropriate premedications, dose reduction, and use of growth factors to combat toxicities associated with cytopenias.

Grading Toxicity

In order to standardize grading of adverse events, the National Cancer Institute (NCI) has developed the Common Terminology Criteria for Adverse Events (CTC, V3.0). Toxicities are graded from 1 to 4, where grade 1 toxicity is mild, 2 is moderate, 3 is severe, and 4 is life-threatening. Selected toxicities and their grading scales are listed in Table 87–7. The full version can be accessed at www.ctep.cancer.gov. In most cases, patients who experience grade 3 or 4 toxicity require a change in therapy with the next cycle of treatment. Common changes include a chemotherapy dose reduction or pharmacologic intervention to prevent or treat the toxicity. This grading scale or a similar one is almost always employed in clinical trials and will be published in the research manuscript. This is an invaluable tool to determine what serious toxicity is most likely with a particular regimen, and this improves the pharmacist's ability to counsel the patient, as well as determine appropriate toxicity-prevention measures.

Dose Intensity and Growth Factors

The term *dose intensity* refers to the percent of drug delivered compared with the planned amount as measured by milligrams per meter squared per week. Maintaining dose intensity (i.e., delivering the planned dose, according to the scheduled time course) has been shown to influence survival in some cancers, such as breast cancer; however, the importance of dose intensity in lung cancer is not well established. In order to maintain dose intensity, pharmacologic agents sometimes are used to combat serious toxicities that may prohibit or delay administration of subsequent doses. The most common grade 3 or 4 toxicity associated with most lung cancer chemotherapy regimens is myelosuppression, more specifically, neutropenia. Patients who experience grade 3 or 4 neutropenia are at a high risk of developing a severe or life-threatening bacterial infection. Consequently, patients with neutropenia who develop a fever are empirically given broad-spectrum antibiotics. If a patient experiences neutropenic fever, intervention with growth factors (e.g., filgrastim or sargramostim) to maintain dose intensity or dose reduction should occur prior to the next cycle of chemotherapy. In lung cancer patients, no survival benefit has been demonstrated by using a colony-stimulating factor to maintain dose intensity. ❾ *While some evidence does exist that the use of a colony-stimulating factor reduces the number of neutropenic fever episodes, hospital stay, and antibiotic administration in certain subsets of lung cancer patients, routine front-line (prophylactic) use of a colony-stimulating factor is not recommended owing to lack of a survival benefit.*[56]

Nausea and Vomiting

Platinum agents are the most active lung cancer agents and historically have very high rates of nausea and vomiting. This is particularly true of high-dose cisplatin, which is used in many regimens. Understanding how to prevent and treat

TABLE 87–7. Selected NCI CTC V3.0 (www.cstep.cancer.gov)

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
General	Mild	Moderate	Severe	Life-threatening	Death
Neutropenia	Lowest baseline: 1500/mm^3 (1.5×10^9/L)	Less than 1500–1000/mm^3 ($1.5–1 \times 10^9$/L)	Less than 1000–500/mm^3 ($1–0.5 \times 10^9$/L)	Less than 500/mm^3 (5×10^9/L)	
Thrombocytopenia	Lowest baseline: 75,000/mm^3 (75×10^9/L)	Less than 75,000–50,000/mm^3 ($75–50 \times 10^9$/L)	Less than 50,000–25,000/mm^3 $50–25 \times 10^9$/L)	Less than 25,000 mm^3 (25×10^9/L)	Death
Diarrhea	Increase of less than 4 stools per day over baseline or mild increase in ostomy output	Increase of 4–6 stools per day over baseline, IV fluids indicated less than 24 hours moderate increase in ostomy output compared with baseline, not interfering with ADL	Increase of greater than or equal to 7 stools per day over baseline, incontinence, IV fluids greater than or equal to 24 hours; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death
Esophagitis	Asymptomatic pathologic, radiographic, or endoscopic findings only	Symptomatic altered eating/swallowing IV fluids indicated less than 24 hours	Symptomatic and severely altered eating/swallowing; IV fluids, tube feedings, or TPN indicated greater than or equal to 24 hours	Life-threatening consequences	Death
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated less than 24 hours	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated greater than 24 hours	Life-threatening consequences	Death
Vomiting	1 episode in 24 hours	2–5 episodes in 24 hours; IV fluidsindicated less than 24 hours	Greater than or equal to 6 episodes in 24 hours; IV fluids or TPN indicated greater than or equal to 24 hours	Life-threatening consequences	Death

chemotherapy-induced nausea and vomiting (CINV) in lung cancer patients is crucial because nearly all the regimens are highly emetogenic. Although the pathology of CINV is not fully understood, there are three classifications of CINV based on the time of occurrence in relationship to chemotherapy administration: acute CINV (1–24 hours after the dose), delayed (24 hours to 5 days after the dose), and anticipatory (before the dose following one or more previous cycles). Acute CINV appears to be influenced predominantly by serotonin binding to 5-HT_3 receptors on the vagal nerve, where it innervates the GI tract. Delayed CINV has been attributed to a variety of mechanisms but appears to be influenced by substance-P stimulation of neurokinin-1 (NK-1) receptors in the CNS, as well as a corticosteroid-responsive element. Anticipatory CINV is thought to be a learned or conditioned behavior. The major influencing factors appear to be prior acute or delayed CINV and anxiety. Anticipatory CINV may be prevented or treated with benzodiazepines such as lorazepam or alprazolam not because they possess antiemetic properties but rather because they contain amnestic and antianxiety properties.

There are three main drug targets that are antagonized to prevent or treat acute and delayed CINV: 5-HT_3 receptors, dopamine type 2 receptors (D_2), and NK-1 receptors. 5-HT_3-receptor antagonists are the most effective agents for preventing acute CINV. However, they are commonly recommended only for moderate- to high-emetogenic-potential regimens, primarily owing to cost (see Table 87–8 for a comparison of agents). Aprepitant is the only available NK-1-receptor antagonist that is approved to prevent CINV. It has modest but additive activity in acute CINV and appears to be highly active against delayed CINV. It was approved for use in highly emetogenic regimens but also works in patients receiving moderately emetogenic chemotherapy. The use of aprepitant is somewhat limited by the cost. Dopamine type 2 receptor antagonists, which are approved commonly to manage schizophrenia, also have antiemetic activity in both acute and delayed CINV. As a group, these agents do not appear to be as effective as 5-HT_3-receptor antagonist in acute CINV or as effective as aprepitant in delayed CINV. Consequently, their use is limited commonly to patients receiving mild or moderate emetogenic chemotherapy as prevention or as treatment following full-dose 5-HT_3-receptor antagonist and/or aprepitant. They are attractive owing to their relatively low cost but also cause a significant number of side effects. Interestingly, corticosteroids, most commonly dexamethasone, is an active antiemetic agent that can be used as monotherapy to prevent acute CINV in patients receiving mild to moderate emetogenic chemotherapy. They are also synergistic with 5-HT_3-receptor antagonists, aprepitant, and D_2-receptor antagonists in acute and

TABLE 87–8. Pharmacotherapy for Chemotherapy Induced Nausea and Vomiting

Class	Indication	Drug	Dose	Half-life
NK-1 inhibitors	Acute/delayed NAV	Aprepitant	125 mg PO on day 1 80 mg PO daily on days 2–3	9–13 hours
5-HT_3 inhibitors	Acute NAV	Ondansetron	16–24 mg PO or 8–12 mg IV on day 1 16 mg PO daily or 8 mg IV daily on days 2–4	3–6 hours
		Palonosetron	0.25 mg IV on day 1	40 hours
		Granisetron	1–2 mg PO or 0.01 mg/kg IV on days 1–4	4–12 hours
		Dolasetron	100 mg PO or 100 mg IV daily on days 1–4	8 hours (active metabolite)
D_2 antagonists	Acute/delayed NAV, PRN breakthrough treatment	Haloperidol	1–2 mg PO q4–6hours or 1–3 mg IV q4–6hours	20 hours
		Olanzapine	Olanzapine 2.5–5 mg PO bid prn	20–50 hours
Corticosteroids	Adjunctive treatment for acute or delayed NAV	Dexamethasone	12 mg IV or PO on day 1 8 mg IV or PO daily on days 2–4	2–4 hours biologic half-life of 36–54 hours
Benzodiazepines	Anticipatory NAV	Lorazepam	0.5–2 mg PO once on night before and once on morning of treatment	12–16 hours
	Anticipatory NAV	Alprazolam	0.5–2 mg PO tid starting the night prior to treatment	12–16 hours

NAV, nausea and vomiting.

delayed CINV. Although antiemetic choices typically are guided by chemotherapy, patient-specific risk factors that may play a role include the following high-risk features: very young age, very old age, female gender, emesis associated with pregnancy or motion sickness, and those with low alcohol intake.[57]

Diarrhea

Chemotherapy-induced diarrhea can be a significant toxicity in cancer patients and should be managed pharmacologically when necessary. The most common offending agents include irinotecan and fluorouracil. Treatment may include loperamide (4 mg at the onset followed by 2 mg every 2 hours until resolution—may use 4 mg every 4 hours during sleep) or octreotide (starting at 100 mcg subcutaneously every 8 hours and titrated to effect). The goals of therapy are resolution of diarrhea and improvement in quality of life.[58]

Surveillance

Following response to surgery or pharmacologic treatment, the patient should be monitored regularly to detect recurrence. NCCN guidelines suggest a physical examination and chest x-ray every 3 to 4 months for 2 years. If no disease is detected during this time, follow-up frequency can be prolonged to every 6 months for 3 years and then annually. Low-dose spiral CT scanning is also recommended annually. Additionally, smoking-cessation counseling with or without pharmacologic treatment should be a priority.[18–33]

Complications

Cachexia and Anorexia

Cachexia is a severe wasting syndrome that is seen in many cancer patients. Although it is more common in advanced disease, it is often seen in localized disease as well. Cachexia is characterized by a catabolic state that leads to significant loss of body mass, both lean muscle and fat. The causes of cachexia are poorly understood, but it is thought that they involve inflammatory cytokines such as tumor necrosis factor α (originally described as cachexin). **Anorexia** is the patient's loss of appetite or willingness to eat. The presence of anorexia can aggravate cachexia and contribute to morbidity. When anorexia contributes to cachexia, it is important to assess the patient for the underlying cause of the anorexia.

Causes for anorexia in lung cancer patients can be widespread and include CINV, esophagitis and mucosal irritation from combined radiotherapy and chemotherapy, gastrointestinal obstruction owing to tumors, constipation from analgesics, and psychological factors such as anxiety or depression. Many of these issues may be improved with pharmacologic treatment of the underlying cause (i.e., antidepressant therapy for psychological factors) or with palliative treatment of the offending tumor.[59] Additionally, appetite stimulants such as the cannabinoid drobinol (2.5 mg twice daily with meals, titrated to a maximum of 20 mg/day) and megesterol acetate (400–800 mg/day orally) can aid in increasing caloric intake.

Cachexia is more difficult to treat, although it may resolve following treatment of the underlying malignancy. Nutritional consultation may be of aid, although cachexia is thought to be more attributable to internal pathophysiologic processes than malnutrition.

Paraneoplastic Syndromes

Paraneoplastic syndromes are clinical syndromes owing to nonmetastatic systemic effects of cancer. Tumors make and secrete biologically active products that can stimulate or inhibit hormone production, autoimmunity, immune complex production, or immune suppression. Lung cancer, particularly small cell lung cancer, is associated with a high rate of paraneoplastic



Patient Encounter, Part 4

Based on the information provided, develop a care plan for this patient. Include (1) treatment goals, (2) monitoring parameters for anticipated toxicities, and (3) a follow-up plan to determine response to treatment and surveillance.

syndromes. Pharmacologic therapy is necessary when the abnormality causes the patient acute physical or psychological stress or adversely affects his or her health. When possible, therapy should be directed at the primary tumor, and a response often leads to resolution of symptoms.

Palliative Care

Ultimately, most lung cancer patients succumb to their disease. Palliative care involves management of symptoms and improvement of quality of life when curative treatment options are no longer available. Often, problematic metastases can be removed by surgery (depending on location) or can be treated with radiotherapy to reduce the size. In selecting options at this point in treatment, it is important to keep the goals of therapy in mind, those being maximizing the duration and quality of life. Low-toxicity single-agent chemotherapy, targeted therapy, and best supportive care, which includes fatigue and pain management, are commonly the mainstays of palliative care.

OUTCOME EVALUATION

Following treatment, evaluate the goals of therapy versus the response that was achieved. Was there response to treatment or progression of disease? If the patient is being treated with supportive care, then alleviation of symptoms and improvement in quality of life should be of primary importance. Be sure to document objective evaluations of the outcome in the care plan.

TABLE 87–9. RECIST Criteria

Term	Description
Complete response (CR):	Disappearance of all targeted lesions
Partial response (PR):	At least a 30% decrease in the sum of the longest diameter of target lesions from baseline
Progressive disease (PD):	At least a 20% increase in the sum of the longest diameter of target lesions from baseline, including new lesions discovered during treatment
Stable disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD



Patient Care and Monitoring

1. Review the patient's medical and social history. Was the patient exposed to clinical risk factors for lung cancer?
2. Verify the histology and clinical stage of disease. Evaluate the patient's performance status. Is the patient a surgical candidate? How does this influence treatment recommendations?
3. Develop a care plan based on treatment goals. If the goal is palliative care, how does treatment-related toxicity influence therapy?
4. If chemotherapy is the treatment of choice, counsel the patient on risks and benefits of undergoing such therapy. Be sure that the patient understands the issues fully before moving forward.
5. Verify dosing of all agents in the chemotherapy regimen. What are the major expected toxicities?
6. Evaluate toxicity as treatment progresses. Is the toxicity severe enough to warrant dose reduction or pharmacologic treatment? Record graded toxicities according to the NCI CTC V3.0 criteria.
7. Evaluate the response to treatment. Did the patient experience a complete response, partial response, stable disease, or disease progression? How does this change future treatment?
8. If the patient is in remission, develop a monitoring plan. What signs or symptoms denote disease progression?
9. Recommend a smoking-cessation program or other risk-reduction plan for the patient.

RECIST Criteria

The RECIST (Response Evaluation Criteria in Solid Tumors) criteria are guidelines that objectively measure a patient's response to a therapeutic intervention. The RECIST criteria define a complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) in objective terms.[60] The RECIST guidelines were put into place to standardize reporting of response end points in clinical lung cancer trials. The patient's response to therapy is key because it guides therapy decisions (i.e., continue therapy, change regimens, etc.). These terms are defined in Table 87–9. The full guidelines can be accessed at www.eortc.be/recist.

ABBREVIATIONS

5-FDG:	5-fluorodeoxyglucose
CAV:	cyclophosphamide, doxorubicin, vincristine
CT:	computed tomography
CXR:	chest x-ray
ECOG:	Eastern Cooperative Oncology Group

EGF:	epidermal growth factor
EGFR:	epidermal growth factor receptor
EP:	etoposide, cisplatin
ETS:	environmental tobacco smoke
GM-CSF:	granulocyte-macrophage colony-stimulating factor
G-CSF:	granulocyte colony-stimulating factor
NSCLC:	non–small cell lung cancer
PCI:	prophylactic cranial irradiation
PET:	positron-emission tomography
PS:	performance status
SCLC:	small cell lung cancer
SVC:	superior vena cava
VEGF:	vascular endothelial-derived growth factor

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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88 Colorectal Cancer

Patrick J. Medina



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Identify the risk factors for colon cancer.
2. Recognize the signs and symptoms of colon cancer.
3. Describe the treatment options for colon cancer based on patient-specific factors, such as stage of disease, age of patient, and previous treatment received.
4. Outline the pharmacologic principles for agents used to treat colon cancer.
5. Develop a monitoring plan to assess the efficacy and toxicity of agents used in colon cancer.
6. Educate patients about the adverse effects of chemotherapy that require specific patient counseling.
7. Outline preventive and screening strategies for individuals at average and high risk for colon cancer.

Key Concepts

❶ Although there are numerous risk factors for developing colon cancer, age is the biggest risk factor.

❷ Dietary and pharmacologic agents influence the risk of colon cancer. Diets high in fat and low in fiber are associated with increased colon cancer risk, whereas the regular use of aspirin (and other NSAIDs) and calcium supplementation may decrease the risk of colon cancer.

❸ Most patients with colon cancer are asymptomatic early but may develop changes in bowel or eating habits, fatigue, abdominal pain, and blood in stool.

❹ The stage of colorectal cancer is determined by the TNM staging system and is the most important prognostic factor for patient survival. Stage I to III disease is curable, whereas patients with stage IV disease are treated with the goal of palliation.

❺ **Adjuvant chemotherapy** is not needed in patients with stage I colon cancer, is controversial in patients with stage II colon cancer, and is standard of care in patients with stage III colon cancer.

❻ 5-Flurouracil-based chemotherapy is the standard regimen used in adjuvant treatment of colon cancer. It is usually given for 6 months with leucovorin, and based on recent clinical trials, oxaliplatin also may be added to the combination.

❼ Triple-drug therapy consisting of 5-fluorouracil and leucovorin with oxaliplatin or irinotecan improves survival compared with 5-fluorouracil plus leucovorin alone and is considered as standard first-line therapy for metastatic disease. Bevacizumab, in combination with 5-fluorouracil-based chemotherapy, is also indicated for initial treatment of metastatic colorectal cancer.

❽ Adjuvant therapy consisting of 5-fluorouracil-based chemotherapy in combination with radiation therapy should be offered to patients with stage II or III cancer of the rectum.

❾ Patients should be evaluated during every treatment visit for the presence of anticipated side effects from their treatment, and health care practitioners should anticipate these adverse reactions and treat them aggressively and attempt to prevent them from occurring.

❿ Effective colorectal cancer screening programs incorporate annual fecal occult blood testing in combination with regular examination of the entire colon starting at age 50 for average-risk individuals and should be recommended by all health care providers.

Colon cancer is one of the three most common cancers diagnosed in the United States and includes cancers of the colon and rectum. In 2007, approximately 153,760 new cases were diagnosed and an estimated 52,180 deaths occurred, making colon cancer the second leading cause of cancer-related deaths in the United States.[1] Patient prognosis is determined primarily by the extent or stage of disease, with most patients with early-stage disease being cured. Treatment for colon cancer

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includes surgery, radiation, chemotherapy, and new targeted molecular therapies.

EPIDEMIOLOGY AND ETIOLOGY

Colon cancer occurs at a much higher rate in industrialized parts of the world such as North America and Europe, whereas the lowest rates are seen in less-developed areas, suggesting that environmental and dietary factors influence the development of colon cancer.[2] In addition to these environmental factors, colon cancers are known to develop more frequently in certain families, and genetic predisposition to this cancer is well known.

The incidence of colon cancer is greatest among males, who have an approximately 1.5 times greater risk for developing colorectal cancer than women. Overall, colon and rectal cancers make up approximately 10% of all cancers in men and women in the United States.[1] The median age at diagnosis is 72 years, with very few cases occurring in individuals younger than 45 years of age.[3] ❶ *Age appears to be the biggest risk factor for the development of colon cancer, with 70% of cases diagnosed in adults older than 65 years of age.*

Though still the second leading cause of cancer death, mortality rates for colon cancer have declined over the last 30 years as a result of better and increasingly used screening programs and more effective and better tolerated treatments.

PATHOPHYSIOLOGY

Anatomy and Bowel Function

The large intestine consists of the cecum; the ascending, transverse, descending, and sigmoid colon segments; and the rectum (Fig. 88–1). The function of the large intestine is to receive contents from the ileum. Absorption of materials occurs in segments of the colon proximal to the middle of the transverse colon, with movement and storage of fecal material in the left colon and distal segments of the colon.

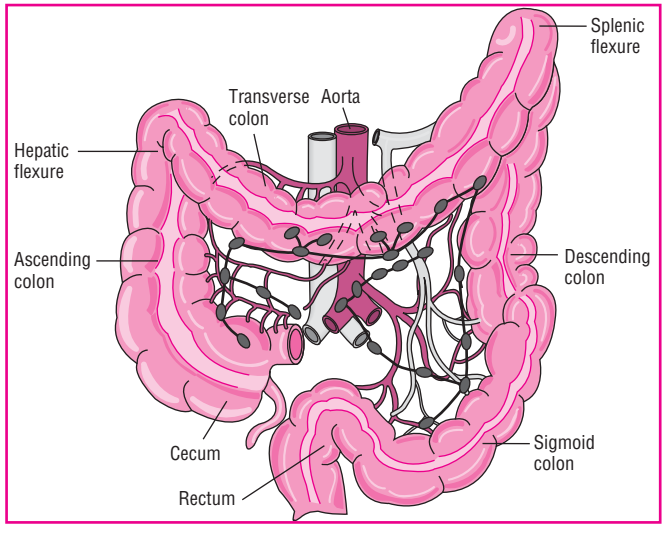


FIGURE 88–1. Colon and rectum anatomy. (From DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: Fig. 127-2.)

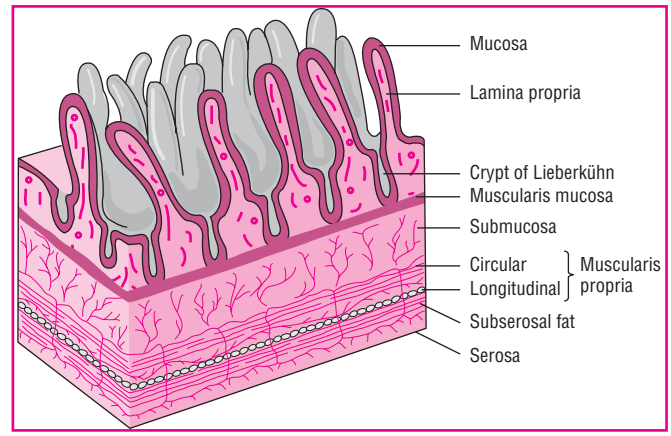


FIGURE 88–2. Cross section of bowel wall. (From DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: Fig. 127-3.)

Four major tissue layers, from the lumen outward, form the large intestine: the mucosa, submucosa, muscularis externa, and serosa (Fig. 88–2). Complete replacement of surface epithelial cells occurs approximately weekly, with the total number of epithelial cells remaining constant in normal colonic tissue. As patients age, abnormal cells accumulate on the surface epithelium and protrude into the stream of fecal matter; their contact with fecal mutagens can lead to further cell mutations and eventual adenoma formation.[4]

Colorectal Tumorigenesis

The development of a colorectal neoplasm is a multistep process of several genetic and phenotypic alterations of normal bowel epithelium structure and function leading to unregulated cell growth, proliferation, and tumor development. A genetic model has been proposed for colorectal tumorigenesis that describes a process of transformation from adenoma to carcinoma. This model of tumor development reflects an accumulation of mutations within colonic epithelium that gives a selective growth advantage to the cancer cells.[4,5] Genetic changes include activating mutations of **oncogenes,** inactivating mutations of **tumor-suppressor genes,** and defects in **DNA mismatch repair genes.**

Additional genes and protein receptors are believed to be important in colorectal tumorigenesis. Cyclooxygenase 2 (COX-2), which is induced in colorectal cancer cells, influences apoptosis and other cellular functions in colon cells, and overexpression of the epidermal growth factor receptor (EGFR), a transmembrane glycoprotein involved



Patient Encounter, Part 1

GW is a 61-year-old man who presents to your clinic with a chief complaint of abdominal discomfort and cramping for the past 3 weeks not relieved with over-the-counter medications. While obtaining your medical history, he states that he also has seen small amounts of blood in his stool on and off for 4 months. He has a past medical history positive for hypertension and obesity. He states that he has smoked 1 pack of cigarettes per day for the past 40 years and drinks 4 to 6 beers every couple of days.

- What risk factors does GW have for colon cancer?
- Does he have clinical symptoms suggestive of colon cancer?
- What additional tests need to be ordered to diagnosis colon cancer?

in signaling pathways that affect cell growth, differentiation, proliferation, and **angiogenesis,** occurs in the majority of colon cancers.[6,7] These mechanisms are potentially important because of the availability of pharmacologic agents targeted to inhibit them.

Over 90% of colon cancers are adenocarcinomas and are assigned a grade of I to III based on how similar they are to normal colon cells. Grade I tumors most closely resemble normal cellular structure, whereas, grade III tumors frequently have lost the characteristics of mature normal cells. Grade III tumors are associated with a worse prognosis than grade I tumors.[8]

RISK FACTORS

Besides age, the development of colorectal cancer appears to be caused by variety of dietary or environmental factors, comorbid disease states, and genetic susceptibility to the disease. Table 88-1 lists well-known risk factors for developing colon cancer. Epidemiologic studies of worldwide incidence of colorectal cancer suggest that dietary habits strongly influence its development.

TABLE 88–1. Risk Factors for Colon Cancer[a]

Dietary
High-fat, low-fiber diets
Lifestyle
Alcohol
Smoking
Obesity/physical inactivity
Comorbid Conditions
Inflammatory bowel disease (ulcerative colitis and Crohn's disease)
Hereditary/Genetic
Familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC)
Family history

[a]Age is the primary risk factor.

❷ *High-fat, low-fiber diets, which usually occur in tandem, have been associated with an increased risk of colon cancer.* The association between red meat consumption and colorectal cancer is strongest, possibly a result of the heterocyclic amines formed during cooking or the presence of specific fatty acids in red meat such as arachidonic acid. While data indicate that animal meat and saturated fat intake are associated with an increased risk of colorectal cancer, the exact increase in risk is unknown. The evidence for low-fiber diets as a risk factor is based on the ingestion of large amounts of dietary fiber being associated with a small, inconsistent reduced colon cancer risk. Foods that are high in fiber include vegetables, fruit, grains, and cereals. The protective effects of fiber[4] may be a result of

- Reduced absorption of carcinogens in the bowel
- Reduced bowel transit time
- Reduced dietary fat intake associated with high-fiber diets

The degree of colorectal cancer risk reduction associated with increased consumption of vegetables and fruit is variable but generally modest and has ranged from no difference to a 25% decrease in cancer risk in prospective studies.[9,10]

❷ The risk of colon cancer appears to be inversely related to calcium and folate intake. Calcium's protective effect may be related to a reduction in mucosal cell proliferation rates or through its binding to bile salts in the intestine, whereas dietary folate helps in maintaining normal bowel mucosa. Additional micronutrient deficiencies have been demonstrated through several studies to increase colorectal cancer risk and include selenium, vitamin C, vitamin D, vitamin E, and β-carotene; however, the benefit of dietary supplementation does not appear to be substantial.[11]

Chronic use of several medications has been shown to influence the risk of developing colon cancer. ❷ *Studies have consistently demonstrated that regular (at least two doses per week) nonsteroidal anti-inflammatory drug (NSAID) or aspirin use is associated with a reduced risk of colorectal cancer.*[4] Additional studies support these findings that regular aspirin or NSAID use may decrease the risk of colorectal cancer by as much as 50%.[12] The potential anticancer mechanism of NSAIDS is inhibition of cyclooxygenase-2 (COX-2). Exogenous hormone use, particularly postmenopausal hormone-replacement therapy, is associated with a significant reduction in colorectal cancer risk in most studies,[4,13] with the greatest benefit in women who are on current hormone-replacement therapy.

Personal attributes such as physical inactivity and elevated body mass index (BMI) are associated with up to a twofold increase in the risk of colon cancer. Decreased bowel

transit time and exercise-induced alterations in body glucose, insulin levels, and perhaps other hormones may reduce tumor cell growth.[4] Type 2 diabetes mellitus, independent of body mass and physical activity level, is also associated with an increased risk of colorectal cancer in women and supports a role for hyperinsulinemia as a possible link between obesity, sedentary lifestyle, diabetes mellitus, and colon cancer.[14] Additional lifestyle choices that increase the risk of colon cancer include alcohol consumption and smoking, which may increase the risk of colon cancer by generating carcinogens or their direct toxic effects on bowel tissue.[11]

Comorbid conditions, such as chronic ulcerative colitis, particularly when it involves the entire large intestine, and to lesser extent Crohn's disease, also increase the risk of colon cancer. Overall, persons diagnosed with either disease constitute about 1% to 2% of all new cases of colorectal cancer each year.

Finally, as many as 10% of cases are thought to be hereditary, resulting from genetic mutations. The two most common forms of hereditary colon cancer are familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC).[5] FAP is a rare autosomal dominant trait that is caused by mutations of the **adenomatous polyposis coli** (***APC***) gene and accounts for 1% of all colorectal cancers. The disease is manifested by hundreds to thousands of **polyps** arising during adolescence.[4,5] The risk of developing colorectal cancer for individuals with untreated FAP is close to 100%, and patients will require early screening for the disease. HNPCC, also an autosomal dominant syndrome, accounts for up to 5% of colon cancer cases.[4,5] In contrast to FAP, polyps occur rarely, and the average age of colorectal cancer in these patients is much older, with most patients diagnosed in their forties. Testing for HNPCC mutations is available but reserved for individuals who meet stringent diagnostic criteria.

Up to 25% of patients who develop colorectal cancer will have a family history of colorectal cancer unrelated to one of the mutations just described. First-degree relatives of patients diagnosed with colorectal cancer have an increased risk of the disease that is at least two to four times that of persons in the general population without a family history.[15]

Summary of Risk Factors

In summary, the true association between most dietary factors and the risk of colon cancer is unclear. The protective effects of fiber, calcium, and a diet low in fat are not completely known. Lifestyle factors such as NSAID use and hormone use appear to decrease the risk of colorectal cancer, whereas physical inactivity, alcohol use, and smoking appear to increase the risk of colon cancer. Clinical risk factors and genetic mutations are well-known risks for colon cancer.

CLINICAL PRESENTATION AND DIAGNOSIS

The signs and symptoms associated with colorectal cancer can be extremely varied, subtle, and nonspecific.

Patients presenting with symptoms suggestive of colon cancer are evaluated by a colonoscopy. If abnormalities in the bowel are identified, a biopsy is performed, and the diagnosis of colon cancer is made by a pathologist. The extent and spread of colon cancer then are evaluated by CT scans and other diagnostic imaging techniques; this evaluation is commonly called *staging*. Staging of patients is required to determine the extent of disease and is necessary in developing treatment options and determining prognosis. The TNM classification system, which takes into account T (tumor size and depth of tumor invasion), N (lymph node involvement), and M (presence or absence of metastases) is used to stage patients from stage I to stage IV. Figure 88–3 depicts how the three categories are used in combination to determine the stage of disease. ❹ *The stage of colorectal cancer on diagnosis is the most important prognostic factor for survival and disease recurrence. Stages I, II, and III disease is considered potentially curable and is treated aggressively in an attempt to cure these patients. Patients who develop stage IV disease are treated to reduce symptoms, avoid disease-related complications, and prolong survival.*



❸ Presentation of Colon Cancer

General
Patients are often asymptomatic in early stages of disease.

Symptoms
Changes in bowel habits, anorexia, nausea and vomiting, weakness (if anemia is severe)

Signs
Blood in stool, weight loss, abdominal pain

Laboratory Tests
- Patients may have a low hemoglobin level from blood loss.
- Positive fecal occult blood test (FOBT)
- Liver function tests [international normalization ratio (INR), activated partial thromboplastin time (aPTT), and bilirubin] may be abnormal if disease has metastasized to the liver.
- **Carcinoembryonic antigen (CEA)** level may be high. Normal level is less than 3 ng/mL (3 mcg/L) in nonsmokers and less than 5 ng/mL (5 mcg/L) in smokers.

Imaging Tests
Chest x-ray, CT scan, or **PET scan** may be positive if cancer has spread to the lungs, liver, or peritoneal cavity.



Patient Encounter, Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH
- Hypertension since age 47, which is not well controlled.
- Obesity; the patient is 65% over his ideal body weight.

FH
Mother and father both dead. Father died of a myocardial infarction at the age of 62. Mother died of colon cancer at the age of 64. Patient states that "many" relatives have cancer in his family.

SH
Works as an auto mechanic. Drinks alcohol frequently, and smokes 1 pack of cigarettes daily. Patient also does no exercise and states that he eats fast food daily. He is married with twin boys aged 29.

Meds
Atenolol 50 mg orally once daily

ROS
(+) abdominal cramping, mild nausea and loss of appetite, blood in stool, fatigue

PE
- **VS:** 153/90, P 78, RR 16, T 37.2°C (99°F), 72 in, 128 kg (282 lbs)
- **Abd:** Distended and tender to touch, (+) bowel sounds, heme (+) stools
- **Labs:** Positive Hemoglobin 11.3 g/dL (113 g/L 7 mmol/L) [decreased from 14.8 g/dL (148 g/L 9.2 mmol/L) last year]

Imaging and Diagnostic Studies
- Colonoscopy revealed multiple polyps in his transverse colon.
- Biopsy revealed three polyps positive for adenocarcinoma of the colon.
- Staging computed tomographic (CT) scan revealed metastatic disease in the liver.
- All other findings negative.

- Since GW has stage IV colon cancer, how does this affect
- your treatment plan compared with stage I–III disease?
- What is your treatment goal for him?
- What nonpharmacologic and pharmacologic options are available to GW?

TREATMENT

Desired Outcome

The treatment approaches for colorectal cancer reflect two primary treatment goals: curative therapy for localized disease (stages I to III) and palliative therapy for metastatic cancer (stage IV). Surgical resection of the primary tumor is the most important part of therapy in patients who clinicians are attempting to cure.[16] Depending on the stage of disease and whether the tumor originated in the colon or rectum, further adjuvant chemotherapy or chemotherapy plus radiation may be needed after surgery to cure these patients. In the metastatic setting, pharmacologic intervention is the main treatment option.

Nonpharmacologic Therapy

Operable Disease (Stages I–III)

Surgery

Individuals with stage I to III colorectal cancer should undergo a complete surgical resection of the tumor mass with removal of regional lymph nodes as a curative approach for

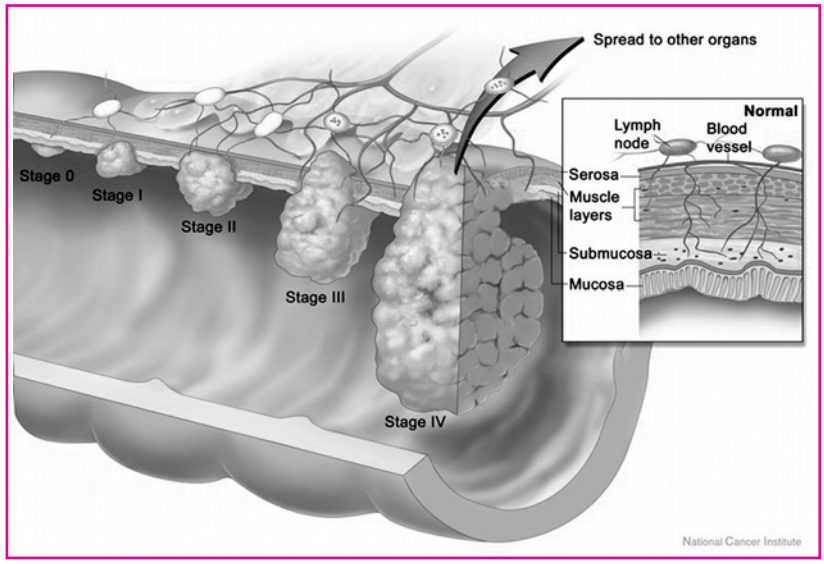


FIGURE 88–3. Stage I: Cancer is confined to the lining of the colon. Stage II: Cancer may penetrate the wall of the colon into the abdominal cavity but does not invade any local lymph nodes. Stage III: Cancer invades one or more lymph nodes but has not spread to distant organs. Stage IV: Cancer has spread to distant locations in the body, which may include the liver, lungs, or other sites. (From www.cancer.gov/cancertopics/pdq/treatment/colon/Patient/page2.)

their disease.[16] Surgery for rectal cancer depends on the region of tumor involvement, with an attempt to retain rectal function a goal of the surgical procedure. Overall, surgery for colorectal cancer is associated with low morbidity and mortality. Common complications associated with colorectal surgery include infection, anastomotic leakage, obstruction, adhesion formation, and malabsorption syndromes.

Radiation Therapy

There is currently no definitive role for adjuvant radiation in colon cancer. However, patients who receive surgery for rectal cancer receive radiation therapy to reduce local tumor recurrence. Adjuvant radiation plus chemotherapy is considered standard treatment for patients with stage II or III rectal cancer after the surgical procedure is complete.[17] Preoperative radiation may be used to reduce the initial size of rectal cancers in order to make the surgical procedure easier.

Metastatic Disease (Stage IV)

Surgery

Unlike stage I to III disease, the benefit of surgical resection in most patients with metastatic disease is limited to symptomatic improvement. Select patients who have from one to three small nodules isolated to the liver, lungs, or abdomen may have a prolongation of survival, although cure is rare. Five-year survival for patients who undergo surgical resection of metastases isolated to the liver is approximately double that of patients who are not surgical candidates.[18]

Alternatives to surgery include destroying the tumor through freezing and thawing (cryoablation), heat (radiofrequency), or alcohol injection, although these appear to be less successful than surgical interventions.[18] Because the majority of these patients will relapse, many practitioners offer adjuvant chemotherapy to selected patients following potentially curative resection, but further studies are needed to determine an optimal treatment regimen.

Radiation

Symptom reduction is the primary goal of radiation for patients with advanced or metastatic disease colorectal cancer.

Pharmacologic Therapy

Tables 88–2 and 88–3 list common chemotherapy regimens and the abbreviations often used in colon cancer.

Operable Disease (Stages I–III)

❺ *Adjuvant chemotherapy is administered after tumor resection to decrease relapse rates and improve survival in patients with colon cancer by eliminating micrometastatic disease that is undetected on imaging studies. Patients diagnosed with stage I colon or rectal cancer usually are cured by surgical resection, and adjuvant chemotherapy is not indicated in these patients.*[16] *The role of adjuvant chemotherapy for stage II colon cancer is controversial.* Adjuvant chemotherapy for patients with stage II disease has not been shown to be superior to surgery alone, with the exception of high-risk patients, who are ill-defined. Consequently, the American Society of Clinical Oncology does not recommend the routine use of adjuvant chemotherapy in the general patient population unless part of a clinical trial.[19] Patients with stage II colon cancer should be enrolled in carefully controlled clinical trials to assess the impact of new agents and prognostic models that predict who may benefit. ❺ *Adjuvant chemotherapy is standard therapy for patients with stage III colon cancer.* The presence of lymph node involvement with tumor places patients with stage III colon cancer at high risk for relapse; the risk of death within 5 years of surgical resection alone is as high as 70%.[16] In this population of patients, adjuvant chemotherapy significantly decreases risk of cancer recurrence and death and is considered standard of care.

❻ *5-Fluorouracil-based chemotherapy is the standard of care for the adjuvant treatment of colorectal cancer either as a single agent or, more commonly, in combination with other agents.* 5-Fluorouracil (5-FU) alone results in a small improvement in survival that can vary based on the method of 5-FU administration. Studies suggest that protracted or continuous intravenous (IV) 5-FU infusion treatment schedules are more effective than bolus therapy.[20]

More often 5-FU is administered as part of a combination regimen. ❻ *The most frequently used combination is 5-FU and leucovorin.* The combination of 5-FU and leucovorin has undergone extensive study in the adjuvant setting, with decreased rates of recurrence and improved survival seen in patients receiving 5-FU and leucovorin compared with surgery alone.[21] The International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) demonstrated that recurrence and death rates were reduced by 35% and 22%, respectively, with the combination.[22] 5-FU and leucovorin can be administered in a variety of treatment schedules, but none has proven superior with regard to overall patient survival. In the past, the United States favored bolus regimens based on patient convenience. However, improved availability and comfort in use of portable infusion pumps has led to an increased use of the continuous intravenous schedule of 5-FU commonly advocated in Europe. Patients are treated with 6 months of adjuvant therapy because longer regimens do not improve patient outcomes. No standard exists for the best schedule of 5-FU and leucovorin administration, although continuous infusions may be less toxic and have improved response rates (although no survival advantage) than bolus regimens. Recently, oxaliplatin added to the combination of 5-FU and leucovorin has further improved disease-free survival in the adjuvant setting. ❻ *The MOSAIC trial, conducted in over 2200 patients, demonstrated that the addition of oxaliplatin to 5-FU and leucovorin decreases disease recurrence and improves disease-free survival.*[23] *These results led to the approval of the FOLFOX4 regimen, given for 6 months, for the adjuvant treatment of colon cancer.*

TABLE 88–2. Dosing Schedules of Chemotherapy Regimens for Colon Cancer[a]

Regimen	Dosing
5-Fluorouracil	300 mg/m^2 per day IV infused indefinitely or 250–1000 mg/m^2 per day IV over 24 hours × 5 days
5-Fluorouracil + leucovorin (bolus)	Leucovorin 500 mg/m^2 IV 5-Fluorouracil 500 mg/m^2 IV Every week × 6 weeks, followed by 2-week rest
5-Fluorouracil + leucovorin (continuous infusion)	Leucovorin 200 mg/m^2 IV 5-Fluorouracil 400 mg/m^2 IV bolus and then 600 mg/m^2 of 5-fluorouracil as a 22-hour continuous infusion On days 1 and 2; repeat every 2 weeks
5-Fluorouracil + leucovorin + irinotecan (IFL)	Leucovorin 20 mg/m^2 IV 5-Fluorouracil 500 mg/m^2 IV bolus Irinotecan 125 mg/m^2 IV Every week × 4 weeks, followed by 2-week rest
IFL + bevacizumab	IFL as above plus bevacizumab 5 mg/kg IV every 2 weeks
FOLFIRI	Irinotecan 180 mg/m^2 IV day 1 Folinic acid (leucovorin) 200 mg/m^2 IV day 1 5-Fluorouracil 400–500 mg/m^2 IV bolus, after folinic acid; then 2400–3000 mg/m^2 of 5-fluorouracil IV over 46 hours Repeat every 14 days
FOLFOX4	*Day 1* Oxaliplatin 85 mg/m^2 IV + leucovorin 200 mg/m^2 IV, followed by 5-fluorouracil 400 mg/m^2 IV bolus and then 5-fluorouracil 600 mg/m^2 IV over 22 hours *Day 2* Leucovorin 200 mg/m^2, followed by 5-fluorouracil 400 mg/m^2 IV bolus and then 5-fluorouracil 600 mg/m^2 IV over 22 hours Repeat every 2 weeks
Capecitabine	1250 mg/m^2 twice a day orally for 14 days Repeat every 3 weeks
CAPOX	Capecitabine 1000 mg/m^2 twice a day orally for 14 days Oxaliplatin 130 mg/m^2 IV on day 1 Repeat every 3 weeks
CAPIRI	Capecitabine 1000 mg/m^2 twice a day for 14 days Irinotecan 100 mg/m^2 IV days 1 and 8 Repeat every 22 days

Note: Many variations exist, and current literature should be checked prior to administering any chemotherapy regimen.

TABLE 88–3. Common Regimens Used in Colon Cancer

Acronym	Regimen
5-Fluorouracil	5-Fluorouracil given alone as a bolus or continuous infusion
LV/5-fluorouracil	Leucovorin + 5-fluorouracil given as a bolus or continuous infusion
IFL	Irinotecan + 5-fluorouracil + leucovorin given as IV boluses
IFL + bevacizumab	IFL as above plus bevacizumab
FOLFIRI	Folinic acid (leucovorin) + 5-fluorouracil + Irinotecan given as combined IV boluses and continuous infusions
FOLFOX	Folinic acid (leucovorin) + 5-fluorouracil + oxaliplatin given as combined IV boluses and continuous infusions
CAPOX	Capecitabine + Oxaliplatin given as oral therapy and IV boluses
CAPIRI	Capecitabine + Irinotecan given as oral therapy and IV boluses

Note: Many variations exist, and current literature should be checked prior to administering any chemotherapy regimen.

Capecitabine is an oral prodrug of 5-FU that also is effective in the adjuvant setting and is being evaluated as a replacement for 5-FU for patient convenience and safety reasons. Data suggest that capecitabine is at least equivalent to 5-FU and leucovorin in efficacy and is better tolerated by patients.[24] Consequently, most practitioners feel that capecitabine is an acceptable alternative to IV 5-FU plus leucovorin. However, the role of capecitabine with additional chemotherapy agents such as oxaliplatin requires further study.

Following resection of liver metastases, infusion of chemotherapy through the portal vein provides an additional adjuvant treatment approach. Historically, 5-FU and floxuridine have been the agents used most commonly for hepatic portal vein infusion owing to their high metabolism in the liver. Although some studies demonstrate a decrease in recurrence rates, the value of portal vein infusion of chemotherapy for colon cancer remains to be determined.[25] Table 88–4 summarizes adjuvant treatment recommendations for colon cancer.

TABLE 88–4. Treatment Regimens for Adjuvant Colon Cancer[a]

Stage II[b]	Stage III
High Risk	**Good Performance Status**
• FOLFOX	• FOLFOX
• Capecitabine or 5-fluorouracil plus leucovorin	• Capecitabine or 5-fluorouracil plus leucovorin
Low Risk	**Poor Performance Status**
• Observation or clinical trial	• Capecitabine

[a]CAPOX or CAPIRI may replace FOLFOX or FOLFIRI in select patients.
[b]Individualized assessment of patient risk is necessary to determine if treatment is required.

Metastatic Disease (Stage IV)

Traditional chemotherapy and targeted biologic therapies are the mainstay of treatment for metastatic colon or rectal cancer.[26] Most often a combination of chemotherapy agents with biologic therapies is administered to these patients. Currently, metastatic colorectal cancer is incurable, and treatment goals are to reduce patients' symptoms, improve quality of life, and extend survival. Combination-chemotherapy regimens have been demonstrated to result in prolongation of survival with tolerable adverse effects. Similar to the adjuvant setting, 5-FU plus leucovorin continues to be in most first-line chemotherapy regimens used for metastatic colorectal cancer. A variety of continuous IV infusion 5-FU and bolus regimens can be used, but in comparison with IV bolus 5-FU, response rates with continuous-infusion 5-FU are approximately doubled. In a meta-analysis of six randomized trials evaluating over 1200 patients with advanced colorectal cancer, continuous infusions of 5-FU had a significantly higher tumor response rate, a small increase in survival, and a lower incidence of myelosuppression, diarrhea, and mucositis than bolus regimens.[27]

Additional agents have been added to the 5-FU and leucovorin regimen with superior response and survival rates than the two drugs used alone. The addition of irinotecan to 5-FU plus leucovorin (IFL) significantly improves response rates and survival without adversely affecting quality of life. In a landmark trial, this regimen was superior to 5-FU plus leucovorin with regard to tumor response, survival, and quality of life.[28] As a result, irinotecan received approval from the Food and Drug Administration (FDA) in 2000 as first-line therapy for metastatic colorectal cancer in combination with 5-FU and leucovorin. This regimen was the most commonly administered schedule for irinotecan plus 5-FU and leucovorin in the United States until recently, when oxaliplatin in combination with 5-FU and leucovorin (FOLFOX4) demonstrated improvement in median survival when compared with the IFL regimen described earlier. A comparison of oxaliplatin plus 5-FU and leucovorin (FOLFOX4) with weekly irinotecan plus IV bolus 5-FU and leucovorin (IFL) showed the superior efficacy of FOLFOX4 compared with IFL with regard to response rates and survival.[29] Several study design-questions, including the **crossover design** and differing methods of 5-FU administration led several practitioners to debate the significance of these results. Patients on the IFL arm received weekly IV bolus 5-FU, whereas FOLFOX4 patients received 5-FU as an IV bolus followed by a continuous IV infusion, which is known to increase response rates. A larger European study validated these concerns when it compared a combined bolus and infusional 5-FU regimen plus irinotecan (FOLFIRI) with the FOLFOX regimen (using a slightly different schedule) with crossover to the opposite arm on relapse.[30] No difference in patient survival was seen with either regimen, and toxicity was as expected. Neuropathy and neutropenia were more common with FOLFOX, and diarrhea, nausea, vomiting, dehydration, and febrile neutropenia were more common with FOLFIRI.

The treatment of metastatic colon cancer has been changed with the approval of targeted or biologic agents. Bevacizumab, in combination with intravenous 5-FU-based chemotherapy, is approved by the FDA for the initial treatment of patients with metastatic colorectal cancer and represents an additional regimen for the first-line treatment of these patients. Results from randomized trials show increased benefit compared with chemotherapy alone. One phase III trial of bevacizumab in combination with IFL as first-line therapy in patients with metastatic colorectal cancer also has been completed, with a 5-month increase in median survival seen with the addition of bevacizumab with manageable adverse effects.[31] The results of this study show the relevance of angiogenesis as an important target for the treatment of metastatic colorectal cancer. How the addition of bevacizumab to FOLFOX or the other irinotecan-based combinations is the first-line treatment of metastatic colon cancer remains to be seen.

❼ *In summary, most practitioners select first-line treatment for metastatic colorectal cancer from among these currently approved treatments: oxaliplatin plus 5-FU plus leucovorin (FOLFOX), irinotecan plus 5-FU plus leucovorin (IFL or FOLFIRI), bevacizumab plus 5-FU chemotherapy.* In addition, capecitabine is approved for use in metastatic colon cancer when monotherapy is desired and appears to be an appropriate substitute for intravenous fluorouracil in the combination regimens mentioned earlier. 5-FU plus leucovorin alone is appropriate first-line treatment only for individuals for whom three-drug combination regimens are believed too toxic. The site(s) of tumor involvement, history of prior chemotherapy, and patient-specific factors help to define the appropriate management strategy. The most important factor in patient survival is not the initial regimen but whether or not patients receive all three active chemotherapy drugs (i.e., 5-FU, irinotecan,, and oxaliplatin) at some point in his or her treatment course.[32]

Second-Line Therapy

Treatment options on disease progression following standard initial therapy are based on the type of prior therapy received. Since most patients will have received a combination of 5-FU and either irinotecan or oxaliplatin, second-line therapy with the alternate regimen should be considered.[26,33] If targeted agents such as bevacizumab were not part of the initial regimen, addition to the second-line regimen should be strongly considered.



Patient Encounter, Part 3: Creating a Care Plan

Based on the information presented, create a care plan for this patient's colon cancer. Your plan should include (1) the patient's drug- and non-drug-related needs and problems, (2) the goals of therapy, (3) a treatment plan specific to GW that includes strategies to prevent adverse effects of chemotherapy, (4) a follow-up plan to determine whether the goals have been achieved and the adverse effects of chemotherapy have been minimized, and (5) a plan for treatment options when the initial therapy is no longer achieving the goals of therapy.

An additional option includes the use of cetuximab either alone or in combination with irinotecan-based chemotherapy.[34] Cetuximab is FDA approved for use in EGFR-expressing metastatic colorectal cancer in combination with irinotecan but can be used as a single agent in patients who cannot tolerate irinotecan-based chemotherapy. The results appear to be best when irinotecan is continued owing to synergy demonstrated between the two agents.[26,34] Cetuximab is given as at loading dose of 400 mg/m^2 followed by weekly IV infusions of 250 mg/m^2 until disease progression. The incidence of grade 3 or 4 adverse effects was as anticipated based on previous trials; asthenia and an acne-like rash occurred most commonly with cetuximab alone. The benefit of adding cetuximab to oxaliplatin-based regimens or as part of initial therapy for metastatic colorectal cancer is an area of active investigation. Immunohistochemical evidence of EGFR-positive staining in tumors should be obtained prior to initiating therapy, although the clinical relevance of this is uncertain.

Finally, patients who fail standard treatment for metastatic colorectal cancer should be encouraged to participate in a clinical trial evaluating new treatment approaches for this incurable disease. Table 88–5 lists options for first- and second-line treatment of metastatic colon cancer. Patients with good **performance status** are treated more aggressively than those with poor performance status because of their better ability to tolerate chemotherapy.

TABLE 88–5. Treatment Options for Metastatic Colon Cancer[a]

First-Line Therapy	Second-Line Therapy
Good Performance Status	**If First Line Irinotecan**
• FOLFIRI with or without bevacizumab	• FOLFOX with or without bevacizumab[b]
• FOLFOX with or without bevacizumab	• Irinotecan and cetuximab (if EGFR-positive)
• IFL and bevacizumab	• Capecitabine or 5-fluorouracil plus leucovorin
Poor Performance Status	**If First Line Oxaliplatin**
• Capecitabine or 5-fluorouracil plus leucovorin with or without bevacizumab	• FOLFIRI with or without bevacizumab[b]
	• Irinotecan with or without cetuximab
	• Capecitabine or 5-fluorouracil plus leucovorin

[a]CAPOX or CAPIRI may replace FOLFOX or FOLFIRI in select patients.
[b]Bevacizumab may be given if not part of the first-line therapy.

SPECIFIC AGENTS USED IN COLON CANCER

Table 88–6 lists all FDA-approved drugs used in colon cancer, along with their mechanism of action and common toxicities.

5-Flurouracil

5-Fluorouracil (5-FU) acts as a "false" pyrimidine, inhibiting the formation of the DNA base thymidine.[26,35] The main mechanism by which it accomplishes this is by inhibiting the enzyme thymidylate synthase, the rate-limiting step in thymidine formation. 5-FU first must be metabolized to its active metabolite (F-dUMP). Additionally, metabolites of 5-FU may incorporate into RNA, inhibiting its synthesis.

5-FU is used commonly in the adjuvant and metastatic treatment of colon and rectal cancers. Various dosing administration techniques and schedules have been developed with 5-FU, including an IV bolus every 3 to 4 weeks, an IV continuous infusion, weekly IV boluses, and IV boluses followed by continuous infusions. Clinical studies comparing the efficacy of bolus and continuous-infusion schedules generally favor continuous infusion of 5-FU. This is consistent with evidence that suggests that the duration of infusion may be an important determinant of the biologic activity of 5-FU, particularly because of its short plasma half-life and S-phase specificity and the relatively slow growth of colon tumors.[16,26]

Clinically significant differences in toxicity also are based on the dose, route, and schedule of 5-FU administration. Leukopenia and mucositis are the primary dose-limiting toxicities of bolus 5-FU, whereas palmar-plantar erythrodysesthesia (hand-foot syndrome) and diarrhea occur most frequently with continuous infusions of 5-FU.[36] Health care practitioners can offer valuable patient advice to decrease the impact of these adverse effects. Patients can be informed to suck on ice chips prior to and for up to 30 minutes after 5-FU boluses to decrease the incidence of mucositis. Hand-foot syndrome, characterized by painful swelling and redness of the soles of the feet and palms of the hand, can be minimized with loose-fitting clothing and keeping the skin moist. Additional toxicities include moderate nausea and vomiting, skin discoloration, nail changes, photosensitivity, and neurologic toxicity. 5-FU administered with warfarin can result in significant increases in a patient's INR and requires close monitoring to prevent bleeding.

An additional determinate of 5-FU toxicity, regardless of the method of administration, is related to its catabolism and **pharmacogenomic** factors. Dihydropyrimidine dehydrogenase (DPD) is the main enzyme responsible for the catabolism of 5-FU to inactive metabolites.[37] A pharmacogenetic disorder has been identified in which patients have a complete or near-complete

TABLE 88–6. FDA-Approved Drugs Used in Colon Cancer

Name	Mechanism of Action	Common Toxicities
5-Fluorouracil	Inhibition of the enzyme thymidylate synthase, the rate-limiting step in thymidine formation.	*Dose-limiting* Myelosuppression and mucositis with bolus administration Diarrhea and hand-foot syndrome with continuous infusion *Additional toxicities* Skin discoloration, nail changes, photosensitivity, and neurologic toxicity
Capecitabine (Xeloda®)	Orally active prodrug of 5-fluorouracil. Once activated, the mechanism of action is the same.	Similar to continuous infusion 5-fluorouracil
Irinotecan (Camptosar®)	Topoisomerase inhibitor that forms a complex with the covalently bound DNA topoisomerase enzyme and interferes with the DNA breakage-resealing process.	*Dose-limiting* Early and late diarrhea *Additional toxicities* Neutropenia, nausea, and vomiting
Oxaliplatin (Eloxatin®)	Similar to other platinum analogs (cisplatin) in that it binds to the N-7 position of guanine, which results in cross-linking of DNA and double-stranded DNA breaks.	*Dose-limiting* Acute (within first 2 days) and persistent (greater than 14 days) neuropathies *Additional toxicites* Anaphylactic-like reactions, dyspnea
Bevacizumab (Avastin®)	Monoclonal antibody that binds to vascular endothelial growth factor (VEGF) and inhibits angiogenesis.	*Dose-limiting* Hypertension, bleeding episodes, thrombotic events *Additional toxicities* Rare perforation of the bowel, proteinurea
Cetuximab (Erbitux®)	Binds to the cell surface epidermal growth factor receptor (EGFR), preventing EGF and TGF-α binding. This decreased cell proliferation of cancer cells.	*Dose-limiting* Infusion-related reactions, acneiform skin rash *Additional toxicities* Diarrhea, nausea and vomiting, interstitial lung disease

deficiency of this enzyme. This results in unusually severe toxicity, including death, after the administration of 5-FU. Approximately 3% of patients have a complete lack of DPD activity, with other patients demonstrating a partial deficiency in enzyme activity. Although patients may be tested for their level of DPD activity, it is not done commonly but may be considered in patients who develop severe toxicity after 5-FU administration.

Leucovorin is given commonly with 5-FU. Leucovorin acts to increase the affinity of 5-FU for thymidine synthase, increasing the pharmacologic activity of 5-FU.[16,22] Leucovorin is most effective when administered prior to 5-FU and can be given by IV bolus, continuous infusion, or orally. Health care practitioners also can expect an increase in 5-FU toxicities when leucovorin is given in combination with 5-FU, in particular leukopenia, mucositis, and diarrhea.

Capecitabine

Capecitabine (Xeloda®) is an oral prodrug of 5-FU. Capecitabine undergoes a three-step conversion to 5-FU, the last step being phosphorylation by thymidine phosphorylase (TP). TP levels are reported to be higher in tumor cells than in normal tissues; therefore, the systemic exposure of active drug is minimized, and tumor concentrations of the active drug are optimized.[24,26] Once the drug is converted to 5-FU, it has the same mechanism of action described for that agent. The current FDA-approved indication for capecitabine is for use in metastatic and adjuvant colon cancer when monotherapy is desired, although it is actively being investigated as a replacement for 5-FU in most combination colon and rectal cancer regimens. Capecitabine has been demonstrated to be at least equivalent to IV 5-FU in the metastatic and adjuvant setting with improved patient tolerability.[24,38] Hand-foot syndrome and diarrhea are common with capecitabine because its toxicities (and pharmacologic activity) appear to mimic those of continuous infusions of 5-FU. Both irinotecan and oxaliplatin have been combined with capecitabine, and these combinations appear to be as safe and effective as IV 5-FU in the treatment of colorectal cancer.

The dose of capecitabine begins at 1250 mg/m^2 twice a day when used by itself; lower doses are used often when it is given in combination with irinotecan or oxaliplatin or in patients with renal insufficiency. The dose should be taken on a full stomach with breakfast and dinner. Capecitabine administered with warfarin can result in significant increases in the patient's INR and requires close monitoring to prevent bleeding. The convenience of oral administration and an improvement in toxicity make capecitabine a useful alternative to IV 5-FU both by itself and incorporated into other regimens used in colon cancer.

Irinotecan

Irinotecan (Camptosar®) is a **topoisomerase** I inhibitor that forms a complex with the covalently bound DNA topoisomerase

I enzyme and interferes with the DNA breakage-resealing process.[26] Binding permits uncoiling of the double-stranded DNA, but it prevents subsequent resealing of the DNA, resulting in double-stranded DNA breaks. Irinotecan is a prodrug that is converted by carboxylesterases to its active form SN-38. Irinotecan is indicated for the first-line treatment of metastatic colon cancer in combination with 5-FU and leucovorin or as a single agent in patients who fail first-line therapies. Irinotecan is not recommended as part of the adjuvant treatment of colon cancer at this time.

The major toxicity of irinotecan is diarrhea, which can occur both early and late in therapy.[26] The early diarrhea is a cholinergic reaction that occurs in the first 24 hours (often during the infusion) in up to 10% of patients and responds to atropine 0.25 to 1 mg IV. The late diarrhea seen in a larger percent of patients occurs 7 to 14 days after the irinotecan infusion. Health care practitioners must explain this adverse effect to patients and counsel them on the proper use of antidiarrheals. At the first change in bowel habits, an intensive loperamide regimen should be started by patients (4 mg initially, followed by 2 mg every 2 hours until diarrhea-free for 12 hours). If diarrhea does not stop or worsens, patients should be instructed to call their health care provider immediately. Late-onset diarrhea may require hospitalization or discontinuation of therapy, and fatalities have been reported. Additional toxicities with irinotecan include leukopenia (including neutropenic fever) and moderate nausea and vomiting. Toxicities of irinotecan appear to be greater when the drug is given weekly compared with other administration schedules.

Similar to 5-FU, there is a polymorphism associated with irinotecan toxicity. UDP-glucuronosyltransferase (*UGT1A1*) is an enzyme responsible for the glucuronidation of SN-38 to inactive metabolites, and reduced or deficient levels of this enzyme correlate with irinotecan-induced diarrhea and neutropenia.[39] Recently the FDA approved a blood test that detects variations in this gene. This test will assist health care providers in predicting which patients may develop severe toxicities from "normal" doses of irinotecan and can be ordered prior to patients receiving irinotecan. Irinotecan is administered as an IV bolus over 60 to 90 minutes in a variety dosing schedules.

Oxaliplatin

Oxaliplatin (Eloxatin®) is similar to other platinum analogs (e.g., cisplatin) in that it binds to the N-7 position of guanine, which results in cross-linking of DNA and double-stranded DNA breaks.[26,40] Oxaliplatin differs from cisplatin in that the DNA damage induced by oxaliplatin may not be as easily recognized by DNA repair genes often seen in colorectal cancer. Oxaliplatin, in combination with 5-FU-based regimens, is indicated for the first- and second-line treatment of metastatic colon cancer, as well as the adjuvant treatment of colon cancer.

The dose-limiting toxicity of oxaliplatin is acute and chronic neuropathy.[41] Acute neuropathies occur within 1 to 2 days of dosing, resolve within 2 weeks, and usually occur peripherally. These acute neuropathies occur in almost all patients to some degree and are exacerbated by exposure to cold temperature or cold objects. Health care providers should instruct patients to avoid cold drinks and the use of ice and to cover the skin before exposure to cold or cold objects. In addition, carbamazepine, gabapentin, amifostine, and calcium and magnesium infusions are sometimes used to both prevent and treat oxaliplatin-induced neuropathies, although no strong evidence demonstrating their efficacy exists. Until definitive trials are conducted, calcium and magnesium infusions may be used because they have few adverse effects and are relatively inexpensive. Persistent neuropathies generally occur after eight cycles of oxaliplatin and are characterized by defects that can interfere with daily activities (e.g., writing, buttoning, swallowing, and walking). These neuropathies occur in up to half of patients receiving oxaliplatin but usually resolve with dosage reductions or after oxaliplatin is stopped.[26,41] Oxaliplatin has minimal renal or mylesuppressive effects and nausea/vomiting when compared with other platinum drugs. Oxaliplatin is given intravenously in a variety of dosing schedules, with a typical dose being 85 mg/m^2 IV every 2 weeks.

Bevacizumab

Bevacizumab (Avastin®) is a recombinant humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF). VEGF is a proangiogenic growth factor found in many cancers, including colon cancer, and is thought to promote blood vessel formation and metastasis of the tumor by binding to VEGF receptors on tumors. Bevacizumab inhibits circulating VEGF, preventing it from binding to receptors and decreasing the formation of new blood vessels.[26,31] Additionally, bevacizumab may allow for increased concentrations of traditional chemotherapy such as irinotecan to reach the tumor to exert its pharmacologic effect. Bevacizumab is not effective alone and must be used in combination with other agents effective in colorectal cancer. It is indicated for first-line treatment of patients with metastatic colorectal cancer in combination with intravenous 5-FU-based regimens. Bevacizumab also has been shown to increase survival in the second-line setting when used in combination with the FOLFOX regimen in patients who have not yet received bevacizumab.

Adverse effects associated with bevacizumab include dose-limiting hypertension, which is common but manage with oral antihypertensive agents.[42] Thrombotic events (including myocardial infarctions, pulmonary embolisms, and deep vein thromboses) occur more frequently in the elderly patients with cardiovascular risk factors, and the risk/benefit of bevacizumab must be considered. Since bevacizumab interferes with normal wound healing, it should not be given shortly before or after surgical procedures.[42] Initiation within 28 days

of surgery is not recommended to allow for proper would healing and decrease the risk of bleeding. The amount of time needed after bevacizumab discontinuation to perform elective surgical procedures is less clear, but health care providers should take into consideration bevacizumab's half-life of approximately 20 days when making clinical decisions.[42] Patients should have their urine checked for protein prior to each dose of bevacizumab to assess for potential kidney damage. Patients who have a develop 2+ protein on the urinalysis require additional testing prior to receiving therapy. Finally, there is a risk of gastrointestinal perforation, which is rare but potentially fatal. Patients complaining of abdominal pain associated with vomiting or constipation should be counseled to call their physician immediately. Bevacizumab is commonly given at a dose of 5 mg/kg IV every 14 days until disease progression. Once disease progresses and salvage chemotherapy is initiated, the benefit of continuing bevacizumab is unclear.

Cetuximab

Cetuximab (Erbitux®) is a chimeric monoclonal antibody directed against the EGFR. The EGFR is overexpressed in some colon cancers and leads to an increase in tumor proliferation and growth.[26,34] Cetuximab received FDA approval for use in EGFR-expressing metastatic colorectal cancer. Cetuximab should be administered in combination with irinotecan but can be used as a single agent in patients who cannot tolerate irinotecan-based chemotherapy.

Cetuximab is well tolerated, with infusion-related reactions its dose-limiting toxicity. Patients require premedication with acetaminophen and diphenhydramine and may require dose modifications if they develop severe toxicity. An acneiform skin rash and diarrhea are also seen commonly, and health care practitioners should provide counseling to patients about these adverse effects. Treatment options include common medications used to treat acne (doxycycline) and general skin care. A rare (less than 1%) interstitial lung disease is seen with all agents that inhibit the EGFR, and patients should be instructed to report any new-onset shortness of breath. An initial loading dose of 400 mg/m^2 is given as an IV infusion, followed by weekly doses of 250 mg/m^2. At this time, immunohistochemical evidence of EGFR-positive staining should be obtained prior to initiating therapy with cetuximab.

RECTAL CANCER

Although often treated similarly to colon cancer, there are some important differences in the treatment of rectal cancer compared with colon cancer, especially in the adjuvant setting and the role of radiation. Rectal cancer involves tumors found in distal 15 cm of the large bowel and, as such, is very distinct from colon cancer in that it may recur both locally and distally. The higher incidence of local failure and poorer overall prognosis associated with rectal cancer are due to limitations in surgical techniques. Therefore, multimodal therapies with a combination of chemotherapy, radiation, and surgery are at the forefront of the treatment of rectal cancer, with the main goal of survival and quality of life by preserving the function of the anal sphincter. In addition, because treatment with surgery, radiation, or systemic chemotherapy at the time of the recurrence is often suboptimal, adjuvant therapy after tumor resection is an important aspect of treatment of the primary tumor. Similar to adjuvant therapy for colon cancer, 5-FU provides the basis for chemotherapy regimens for rectal cancer. ❽ *For stage II or III rectal cancer, six cycles of 5-FU combined with radiation is standard after surgical resection.*[43] The radiation therapy decreases the rate of local recurrence, whereas the 5-FU decreases the risk of distant tumor recurrence, as well as acting as a radiosensitizer. Toxicities from combined-modality therapy include severe hematologic toxicity, enteritis, and diarrhea. Additional trials have sought to determine optimal combinations of concurrent radiation and 5-FU. Again, similar to tumors in the colon, continuous infusions of 5-FU appear to be superior to bolus doses. However, leucovorin does not appear to improve efficacy of adjuvant treatment for rectal cancer. Use of oral alternatives to 5-FU that are also known to enhance radiation effects, such as capecitabine, are under investigation, with preliminary data suggesting that the combination of capecitabine and radiation will be safe and effective.

Another unique aspect of rectal cancer is the use of **neoadjuvant therapy.** Preoperative radiation with or without chemotherapy is given to downstage the tumor prior to surgical resection to improve sphincter preservation by making the surgical procedure easier to perform. The issue of preoperative versus postoperative radiation is a subject of debate and investigation in the United States and will require further data to determine the superiority of one method over the other.

OUTCOME EVALUATION

Disease Assessment

The goal of monitoring is to evaluate whether the patient is receiving any benefit from the management of the disease, to detect recurrence, and to minimize the adverse effects of treatment. During treatment for active disease, patients should undergo monitoring for measurable tumor response, progression, or new metastases; these tests may include chest CT scans or x-rays, abdominal or pelvic CT scans or x-rays depending on the site of disease being evaluated for response, and CEA measurements every 3 months if the CEA is or was elevated previously.[44] A PET scan can be considered to identify localized sites of metastatic disease in situations where a rising CEA level suggests metastatic disease but CT scans and other imaging studies are negative. Symptoms of recurrence such as pain, changes in bowel habits, rectal bleeding, pelvic masses, anorexia, and weight



Patient Encounter, Part 4: Screening and Preventing Colon Cancer

GW is concerned about his twin boys developing colon cancer given his disease and his family history of cancer. He asks for advice on preventing colon cancer and ways to detect the disease earlier in his children.

- What is the role for chemoprevention for GW's children?
- What are the screening recommendations for colon cancer? Do these change for GW's children?

loss develop in fewer than 50% of patients. Patients who undergo curative surgical resection, with or without adjuvant therapy, require close follow-up because early detection and treatment of recurrence still could result in patient cure. In addition, early treatment for asymptomatic metastatic colorectal cancer appears superior to delayed therapy.[44]

Monitoring of Chemotherapy

Laboratory monitoring is performed before initiating therapy and before each cycle of chemotherapy. A complete blood count should be obtained prior to each course of chemotherapy to ensure that hematologic values are adequate. In particular, white blood cell counts and absolute neutrophil counts can be decreased in patients receiving chemotherapy such as irinotecan and 5-FU and increase the risk of infection. Baseline liver function tests and an assessment of renal function should be done prior to and periodically during therapy. Other selected laboratory tests include checking for the presence of protein in the urine in patients receiving oxaliplatin and bevacizumab.

❾ *Patients should be evaluated during every treatment visit for the presence of anticipated side effects, which generally include loose stools or diarrhea from irinotecan, 5-FU, and capecitabine, hand-foot syndrome from 5-FU and capecitabine, nausea or vomiting from irinotecan, 5-FU, and oxaliplatin, mouth sores from 5-FU, neuropathies from oxaliplatin, bleeding and hypertension from bevacizumab, and skin rash associated with cetuximab. Health care practitioners should anticipate these adverse reactions and treat them aggressively and attempt to prevent them from occurring. Refer to summary section for complete patient care and monitoring recommendations.*

SCREENING

❿ *Health care professionals must be aware of and promote appropriate screening recommendations for colon cancer in their patients.* Proper screening of patients at normal and high risk for colon cancer leads to the detection of smaller, localized lesions and higher cure rates.[45] Screening techniques include a digital rectal examination, fecal occult blood tests (FOBTs), and imaging of the colon. The use of FOBTs annually in combination with digital rectal examinations has led to earlier diagnosis of early stages of disease and may reduce colorectal cancer mortality by up to a third. Two main methods are available to detect occult blood in the feces: guaiac dye and immunochemical methods. The Hemoccult II is the most commonly used FOBT in the United States and is a guaiac-based test. Proper counseling by health care providers is required to receive accurate test results. Table 88–7 lists common reasons for inaccurate results with the guaiac tests, and such results require proper counseling of patients on the use of these tests. Immunochemical tests (InSure® and others), which use antibodies to detect hemoglobin, are also available for use. One advantage of immunochemical tests is that they do not react with dietary factors or medications. Both FOBTs can be recommended in screening protocols for patients.

TABLE 88–7. Common Reasons for Inaccurate Results from Guaiac Stool Tests

False Positives	False Negatives
Red meat, blood soup, blood sausage	Vitamin C
Vegetables with peroxidase activity	Dehydrated samples
Iron	
Gastric irritation (NSAIDs)	
Avoid these foods and medications for 3 days prior to test	

In addition, imaging of the colon with a sigmoidoscopy, colonoscopy, or double-contrast barium enema is required every 5 to 10 years in most individuals over age 50. Colonoscopy is the preferred procedure because it allows for greater visualization of the entire colon and simultaneous removal of lesions found during screening.[45] A sigmoidscope only examines the lower half of the colon, and a double-contrast barium enema (DCBE) requires a supplemental colonoscopy to remove any lesions found during the screening process. ❿ *Table 88–8 is a summary of the current American Cancer Society guidelines for screening and surveillance for early detection of colorectal polyps and cancer.*[45]

TABLE 88–8. Colon Cancer Screening Guidelines

Average risk	Annual DRE after age 50 ***and***
	Annual FOBT after age 50, at the time of DRE, ***and***
	One of the following after age 50:
	Sigmoidoscopy every 5 years
	Colonoscopy every 10 years
	Barium enema every 5–10 years
Family history	Screening at ages 35–40
HNPCC	Screening at age 30
FAP	Screening at ages 10–12

COLORECTAL CANCER PREVENTION

Strategies to prevent colon cancer can be carried out with pharmacologic or surgical interventions and involve either preventing the initial development of colon cancer (primary prevention) or preventing cancer in patients who demonstrate early signs of colon cancer (secondary prevention). The most widely studied agents for the chemoprevention of colorectal cancer are agents that inhibit COX-2 (e.g., aspirin, NSAIDs, and selective COX-2 inhibitors) and calcium supplementation.[46] COX-2 appears to play a role in polyp formation, and COX-2 inhibition suppresses polyp growth. In 1999, the FDA approved the use of celecoxib to reduce the number of colorectal polyps in patients with FAP, as an adjunct to usual care. This may delay the need for surgical intervention in these patients, but the results cannot be extrapolated to the general population. The dose of celecoxib for this indication is 400 mg orally twice daily, and the risk of cardiovascular damage from COX-2 inhibition needs to be assessed carefully in these patients. The use of aspirin as both a primary and a secondary chemoprevention agent also has been studied. In a prospective, randomized trial, low-dose aspirin (81 mg/day) was shown to decrease the incidence of additional polyps by 19% in patients with a previous history of at least one polyp.[47]

Calcium supplementation appears to be associated with a moderate reduction in risk of recurrent colorectal adenomas, with prospective studies demonstrating a nonstatistical decrease in adenoma recurrence, and the role of calcium as a chemoprevention agent remains under investigation.[47]

Additional agents, including selenium, folic acid, and HMG-CoA reductase inhibitors (statins), show promise as chemopreventive agents in colon cancer, and preliminary and confirmatory studies evaluating their effectiveness have been completed or are ongoing, although none of these agents have been approved for the prevention of colon cancer.[46]

Surgical resection remains an option to prevent colon cancer in individuals at extremely high risk for its development, such as patients diagnosed with FAP. Individuals with FAP who are found to have polyps on screening examinations require total abdominal colectomy. In addition, removal of noncancerous polyps detected during screening colonoscopy is considered a standard of care to prevent the progression of premalignant polyps to cancer.

CONCLUSION

Recent advances in the treatment of cancer of the colon and rectum now offer the potential to improve patient survival, but for many patients, improved disease- and progression-free survival represent equally important therapeutic outcomes. In the absence of the ability of a specific treatment to demonstrate improved survival, important outcome measures should include the effects of the treatment on patient symptoms, daily activities, performance status, and other quality-of-life indicators. Individualized patient care to balance the risks associated with treatment with the benefits of a specific treatment regimen is necessary to optimize patient outcomes.



⑨ Patient Care and Monitoring

1. Review any available diagnostic data to determine the status of the colon cancer.
2. Obtain a thorough history of prescription, nonprescription, and natural drug product use.
3. Evaluate patient-specific factors that may dictate treatment regimen. *Does the patient have a known pharmacogenomic deficiency? What lifestyle issues are important to the patient?*
4. Determine if any dose modifications are required in the chemotherapy regimen prescribed. *Does the patient have adequate blood counts to receive chemotherapy?*
5. Educate the patient on drug therapy and possible treatment-related adverse effects, and counsel the patient on appropriate recommendations to prevent or minimize these adverse effects. *What medications are for the treatment of cancer and what medications are to prevent the adverse effects of chemotherapy?*
6. Develop a plan to prevent treatment-related adverse effects. *Are the antiemetics appropriate? Does the patient understand the possible adverse effects and when to call the physician versus when patient-directed care is appropriate?*
7. Warning signs to report to the physician (depends on regimen used) include fever, diarrhea, mucositis, and hand-foot syndrome.
8. Evaluate the patient for the presence of adverse drug reactions, drug allergies, and drug interactions.

ABBREVIATIONS

APC:	adenomatous polyposis coli
BMI:	body mass index
CAPOX:	capecitabine and oxaliplatin
CAPIRI:	capecitabine and irinotecan
CBC:	complete blood count
CEA:	carcinoembryonic antigen
COX-2:	cyclooxygenase-2
CT:	computed tomography
DCBE:	double-contrast barium enema
DPD:	dihydropyrimidine dehydrogenase
DRE:	digital rectal examination
F-dUMP:	fluoro-deoxy-uridine monophosphate
EGFR:	epidermal growth factor receptor
FAP:	familial adenomatous polyposis
FOBT	fecal occult blood test
FOLFIRI:	folinic acid, fluorouracil, and infusional irinotecan
FOLFOX:	folinic acid, fluorouracil, and oxaliplatin
HNPCC:	hereditary nonpolyposis colorectal cancer
IFL:	irinotecan, fluorouracil, and leucovorin
INR:	international normalized ratio
IV:	intravenous
NSAIDs:	nonsteroidal anti-inflammatory drugs
PET:	positron-emission tomography

TGF-α: transforming growth factor α
TNM: tumor, node, metastasis
TP: thymidine phosphorylase
VEG: Fvascular endothelial growth factor

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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89 Prostate Cancer

Jill M. Kolesar



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Describe the incidence and mortality of prostate cancer.
2. List the risk factors associated with the development of prostate cancer.
3. Understand the pathophysiology underlying the clinical symptoms associated with prostate cancer.
4. Compare placebo versus finasteride for the prevention of prostate cancer.
5. Recommend a prostate cancer screening program for a man based on his age and risk factors.
6. Recommend a treatment for initial treatment of prostate cancer based on stage, Gleason score, age, and symptoms.
7. Compare the efficacy of radiation therapy versus surgical therapy for the initial management of prostate cancer.
8. Outline the role of luteinizing hormone–releasing hormone (LHRH) agonists in the treatment of prostate cancer.
9. Contrast the benefits and risks of luteinizing hormone–releasing hormone (LHRH) single-agent therapy and combined androgen blockade in the first-line therapy of metastatic prostate cancer.
10. Understand the role of chemotherapy in the treatment of metastatic prostate cancer.

Key Concepts

❶ Prostate cancer is the most frequent cancer in United States men. African-American ancestry, family history, and increased age are the primary risk factors for prostate cancer.

❷ Prostate-specific antigen is a useful marker for detecting prostate cancer at early stages, predicting outcome for localized disease, defining disease-free status, and monitoring response to androgen-deprivation therapy or chemotherapy for advanced-stage disease.

❸ The prognosis for prostate cancer patients depends on the histologic grade, the tumor size, and the disease stage. More than 85% of patients with stage A_1 disease but less than 1% of those with stage D_2 can be cured.

❹ Androgen ablation with a luteinizing hormone–releasing hormone (LHRH) agonist plus an antiandrogen should be used prior to radiation therapy for patients with locally advanced prostate cancer to improve outcomes over radiation therapy alone.

❺ Androgen ablation therapy, with either orchiectomy, a luteinizing hormone–releasing hormone (LHRH) agonist alone, or an LHRH agonist plus an antiandrogen (combined hormonal blockade), can be used to provide palliation for patients with advanced (stage D_2) prostate cancer. The effects of androgen deprivation seem most pronounced in patients with minimal disease at diagnosis.

❻ Antiandrogen withdrawal, for patients having progressive disease while receiving combined hormonal blockade with a luteinizing hormone–releasing hormone (LHRH) agonist plus an antiandrogen, can provide additional symptomatic relief. Mutations in the androgen receptor have been documented that cause antiandrogen compounds to act like receptor agonists.

❼ Chemotherapy, with docetaxel and prednisone or docetaxel and estramustine, improves survival in patients with hormone-refractory prostate cancer. Patients with hormone-refractory prostate cancer should be considered for entry into clinical trials investigating new therapies for prostate cancer.

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Prostate cancer is the most commonly diagnosed cancer in American men.[1] For most men, prostate cancer has an indolent course, and treatment options for early disease include expectant management, surgery, and radiation. With expectant management, patients are monitored for disease progression or development of symptoms. Localized prostate cancer can be cured by surgery or radiation therapy, but advanced prostate cancer is not yet curable. Treatment for advanced prostate cancer can provide significant disease palliation for many patients for several years after diagnosis. The endocrine dependence of this tumor is well documented, and hormonal manipulation to decrease circulating androgens remains the basis for the treatment of advanced disease.

EPIDEMIOLOGY AND ETIOLOGY

❶ *Prostate cancer is the most frequent cancer among American men and represents the second leading cause of cancer-related deaths in all males.*[1] In the United States alone, it is estimated that 234,460 new cases of prostatic carcinoma will be diagnosed and more than 27,350 men will die from this disease in 2006.[1] Although prostate cancer incidence increased during the late 1980s and early 1990s owing to widespread prostate-specific antigen (PSA) screening, deaths from prostate cancer have been declining continuously since 1995.[1]

Table 89–1 summarizes the possible factors associated with prostate cancer.[2] The only widely accepted risk factors for prostate cancer are age, race/ethnicity, and family history of prostate cancer.[2] The disease is rare under the age of 40 years, but the incidence increases sharply with each subsequent decade, most likely because the individual has had a lifetime exposure to testosterone, a known growth signal for the prostate.[3]

TABLE 89–1. Risk Factors Associated with Prostate Cancer

Factor	Possible Relationship
Probable Risk Factors	
Age	More than 70% of cases are diagnosed in men greater than 65 years old.
Race	African Americans have higher incidence and death rate.
Genetic	Familial prostate cancer is inherited in an autosomal dominant manner.
	Mutations in *p53, Rb*, E-cahedrin, α-catenin, androgen receptor, *KAII*, microsatellite instability, loss of heterozygocity at 1, 2q, 12p, 15q, 16p, and 16q.
	Candidate prostate cancer gene locus identified on chromosome 1.
Possible Risk Factors	
Environmental	Clinical carcinoma incidence varies worldwide.
	Latent carcinoma similar between regions. Nationalized males adopt intermediate incidence rates between that of the United States and their native country.
Occupational	Increased risk associated with cadmium exposure.
Diet	Increased risk associated with high-meat and high-fat diets.
	Decreased intake of 1, 25-dihydroxyvitamin D, vitamin E, lycopene, and β-carotene increases risk.
Hormonal	Does not occur in eunuchs.
	Low incidence in cirrhotic patients.
	Up to 80% are hormonally dependent. African-Americans have 15% increased testosterone.
	Japanese have decreased 5-α-reductase activities.
	Polymorphic expression of the androgen receptor.

Compiled from Carter et al,[2] Hsieh et al,[3] and Ross et al.[4]

Race and Ethnicity

The incidence of clinical prostate cancer varies across geographic regions. Scandinavian countries and the United States report the highest incidence of prostate cancer, whereas the disease is relatively rare in Japan and other Asian countries.[4] African-American men have the highest rate of prostate cancer in the world, and in the United States, prostate cancer mortality in African Americans is more than twice that seen in Caucasian populations.[1] Hormonal, dietary, and genetic differences, as well as differences in access to health care, may contribute to the altered susceptibility to prostate cancer in these populations.[2] Testosterone, commonly implicated in the pathogenesis of prostate cancer, is 15% higher in African American men than in Caucasian males. Activity of 5-α-reductase, the enzyme that converts testosterone to its more active form, dihydrotestosterone (DHT), in the prostate, is decreased in Japanese men compared with African Americans and Caucasians.[2] In addition, genetic variations in the androgen receptor exist. Activation of the androgen receptor is inversely correlated with CAG repeat length. Shorter CAG repeat sequences have been found in African Americans. Therefore, the combination of increased testosterone and increased androgen receptor activation may account for the increased risk of prostate cancer for African-American men.[2] The Asian diet generally is considered to be low in fat and high in fiber with a high concentration of phytoestrogens, potentially explaining the decreased risk in Asians.[4]

Family History

There appears to a be a family prostate cancer syndrome and genome-wide scans have identified potential prostate cancer susceptibility loci on chromosomes 1, 2q, 12p, 15q, 16p, and

16q; however, none of these susceptibility loci have demonstrated linkage to currently known candidate genes.[5]

An alternative explanation for the familial clustering may be **polymorphisms** in genes important for prostate cancer function and development.[5] Candidate polymorphisms include a polymorphism in the androgen receptor, which has two different nucleotide repeat variants, the CAG and the GCC. The CAG repeat varies in repeat number from 11 to 31 repeats in healthy individuals, and the number of repeats is inversely proportional to the activity of the androgen receptor. Some studies have demonstrated that shorter CAG repeats are associated with increased prostate cancer risk. Another candidate polymorphism is *SRD5A2,* which is the gene that codes for 5-α-reductase, the enzyme that converts testosterone to the more active dihydrotestosterone. A variant in *SRD5A2,* the Ala49Thr, increases the activity and may increase prostate cancer risk.[5]

Diet

A number of epidemiologic studies support an association between high fat intake and the risk of prostate cancer. A strong correlation between national per capita fat consumption and national prostate cancer mortality has been reported, and prospective case-control studies suggest that a high-fat diet doubles the risk of prostate cancer.

Other dietary factors implicated in prostate cancer include retinol, carotenoids, lycopene, and vitamin D consumption.[5,6] Retinol, or vitamin A, intake, especially in men older than age 70, is correlated with an increased risk of prostate cancer, whereas intake of its precursor, β-carotene, has a protective or neutral effect. Lycopene, obtained primarily from tomatoes, decreases the risk of prostate cancer in small cohort studies. The antioxidant vitamin E also may decrease the risk of prostate cancer. Men who developed prostate cancer in one cohort study had lower levels of $1,25(OH)_2$-vitamin D than matched controls, although a prospective study did not support this.[2] Clearly, dietary risk factors require further evaluation, but because fat and vitamins are modifiable risk factors, dietary intervention may be promising in prostate cancer prevention.

Other Factors

Benign prostatic hyperplasia (BPH) is one of the most common problems of elderly men, affecting more than 40% of men over age 70. BPH results in the urinary symptoms of hesitancy and frequency. Since prostate cancer affects a similar age group and often has similar presenting symptoms, the presence of BPH often complicates the diagnosis of prostate cancer, although it does not appear to increase the risk of developing prostate cancer.[2,5]

Smoking has not been associated with an increased risk of prostate cancer, but smokers with prostate cancer have an increased mortality resulting from the disease when compared with nonsmokers with prostate cancer [relative risk (RR) = 1.5–2).[2,5] In addition, in a prospective cohort analysis, alcohol consumption was not associated with the development of prostate cancer.

Chemoprevention

Currently, the most promising agent for the prevention of prostate cancer is finasteride, a 5-α-reductase inhibitor used for BPH.[6] When compared with placebo, the point prevalence of prostate cancer was reduced for those on finasteride by 24.8% [95% confidence interval (CI) = 18.6–30.6%; hazard ratio (HR) = 0.75]. However, in those who did develop prostate cancer, there was an increase in the number of high-grade (Gleason grade 7–10) tumors detected at biopsy in the finasteride group. Overall, finasteride did reduce the frequency of prostate cancer, but the prostate cancers that were diagnosed in the finasteride group were more aggressive.

Therefore, the use of finasteride to prevent prostate cancer is currently under debate.[7] Because of its established benefit in treating BPH, the 20% to 30% of men over age 50 with BPH may derive the additional benefit of prostate cancer prevention and should be offered treatment with finasteride. In the 70% to 80% of men without BPH, the benefits, side effects (primarily impotence), and risks of finasteride should be discussed prior to initiating therapy.

Other agents, including selenium, vitamin E, lycopene, green tea, nonsteriodal anti-inflammatory agents, isoflavones, and statins, are under investigsation for prostate cancer and show promise. Selenium is a naturally occurring trace element that is an essential nutrient in the human diet.[8] However, none of these agents is currently recommended for routine use outside a clinical trial.

Screening

Early detection of potentially curable prostate cancers is the goal of prostate cancer screening. For cancer screening to be beneficial, it must reliably detect cancer at an early stage, when intervention would decrease mortality. Whether prostate cancer screening fits these criteria has generated considerable controversy.[9] Digital rectal examination (DRE) has been recommended since the early 1900s for the detection of prostate cancer. The primary advantage of DRE is its specificity, reported at greater than 85%, for prostate cancer. Other advantages of DRE include low cost, safety, and ease of performance. However, DRE is relatively insensitive and is subject to interobserver variability. DRE as a single screening method has poor compliance and has had little effect on preventing metastatic prostate cancer in one large case-control study.[10]

❷ *Prostate-specific antigen (PSA) is a useful marker for detecting prostate cancer at early stages, predicting outcome for localized disease, defining disease-free status, and monitoring response to*



Patient Encounter 1

HG is 46-year-old Caucasian man. He is not overweight and follows a low-fat diet. He does not have any family members with a history of prostate cancer.

- What are his options for prostate cancer screening?
- Is he a candidate for prostate cancer chemoprevention?
- What are his risk factors for prostate cancer?

androgen-deprivation therapy or chemotherapy for advanced-stage disease. PSA is used widely for prostate cancer screening in the United States, with simplicity its major advantage and low specificity its primary limitation.[11] PSA may be elevated in men with acute urinary retention, acute prostatitis, and prostatic ischemia or infarction, as well as BPH, a nearly universal condition in men at risk for prostate cancer. PSA elevations between 4.1 and 10 ng/mL (10 mcg/L) cannot distinguish between BPH and prostate cancer, limiting the utility of PSA alone for the early detection of prostate cancer. Additionally, only 38% to 48% of men with clinically significant prostate cancer have a serum PSA outside the reference range.[12]

Neither DRE nor PSA is sensitive or specific enough to be used alone as a screening test.[12] Although the relative predictability of DRE and PSA is similar, the tumors identified by each method are different. Catalona and associates[13] confirmed that the combination of a DRE and a PSA determination is a better method of detecting prostate cancer than DRE alone.

The common approach to prostate cancer screening today involves offering a baseline PSA and DRE at age 40, with annual evaluations beginning at age 50, to all men of normal risk with a 10-year or greater life expectancy.

Despite this common practice, the benefits of prostate cancer screening are unproven. PSA measurements can identify small, subclinical prostate cancers, where no intervention may be required. Detecting prostate cancer in those not needing therapy not only increases the cost of care through unnecessary screening and work-ups but also increases the toxicity of therapy by subjecting some patients to unnecessary therapy.[14] Currently, the American College of Physicians recommends that rather than screening all men for prostate cancer as a matter of routine, physicians should describe the potential benefits and known risks of screening, diagnosis, and treatment; listen to the patient's concerns; and then decide on an individual's screening method.

PATHOPHYSIOLOGY

The growth and development of the prostate is under control of androgens, and it is well known that men who undergo castration prior to puberty do not develop prostate cancer. The majority of risk factors for prostate cancer are factors that either increase or decrease testosterone exposure. Despite this, serum testosterone or DHT levels obtained at diagnosis are not associated directly with prostate cancer risk, suggesting a multifactorial cause of prostate cancer.[5]

The normal prostate is composed of acinar secretory cells arranged in a radial shape and surrounded by a foundation of supporting tissue. The size, shape, or presence of acini are almost always altered in the gland that has been invaded by prostatic carcinoma. Adenocarcinoma, the major pathologic cell type, accounts for more than 95% of prostate cancer cases.[15] Much rarer tumor types include small cell neuroendocrine cancers, sarcomas, and transitional cell carcinomas.

Prostate cancer can be graded systematically according to the histologic appearance of the malignant cell and then grouped into well, moderately, or poorly differentiated grades.[16] Gland architecture is examined and then rated on a scale of 1 (well differentiated) to 5 (poorly differentiated). Two different specimens are examined, and the score for each specimen is added. Groupings for total Gleason score are 2 to 4 for well-differentiated, 5 or 6 for moderately differentiated, and 7 to 10 for poorly differentiated tumors. Poorly differentiated tumors grow rapidly (poor prognosis), whereas well-differentiated tumors grow slowly (better prognosis).

Metastatic spread can occur by local extension, lymphatic drainage, or hematogenous dissemination.[17] Lymph node metastases are more common in patients with large, undifferentiated tumors that invade the seminal vesicles. The pelvic and abdominal lymph node groups are the most common sites of lymph node involvement (Fig. 89–1). Skeletal metastases from hematogenous spread are the most common sites of distant

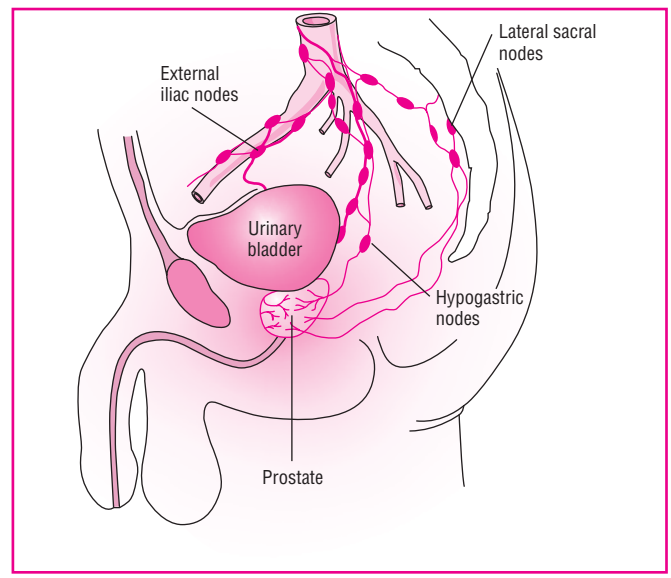


FIGURE 89–1. The prostate gland. (From Kolesar JM. Prostate cancer. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 2423.)

spread. Typically, the bone lesions are osteoblastic or a combination of osteoblastic and osteolytic. The most common site of bone involvement is the lumbar spine. Other sites of bone involvement include the proximal femurs, pelvis, thoracic spine, ribs, sternum, skull, and humerus. The lung, liver, brain, and adrenal glands are the most common sites of visceral involvement, although, these organs usually are not involved initially. About 25% to 35% of patients will have evidence of lymphangitic or nodular pulmonary infiltrates at autopsy. The prostate is a rare site for metastatic involvement from other solid tumors.

The prostate gland is a solid, round, heart-shaped organ positioned between the neck of the bladder and the urogenital diaphragm (see Fig. 89–1). Normal growth and differentiation of the prostate depend on the presence of androgens, specifically DHT.[18] The testes and the adrenal glands are the major sources of circulating androgens. Hormonal regulation of androgen synthesis is mediated through a series of biochemical interactions between the hypothalamus, pituitary, adrenal glands, and testes (Fig. 89–2). Luteinizing hormone–releasing hormone (LHRH) released from the hypothalamus stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. LH complexes with receptors on the Leydig cell testicular membrane and stimulates the production of testosterone and small amounts of estrogen. FSH acts on the Sertoli cells within the testes to promote the maturation of LH receptors and to produce an androgen-binding protein. Circulating testosterone and estradiol influence the synthesis of LHRH, LH, and FSH by a negative-feedback loop operating at the hypothalamic and pituitary level.[19] Prolactin, growth hormone, and estradiol appear to be important accessory regulators for prostatic tissue permeability, receptor binding, and testosterone synthesis.

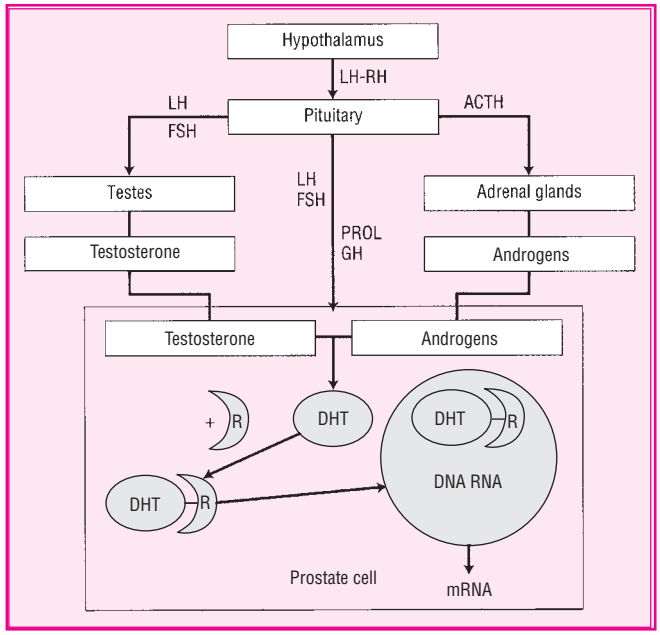


FIGURE 89–2. Hormonal regulation of the prostate gland. ACTH, adrenocorticotropic hormone; DHT, dihydrotestosterone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; LHRH, luteinizing hormone–releasing hormone; PROL, prolactin; R, receptor. (From Kolesar JM. Prostate cancer. In DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 2424.)

Testosterone, the major androgenic hormone, accounts for 95% of the androgen concentration. The primary source of testosterone is the testes; however, 3% to 5% of the testosterone concentration is derived from direct adrenal cortical secretion of testosterone or C-19 steroids such as androstenedione.[17,18]

Hormonal manipulations to ablate or reduce circulating androgens can occur through several mechanisms[17,18] (Table 89–2). The organs responsible for androgen production can be removed surgically (e.g., orchiectomy, hypophysectomy, or adrenalectomy). Hormonal pathways that modulate prostatic growth can be interrupted at several steps (see Fig. 89–2). Interference with LHRH or LH can reduce testosterone secretion by the testes (e.g., estrogens, LHRH agonists, progestogens, and cyproterone acetate). Estrogen administration reduces androgens by directly inhibiting LH release, by acting directly on the prostate cell, or by decreasing free androgens by increasing steroid-binding globulin levels.[17,18]

Isolation of the naturally occurring hypothalamic decapeptide hormone LHRH has provided another group of effective agents for advanced prostate cancer treatment.[20] The physiologic response to LHRH depends on both the dose and mode of administration. Intermittent pulsed LHRH administration, which mimics the endogenous release pattern, causes sustained release of both LH and FSH, whereas high-dose or continuous intravenous administration of LHRH inhibits gonadotropin release owing to receptor down-regulation.[19] Structural modification of naturally occurring LHRH and innovative delivery have produced a series of LHRH agonists that cause a similar down-regulation of pituitary receptors and a decrease in testosterone production.[19]

TABLE 89–2. Hormonal Manipulations in Prostate Cancer

Androgen source ablation	Antiandrogens
Orchiectomy	Flutamide
Adrenalectomy	Bicalutamide
Hypophysectomy	Nilutamide
LHRH or LH inhibition	Cyproterone acetate[b]
Estrogens	Progesterones
LHRH agonists	5-α-reductase inhibition
Progesterones[a]	Finasteride[b]
Cyproterone acetate[b]	
Androgen synthesis inhibition	
Aminoglutethimide	
Ketoconazole	
Progesterones[a]	

[a]Minor mechanisms of action.
[b]Investigational compounds or use.
LH, luteinizing hormone; LHRH, luteinizing hormone–releasing hormone.

Androgen synthesis can be inhibited in the testes or in the adrenal gland. Aminoglutethimide inhibits the desmolase-enzyme complex in the adrenal gland, thereby preventing the conversion of cholesterol to pregnenolone. Pregnenolone is the precursor substrate for all adrenal-derived steroids, including androgens, glucocorticoids, and mineralocorticoids.[21] Ketoconazole, an imidazole antifungal agent, causes a dose-related reversible reduction in serum cortisol and testosterone concentration by inhibiting both adrenal and testicular steroidogenesis.[21,22] As a secondary mechanism to its antiandrogen action, megestrol acetate inhibits the synthesis of androgens. This inhibition appears to occur at the adrenal level, but circulating levels of testosterone also are reduced, suggesting that inhibition at the testicular level also may occur.[21]

Antiandrogens inhibit the formation of the DHT-receptor complex and thereby interfere with androgen-mediated action at the cellular level.[22] Megestrol acetate, a progestational agent, also is available and has antiandrogen actions.[21] Finally, the conversion of testosterone to DHT may be inhibited by 5-α-reductase inhibitors.[6]

CLINICAL PRESENTATION, DIAGNOSIS, AND STAGING

The information obtained from the diagnostic tests is used to stage the patient. There are two commonly recognized staging classification systems (Table 89–3). The formal international classification system [tumor, node, metastases (TNM)], adopted by the International Union Against Cancer in 1974, was updated in 1992 in an effort to provide congruence with the classic American Urologic System (AUS) staging system for prostate cancer.[23] The AUS classification is the most commonly used staging system in the United States (see Table 89–3). Patients are assigned to stages A through D and corresponding subcategories based on size of the tumor (T), local or regional extension, presence of involved lymph node groups (N), and presence of metastases (M).[23] Some studies classify patients who have progressed after hormonal therapy as stage D_3.[38] Based on men diagnosed with prostate cancer at Walter Reed Army Medical Center from 1988 to 1998, including over 2042 prostate cancer diagnoses, localized prostate cancer (stage T_1 and T_2) was diagnosed more frequently (89% versus 68%) and advanced disease (stages T_3, T_4, and D) was diagnosed less frequently (11% versus 32%) when comparing the 1998 to the 1988 incidence rates.

Clinical Presentation

Localized Disease
Asymptomatic

Locally Invasive Disease
- Ureteral dysfunction, frequency, hesitancy, and dribbling
- Impotence

Advanced Disease
- Back pain
- Cord compression
- Lower extremity edema
- Pathologic fractures
- Anemia
- Weight loss

Diagnostic and Staging Work-Up for Prostate Cancer

Diagnostic Tests
- Digital rectal examination (DRE)
- Prostate-specific antigen (PSA)
- Transrectal ultrasonography (TRUS) if either DRE is positive or PSA is elevated
- Biopsy

Staging Tests
- Gleason score on biopsy specimen
- Bone scan
- Complete blood count
- Liver function tests
- Serum phosphatases (acid/alkaline)
- Excretory urogram
- Chest x-ray

Additional Staging Tests
- Depends on tumor classification, PSA, and Gleason score.
- Skeletal films
- Lymph node evaluation
  - Pelvic computed tomography
  - ^{111}In-labeled capromab pendetide scan
  - Bipedal lymphangiogram
- Transrectal magnetic resonance imaging

❸ *The prognosis for patients with prostate cancer depends on the histologic grade, the tumor size, and the local extent of the primary tumor.*[16] The most important prognostic criterion appears to be the histologic grade because the degree of differentiation ultimately determines the stage of disease. Poorly differentiated tumors are highly associated with both regional lymph node involvement and distant metastases.[16]

Between 1992 and 1999, 5-year overall survival rates were estimated at 98% for whites and 93% for African Americans.[1] For this same period, the survival rates for localized or regional disease (100%) and distant disease (33%) in white males were about the same as the survival rates for localized or regional disease (100%), and distant disease (26%) in African Americans.[1] A 6.3% decline in age-adjusted mortality has been documented for the period 1991 to 1995.[24] Ten-year cancer-specific survival is estimated as 95% for stage A_1, 80% for stages A_2 to B_2, 60% for stage C, 40% for stage D_1, and 10% for stage D_2.[25] It is estimated that more than 85% of patients with stage A_1 can be cured, whereas fewer than 1% of patients with stage D_2 will be cured.

TABLE 89–3. Staging and Classification Systems for Prostate Cancer

AUS[a] Stage (A–D)	AJC-UICC[b] Classification (TNM)
A (occult, nonpalpable)	$T_xN_xM_x$ (cannot be assessed) $T_0N_0M_0$ (nonpalpable)
A_1: Focal	T_0 : Focal or diffuse
A_2: Diffuse	
B (confined to prostate)	$T_1N_0M_0$, $T_2N_0M_0$
B_1: Single nodule in one lobe, less than 1.5 cm	T_1: (Clinically inapparent tumor not palpable or visible by imaging) T_{1a}: Tumor incidental histologic finding in 5% or less of tissue resected T_{1b}: Tumor incidental histologic finding in 5% or more of tissue resected T_{1c}: Tumor identified by needle biopsy (e.g., because of elevated PSA)
B_2: Diffuse involvement of whole gland, greater than 1.5 cm	T_2: (Tumor confined within the prostate[c]) T_{2a}: Tumor involves half of a lobe or less T_{2b}: Tumor involves more than half a lobe, but not both lobes T_{2c}: Tumor involves both lobes
C (localized to periprostatic area)	$T_3N_0M_0$, $T_4N_0M_0$
C_1: No seminal vesicle involvement, less than 70 g	T_3: (Tumor extends through the prostatic capsule[d]) T_{3a}: Unilateral extracapsular extension T_{3b}: Bilateral extracapsular extension T_{3c}: Tumor invades the seminal vesicle(s)
C_2: Seminal vesicle involvement, greater than 70 g	T_4: (Tumor is fixed or invades adjacent structures other than the seminal vesicles) T_{4a}: Tumor invades any of bladder neck, external sphincter, or rectum T_{4b}: Tumor invades levator muscles and/or is fixed to the pelvic wall
D (metastatic disease)	Any T, $N_{1–4}$, M_0, or $N_{0–4}$, M_1
D_1: Pelvic lymph nodes or ureteral obstruction	N_1: Metastasis in a single lymph node, 2 cm or less in greatest dimension
D_2: Bone, distant lymph node, organ, or soft tissue metastases	N_2: Metastasis in single lymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph node metastases, none more than 5 cm in greatest dimension N_3: Metastasis in lymph node more than 5 cm in greatest dimension M_{1a}: Nonregional lymph node(s) M_{1b}: Bone(s) M_{1c}: Other site(s)

[a]American Urologic System.
[b]American Joint Committee–International Union Against Cancer.
[c]Tumor found in one or both lobes by needle biopsy but not palpable or visible by imaging is classified as T_{1c}.
[d]Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T_3 but as T_2.

TREATMENT

Desired Outcome

The desired outcome in early-stage prostate cancer is to minimize morbidity and mortality owing to prostate cancer.[26] Unfortunately, the most appropriate therapy for early-stage prostate cancer is unknown. Early-stage disease may be treated with surgery, radiation, or watchful waiting. While surgery and radiation are curative, they are associated with significant morbidity and mortality. Since the overall goal is to minimize morbidity and mortality associated with the disease, watchful waiting is appropriate in selected individuals. Advanced prostate cancer (stage D) is not currently curable, and treatment should focus on providing symptom relief and maintaining quality of life.[27]

General Approach to Treatment

The initial treatment for prostate cancer depends primarily on the disease stage, the Gleason score, the presence of symptoms, and the life expectancy of the patient.[15,26] Prostate cancer usually

TABLE 89–4. Initial Management of Prostate Cancer with Low and Intermediate Recurrence Risk

Recurrence Risk	Expected Survival	Initial Therapy
Low	Less than 10 years	Expectant management or RT
$T_{1–2a}$, Gleason 2–6, PSA less than 10	Greater than or equal to 10 years	Expectant management or RP with or without pelvic lymph node dissection or RT
Intermediate	Less than 10 years	EM, RT or RP with or without pelvic lymph node dissection
$T_{2b–2c}$, or Gleason 7, or PSA 10–20	Greater than or equal to 10 years	RP with or without pelvic lymph node dissection or RT

EM = Expectant management; RT = Radiation therapy; RP = Radical prostatectomy; PSA = Prostate specific antigen.

is diagnosed initially by PSA and DRE and confirmed by a biopsy, where the Gleason score is assigned. Asymptomatic patients with a low risk of recurrence, those with a T_1 or T_2 lesion with a Gleason score of 2 through 6 and a PSA of less than 10 ng/mL (10 mcg/L), may be managed by expectant management or radiation[26] (Table 89–4). Since patients with asymptomatic early-stage disease generally have an excellent 10-year survival, immediate morbidities of treatment must be balanced against the likelihood of dying from prostate cancer. In general, more aggressive treatments of early-stage prostate cancer are reserved for younger men, although patient preference is a major consideration in all treatment decisions. In patients with a normal life expectancy of equal to or greater than 10 years, either observation, radiation (external beam or brachytherapy), or radical prostatectomy may be offered. Radical prostatectomy and radiation therapy generally are considered therapeutically equivalent for localized prostate cancer, although neither has been shown to be better than observation alone.[26–28]

Individuals with T_{2b} and T_{2c} disease or a Gleason score of 7 or a PSA ranging from 10 to 20 ng/mL (10 to 20 mcg/L) are considered at intermediate risk for prostate cancer recurrence.[26] Individuals with less than a 10-year expected survival may be offered expectant managment, radiation therapy, or radical prostatectomy, and those with a greater than or equal to 10-year life expectancy may be offered either radical prostatectomy or radiation therapy (Table 89–5).

Patients at high risk of recurrence [stage T_{3b}, a Gleason score ranging from 8 to 10, or a PSA value greater than 20 ng/mL (20 mcg/L)] should be treated with androgen ablation for 2 to 3 years combined with radiation therapy[26] (see Table 89–5). Selected individuals with a low tumor volume may receive a radical prostatectomy or radiation therapy.[29,30]

Patients with T_{3b} and T_4 disease have a very high risk of recurrence and are not candidates for radical prostatectomy because of extensive local spread of disease.[26] ❹ *Androgen ablation with an LHRH agonist plus an antiandrogen should be used prior to radiation therapy for patients with locally advanced prostate cancer to improve outcomes over radiation therapy alone.* Patients should be offered a combination of radiation therapy and androgen ablation. Recent evidence suggests that androgen ablation should be instituted at diagnosis rather than waiting for symptomatic disease or progression to occur. In a randomized clinical trial enrolling 500 men with locally advanced prostate cancer who were randomized to either immediate initiation of androgen ablation with either orchiectomy or androgen ablation or deferred hormonal therapy, individuals with immediate therapy had a median actuarial cause-specific survival duration of 7.5 years, whereas those with deferred treatment had a median actuarial cause-specific survival duration of 5.8 years.[31]

❺ *Androgen ablation therapy, with either orchiectomy, an LHRH agonist alone, or an LHRH agonist plus an antiandrogen (combined hormonal blockade), can be used to provide palliation for patients with advanced (stage D_2) prostate cancer.* The effects of androgen deprivation seem most pronounced in patients with minimal disease at diagnosis.[26] Estrogens were once used widely; however, the primary estrogen, diethylstilbestrol (DES), was withdrawn from the United States market in 1997 owing to increased cardiovascular risk. Secondary hormonal manipulations, cytotoxic chemotherapy, or supportive care is used for the patient who progresses after initial therapy.[21]

TABLE 89–5. Management of Prostate Cancer with High and Very High Recurrence Risk

Recurrence Risk	Initial Therapy
High	
T_{3a}, or Gleason 8–10, or PSA greater than 20 ng/mL	Androgen deprivation for 2 years and RT or RT or RP
Locally advanced	
Very high	RT + androgen deprivation
$T_{3b}–T_4$	or Androgen deprivation
Metastatic	
Any T, N_1	Androgen deprivation or RT
Any T, any N, M_1	Androgen deprivation

Androgen ablation = serum testosterone levels less than 50 ng/mL.
LHRH agonist (medical castrations or surgical are equivalent).
RT = radiation therapy; RP = radical prostatectomy.

Nonpharmacologic Therapy

Expectant Management

Expectant management, also known as *observation* or *watchful waiting,* involves monitoring the course of disease and initiating treatement if the cancer progresses or the patient becomes symptomatic. A PSA determination and DRE are performed every 6 months, with a repeat biopsy at any sign of disease progression. The advantages of expectant management are avoiding the adverse effects associated with definitive therapies such as radiation and radical prostatectomy and minimizing the risk of unnescessary therapies. The major disadvantage of expectant management is the risk that the cancer progresses and requires a more intensive therapy.[26]

Orchiectomy

Bilateral **orchiectomy,** or removal of the testes, rapidly reduces circulating androgens to castrate levels (androstenedione less than 50 ng/mL, 1.7 nmol/L).[15] However, many patients are not surgical candidates owing to their advanced age, and other patients find this procedure psychologically unacceptable.[15] Orchiectomy is the preferred initial treatment in patients with impending spinal cord compression or ureteral obstruction.

Radiation

The two commonly used methods for radiation therapy are **external-beam radiotherapy** and **brachytherapy.**[26] In external-beam radiotherapy, doses of 70 to 75 Gy are delivered in 35 to 41 fractions in patient with low-grade prostate cancer and 75 to 80 Gy for those with intermediate- or high-grade prostate cancer. Brachytherapy involves the permanent implantation of radioactive beads of 145 Gy of ^{125}I or 124 Gy of ^{103}Pd and generally is reserved for individuals with low-risk cancers.

Radical Prostatectomy

Complications from radical **prostatectomy** include blood loss, stricture formation, incontinence, lymphocele, fistula formation, anesthetic risk, and impotence. Nerve-sparing radical prostatectomy can be performed in many patients; 50% to 80% regain sexual potency within the first year. Acute complications from radiation therapy include cystitis, proctitis, hematuria, urinary retention, penoscrotal edema, and impotence (30% incidence).[15] Chronic complications include proctitis, diarrhea, cystitis, enteritis, impotence, urethral stricture, and incontinence.[15] Since radiation and prostatectomy have significant and immediate mortality when compared with observation alone, many patients may elect to postpone therapy until symptoms develop.



Patient Encounter 2

GG is a 72-year-old man with newly diagnosed prostate cancer. He has no symptoms, and he was diagnosed on routine screening. He is stage T_1, his Gleason score is 2, and his PSA is 6 ng/mL (6 mcg/L).

- What treatment options are available to GG?

Pharmacologic Therapy

LHRH Agonists

Luteinizing hormone–releasing hormone (LHRH) agonists are a reversible method of androgen ablation and are as effective as orchiectomy in treating prostate cancer.[32] Currently available LHRH agonists include leuprolide, leuprolide depot, leuprolide implant, and goserelin acetate implant. Leuprolide acetate is administered once daily, whereas leuprolide depot and goserelin acetate implant can be administered either once monthly, once every 12 weeks, or once every 16 weeks (leuprolide depot, every 4 months). The leuprolide depot formulation contains leuprolide acetate in coated pellets. The dose is administered intramuscularly, and the coating dissolves at different rates to allow sustained leuprolide levels throughout the dosing interval. Goserelin acetate implant contains goserelin acetate dispersed in a plastic matrix of D,L-lactic and glycolic acid copolymer and is administered subcutaneously. Hydrolysis of the copolymer material provides continuous release of goserelin over the dosing period. A recently approved leuprolide implant is a mini-osmotic pump that delivers 120 mcg of leuprolide daily for 12 months. After 12 months, the implant is removed, and a different implant can be placed.

Several randomized trials have demonstrated that leuprolide and goserelin are effective agents when used alone in patients with advanced prostate cancer.[19] Response rates around 80% have been reported, with a lower incidence of adverse effects compared with estrogens.[19] There are no direct comparative trials of the currently available LHRH agonists or the dosage formulations, but a recent meta-analysis reported that there is no difference in efficacy or toxicity between leuprolide and goserelin. Therefore, the choice between the two usually is made based on cost and patient and physician preference for a dosing schedule.

The most common adverse effects reported with LHRH agonist therapy include a disease flare-up during the first week of therapy, hot flashes, erectile impotence, decreased libido, and injection-site reactions.[19] The disease flare-up is thought to be caused by initial induction of LH and FSH by the LHRH agonist and manifests clinically as either increased bone pain or increased urinary symptoms.[19] This flare reaction usually resolves after 2 weeks and has a similar onset and duration pattern for the depot LHRH products.[33,34]

LHRH agonist monotherapy can be used as initial therapy, with similar response rates to orchiectomy and estrogen administration expected. There is a lower incidence of cardiovascular-related adverse effects associated with LHRH agonist therapy than with estrogen administration. Patients should be counseled to expect worsening symptoms during the first week of therapy, and caution should be exercised when initiating LHRH agonist therapy in patients with widely metastatic disease involving the spinal cord or having the potential for ureteral obstruction because irreversible complications may occur.

Antiandrogens

Three antiandrogens, flutamide, bicalutamide, and nilutamide, are currently available (Table 89–6). Antiandrogens have been used as monotherapy in previously untreated patients, but a recent meta-analysis determined that monotherapy with antiandrogens is less effective than LHRH agonist therapy.[34] Efficacy of the antiandrogens was similar.[21,35–37] Objective responses are manifested as decreased bone pain, decreased prostate size, decreased PSA, and/or improved performance status. However, for advanced prostate cancer, all currently available antiandrogens are indicated only in combination with androgen-ablation therapy; flutamide and bicalutamide are indicated in combination with an LHRH agonist, and nilutamide is indicated in combination with orchiectomy.[21] The most common antiandrogen-related adverse effects are listed in Table 89–6.

TABLE 89–6. Antiandrogens

Antiandrogen	Usual Dose	Adverse Effects
Flutamide	750 mg/day	Gynecomastia Hot flushes Gastrointestinal disturbances (diarrhea) Liver function test abnormalities Breast tenderness Methemoglobinemia
Bicalutamide	50 mg/day	Gynecomastia Hot flushes Gastrointestinal disturbances (diarrhea) Liver function test abnormalities Breast tenderness
Nilutamide	300 mg/day for first month, then 150 mg/day	Gynecomastia Hot flushes Gastrointestinal disturbances (nausea or constipation) Liver function test abnormalities Breast tenderness Visual disturbances (impaired dark adaptation) Alcohol intolerance Interstitial pneumonitis

Combined Hormonal Blockade

Although up to 80% of patients with advanced prostate cancer will respond to initial hormonal manipulation, almost all patients will relapse within 2 to 4 years of initiating therapy.[15] The rationale for combination hormonal therapy is to interfere with multiple hormonal pathways to completely eliminate androgen action. In clinical trials, combination hormonal therapy, sometimes also referred to as *maximal androgen deprivation* or *total androgen blockade,* has been used. The combination of LHRH agonists or orchiectomy and antiandrogens is the most extensively studied combined androgen-deprivation approach.

Combining an LHRH agonist with flutamide demonstrated response rates greater than 90% in previously untreated patient, and the median survival was 61 months in the combination arm and 41 months in the leuprolide-alone arm in patients with minimal disease.[38] However, in a comparison of goserelin with goserelin and flutamide conducted in 589 patients with 10 years of follow-up, combined androgen blockade (CAB) showed no benefit over goserelin alone.[39]

The most recent meta-analysis of 27 randomized trials in 8275 patients (4803 treated with flutamide, 1683 treated with nilutamide, and 1784 treated with cyproterone) comparing maximal androgen blockade with conventional medical or surgical castration showed a small survival benefit at 5 years for those treated with flutamide or nilutamide (27.6%) compared with those treated with castration alone (24.7%; $p = 0.0005$).[40]

Although some investigators now consider CAB to be the initial hormonal therapy of choice for newly diagnosed patients, the clinician is left to weigh the costs of combined therapy against potential benefits in light of conflicting results in the randomized trials[21] and the modest benefit seen in the meta-analysis.[40] For trials that did show an advantage for CAB, whether these effects are specific to the testosterone-deprivation method (orchiectomy versus leuprolide versus goserelin), the antiandrogen, the duration of therapy, or patient selection is not clear. Until further carefully designed studies that use survival, time to progression, quality of life, patient preference, and cost as end points are conducted, it is appropriate to use either LHRH agonist monotherapy or CAB as initial therapy



Patient Encounter

CC is a 69-year-old man who presents with metastatic prostate cancer. His disease is metastatic to the bones, and his primary symptom is bone pain.

- What treatment options are available?
- Develop a treatment plan including medication and a monitoring plan for both efficacy and toxicity.

for metastatic prostate cancer. CAB may be most beneficial for improving survival in patients with minimal disease and for preventing tumor flare, particularly in those with advanced metastatic disease. All other patients may be started on LHRH agonist monotherapy, and an antiandrogen may be added after several months if androgen ablation is incomplete.

Estrogens

DES was once a mainstay of prostate cancer therapy. While very effective in androgen ablation, DES-treated patients experienced increased cardiovascular mortality.[41] LHRH agonists, with equivalent efficacy and decreased cardiovascular toxicity, supplanted DES as a mainstay of therapy.

Second-Line Therapy

Secondary or salvage therapies for patients who progress after their initial therapy depend on what was used for initial management.[26] For patients diagnosed initially with localized prostate cancer, radiotherapy can be used in the case of failed radical prostatectomy. Alternatively, androgen ablation can be used in patients who progress after either radiation therapy or radical prostatectomy.

Secondary hormonal manipulations, such as adding an antiandrogen to a patient who incompletely suppresses testosterone secretion with an LHRH agonist, or withdrawing antiandrogens in a patient receiving combination therapy, or using agents that inhibit androgen synthesis, can be attempted in patients treated initially with one hormonal modality. Supportive care, chemotherapy, or local radiotherapy can be used in patients who have failed all forms of androgen-ablation manipulations because these patients are considered to have androgen-independent disease.

For patients who initially received an LHRH agonist alone, castration testosterone levels should be documented. Patients with inadequate total testosterone suppression (greater than 20 ng/dL, or 0.694 nmol/L) can be treated by adding an antiandrogen or performing an orchiectomy. If castration testosterone levels have been achieved, the patient is considered to have androgen-independent disease, and palliative androgen-independent salvage therapy can be used.

❻ *Antiandrogen withdrawal, for patients having progressive disease while receiving combined hormonal blockade with an LHRH agonist plus an antiandrogen, can provide additional symptomatic relief. Mutations in the androgen receptor have been documented that cause antiandrogen compounds to act like receptor agonists.*

If the patient initially received combined androgen blockade with an LHRH agonist with an antiandrogen, then androgen withdrawal is the first salvage manipulation.[42] Objective and subjective responses have been noted following the discontinuation of flutamide, bicalutamide, or nilutamide in patients receiving these agents as part of combined androgen ablation with an LHRH agonist. Mutations in the androgen receptor have been demonstrated that allow antiandrogens such as flutamide, bicalutamide, and nilutamide (or their metabolites) to become agonists and activate the androgen receptor. Patient responses to androgen withdrawal manifest as significant PSA reductions and improved clinical symptoms. Androgen withdrawal responses lasting 3 to 14 months have been noted in up to 35% of patients, and predicting response seems to be related most closely to longer androgen exposure times.[42] Incomplete cross-resistance has been noted in some patients who received bicalutamide after they had progressed while receiving flutamide.[35] Adding an agent that blocks adrenal androgen synthesis, such as aminoglutethimide, at the time that androgens are withdrawn may produce a better response than androgen withdrawal alone. Because of the potential for response immediately after antiandrogen withdrawal, a sufficient observation and assessment period (usually 4–6 weeks) is required before a patient can be enrolled on a clinical trial evaluating a new agent or therapy for advanced prostate cancer.

Androgen synthesis inhibitors, such as aminoglutethimide and ketoconazole, can provide symptomatic relief for a short time in approximately 50% of patients with progressive disease despite previous androgen-ablation therapy.[21] Adverse effects during aminoglutethimide therapy occur in approximately 50% of patients.[21] Central nervous system effects that include lethargy, ataxia, and dizziness are the major adverse reactions. A generalized morbilliform, pruritic rash has been reported in up to 30% of patients treated. The rash is usually self-limiting and resolves within 5 to 8 days with continued therapy. Adverse effects from ketoconazole include gastrointestinal intolerance, transient rises in liver and renal function tests, and hypoadrenalism.

After all hormonal manipulations are exhausted, the patient is considered to have androgen-independent disease, and chemotherapy or palliative supportive therapy is appropriate.[26] Palliation can be achieved by pain management, using radioisotopes for bone-related pain, analgesics, corticosteroids, bisphosphonates,[43] and local radiotherapy.[26] Data are emerging that demonstrate that bisphosphonates such as pamidronate and zoledronic acid may prevent skeletal morbidity, such as pathologic fractures and spinal cord compression, in men with hormone-refractory prostate cancer; however, other studies have shown no benefit. The early use of bisphosphonates also has been shown to prevent bone loss owing to androgen deprivation therapy. The usual dose of pamidronate is 90 mg every month, and the usual dose of zoledronic acid is 4 mg every 3 to 4 weeks. A trial of pamidronate or zoledronic acid can be initiated in prostate cancer patients with bone pain; if no benefit is observed, the drug may be discontinued.[44]

❼ *Chemotherapy, with docetaxel and prednisone or docetaxel and estramustine, improves survival in patients with hormone-refractory prostate cancer. Patients with hormone-refractory prostate cancer also may be considered for entry into clinical*

trials investigating new therapies for prostate cancer. Docetaxel 75 mg/m^2 every 3 weeks and prednisone 5 mg twice a day improve survival in hormone-refractory metastatic prostate cancer.[45,46] (Table 89–7). The most common adverse events reported with this regimen are nausea, alopecia, and bone marrow suppression. In addition, fluid retention and peripheral neuropathy, known effects of docetaxel, are observed. The combination of estramustine (280 mg three times a day on days 1–5) and docetaxel 60 mg/m^2 on day 2 every 3 weeks also improves survival in hormone refractory metastatic prostate cancer. Estramustine causes a decrease in testosterone and a corresponding increase in estrogen; therefore, the adverse effects of estramustine include an increase in thromboembolic events and gynecomastia and decreased libido. Estramustine is an oral capsule and should be refridgerated. Calcium inhibits the absorption or estramustine, so concurrent administration should be avoided. While both the docetaxel-prednisone and the docetaxel-estramustine regimens are effective in hormone-refractory prostate cancer, most clinicians prefer the docetaxel-prednisone regimen because of the cardiovascular adverse effects associated with estramustine. In addition, androgen ablation usually is continued when chemotherapy is initiated.[26]

OUTCOME EVALUATION

Monitoring of prostate cancer depends on the stage of the cancer.[26] When definitive, curative therapy is attempted, objective parameters to assess tumor response include assessment of the primary tumor size, evaluation of involved lymph nodes, and the response of tumor markers such as PSA to treatment. Following definitive therapy, the PSA level is checked every 6 months for the first 5 years and then annually. Local recurrence in the absence of a rising PSA may occur, so DRE is also performed. In the metastatic setting, clinical-benefit responses can be documented by evaluating performance status changes, weight changes, quality of life, and analgesic requirements, in addition to the PSA or DRE at 3-month intervals.



Patient Care and Monitoring

1. Men, starting at age 40, should be offered a baseline PSA determination and DRE, with annual screening offered starting at age 50.
2. There are no currently recommended prostate cancer chemoprevention agents.
3. The diagnosis of prostate cancer is made by biopsy.
4. Prostate cancer treatment depends on the stage, age, Gleason score, and PSA concentration. Treatment options include expectant management, radiation therapy, radical prostatectomy, hormonal therapy, and chemotherapy.
5. While receiving treatment for prostate cancer, patients should be monitored for efficacy and toxicity.
6. Measures of efficacy include disappearance of tumor or decrease in tumor, resolution of symptoms, or a decline in the PSA.
7. Measures of toxicity vary by the treatment; work with patients to ensure that they understand the expected toxicities of their regimen and that they should report them.
8. Counsel patients to be compliant with all treatment regimens and appointments.

ABBREVIATIONS

ACS:	American Cancer Society
AUS:	American Urologic System
BPH:	benign prostatic hyperplasia
CAB:	combined androgen blockade
DES:	diethylstilbestrol
DHT:	dihydrotestosterone
DRE:	digital rectal examination
EGF:	epidermal growth factor
FSH:	follicle-stimulating hormone
IGF:	insulin-like growth factor
LH:	luteinizing hormone
LHRH:	luteinizing hormone–releasing hormone

TABLE 89–7. First-Line Chemotherapy Regimens for Metastatic Hormone-Independent Prostate Cancer

Regimen	Usual Dose	Adverse Effects	Dose Adjustments
Docetaxel	75 mg/m^2 q3-weeks	Fluid retention, alopecia, mucositis, myelosuppression, hypersensitivity	*Hepatic* AST/ALT greater than 1.5 times the upper limit of normal and alkaline phosphatase greater than 2.5 upper limit of normal, do not administer Hematologic Ensure complete blood count recovered

NCCN: National Comprehensive Cancer Network
NCI: National Cancer Institute
PCPT: Prostate Cancer Prevention Trial
PSA: prostate-specific antigen
TRUS: transrectal ultrasound
VACURG: Veterans Administration Cooperative Urologic Research Group

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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90 Malignant Lymphomas

Chris Fausel



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Discuss the underlying pathophysiologic mechanisms of the lymphomas and how they relate to presenting symptoms of the disease.
2. Differentiate the pathologic findings of Hodgkin's lymphoma, follicular indolent non-Hodgkin's lymphoma, and diffuse aggressive non-Hodgkin's lymphoma and how this information yields a specific diagnosis.
3. Describe the general staging criteria for the lymphomas and how they relate to prognosis, and evaluate the role of the International Prognostic Index (IPI) in providing prognostic information for non-Hodgkin's lymphoma patients.
4. Contrast the treatment for early- and advanced-stage disease for Hodgkin's lymphoma.
5. Delineate the clinical course of follicular indolent and diffuse aggressive non-Hodgkin's lymphoma and the implications for disease classification schemes and treatment goals.
6. Outline the general treatment approach to follicular indolent and diffuse aggressive non-Hodgkin's lymphoma for localized and advanced disease.
7. Interpret the current role for monoclonal antibody therapy in non-Hodgkin's lymphoma.
8. Assess the role of autologous hematopoietic stem cell transplantation in relapsed Hodgkin's lymphoma and non-Hodgkin's lymphoma.

Key Concepts

❶ B and T cells can undergo neoplastic transformation that is governed by specific mutations in their chromosomes that result in populations of malignant lymphoma cells.

❷ Specific pathologic characteristics distinguishing Hodgkin's lymphoma from non-Hodgkin's lymphoma include morphology, cell surface antigens, and chromosomal mutations.

❸ Classic signs and symptoms of the lymphomas include lymphadenopathy and B-symptoms (i.e., fever, night sweats, and weight loss).

❹ The diagnosis of malignant lymphomas is established by tumor biopsy sample, analysis of the biopsy tissue, and determination of the extent of the disease in the patient.

❺ The goal of treatment of Hodgkin's lymphoma is cure for all stages of disease and the first relapse.

❻ Follicular indolent non-Hodgkin's lymphoma is incurable, so therapy goals focus on inducing and maintaining remission duration while minimizing treatment-related toxicities.

❼ Diffuse, aggressive non-Hodgkin's lymphoma centers on curative-intent therapy using anthracyline-based combination chemotherapy and high-dose chemotherapy with autologous stem cell transplantation for relapsed disease.

❽ The recombinant monoclonal antibody rituximab is an effective treatment option for some patients with non-Hodgkin's lymphoma as a single agent and enhances the efficacy of combination chemotherapy regimens.

The malignant lymphomas are hematologic cancers that consist of a cluster of diseases of the lymphoid tissue. The primary malignant cells for lymphomas are lymphocytes of B-cell, T-cell, and NK-cell origin. These cells originate from a small population of

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lymphocytes that have undergone malignant transformation secondary to a series of genetic mutations. Lymphoma cells predominate in the lymph nodes; however, they can infiltrate other tissues, such as the bone marrow, central nervous system (CNS), gastrointestinal (GI) tract, liver, mediastinum, skin, and spleen. A diagrammatic overview of the lymph node regions is depicted in Fig. 90–1. Lymphoma is categorized into two general headings: Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL), both containing numerous histologic subtypes that are pathologically distinct disease entities. HL is distinguished from NHL by the presence of the pathognomonic Reed-Sternberg (RS) cell. Other lymphoma disease entities without the RS cells are classified as types of NHL.

The clinical course varies widely among these histologies of HL and NHL. Most lymphoma subtypes are highly proliferating tumor cells that require aggressive therapeutic intervention with chemotherapy, radiation therapy, or both. By contrast, certain subtypes of non-Hodgkin's lymphoma are characterized by a disease course that flares and remits intermittently over a period of several years either with or without treatment.

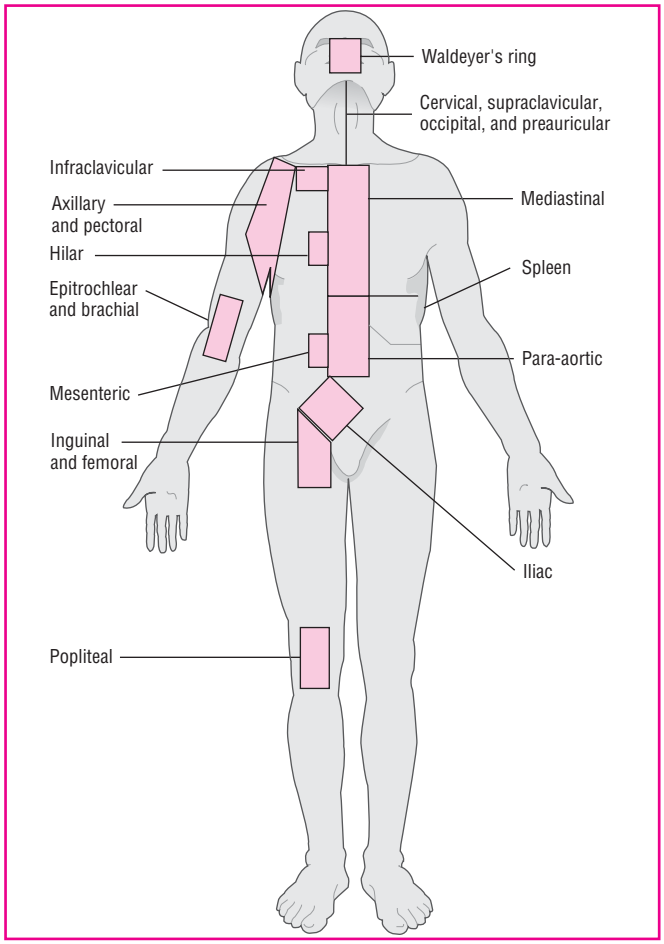


FIGURE 90–1. Representation of the anatomic regions used in the staging of Hodgkin's disease. (Reproduced with permission from Rosenberg SA. Staging of Hodgkin's disease. Radiology 1966; 87:146.)



Patient Encounter, Part 1

A 22-year-old female college student with no remarkable medical history notes shortness of breath when she takes her daily 5-mile run, which has worsened progressively over the past 3 weeks. On review of systems, it is discovered that she has experienced intermittent sensations of chest tightness over the past 2 months that she ascribed to pollen allergies, and 3 days prior to presentation she experienced an episode of hemoptysis. Her only medication is oral contraceptives, and she reports no known drug allergies. A chest x-ray is remarkable for a 10 × 12 cm mediastinal mass.

- What is necessary to establish a diagnosis for this patient?
- Is this age group at risk for a particular malignant diagnosis that presents as a mediastinal mass?

EPIDEMIOLOGY AND ETIOLOGY

Hodgkin's Lymphoma

Approximately 7500 new cases of HL are diagnosed each year in the United States, with 1400 deaths attributed to the disease. The age-specific incidence of HL is bimodal, with its greatest peak in the third decade of life and a smaller peak in the fifth decade of life.[1] The precise cause of HL is unknown, but certain associations have been noted to provide insight about possible etiologic factors. Viruses, such as the Epstein-Barr virus (EBV), have been implicated by epidemiologic, serologic, and molecular studies. The EBV genome has been detected in RS cells in up to 50% of cases in developed countries and more in developing nations. To date, no conclusive studies have correlated HL with human immunodeficiency virus (HIV). Other possible risk factors identified include woodworking and familial factors such as same-sex siblings with HL.[2]

Non-Hodgkin's Lymphoma

There are approximately 55,000 cases of NHL in the United States each year, with the number of deaths approaching 20,000. The incidence of the disease is increasing 4% per year, which has doubled the number of cases in the United States since 1950.[3] This increase is related to the development of aggressive NHL in 20- to 40-year-old men with HIV, although the overall increase is independent of HIV disease, particularly for patients older than 65 years of age. The median age

for diagnosis is 50 years, although children and young adults may be affected. The etiology of certain aggressive NHL subtypes is related to specific endemic geographic factors. Follicular or low-grade lymphoma is more common in the United States and Europe and is relatively uncommon in the Caribbean, Far East, Middle East, or Africa. The human T-cell leukemia virus I (HTLV-I) induces T-cell lymphoma/leukemia in both Japan and the Caribbean. Kaposi's sarcoma–associated herpes virus, or human herpes virus 8 (HHV-8), and hepatitis C have been implicated in inducing NHL. Lymphomas of the gastrointestinal tract are more prevalent in patients with celiac sprue, inflammatory bowel disease, or *Helicobacter pylori* infection. The incidence of Burkitt's NHL is 7 cases per 100,000 population in Africa, compared with 0.1 per 100,000 in the United States. Malaria or EBV is thought to contribute to the chronic B-lymphocyte stimulation that leads to malignant transformation. EBV has been shown to transform lymphocytes in vitro to a monoclonal malignant population, which is believed to drive the development of disease in patients who have received a solid-organ transplant or bone marrow transplant or have other chronic immunosuppressed states. Patients with congenital diseases such as Wiskott-Aldrich syndrome, common-variable hypogammaglobinemia, X-linked lymphoproliferative syndrome, and severe combined immunodeficieny are also at risk.[4]

Environmental factors have been identified as contributing to the development of NHL. Certain occupations such as wood and forestry workers, butchers, exterminators, grain millers, machinists, mechanics, painters, printers, and industrial workers have a higher prevalence of disease. Industrial chemicals such as pesticides, herbicides, organic chemicals (e.g., benzene), solvents, and wood preservatives are also associated with NHL.

PATHOPHYSIOLOGY

Pluripotent stem cells in the bone marrow are able to differentiate to both lymphoid and myeloid progenitor cells. Lymphoid progenitor cells undergo gene rearrangement to yield either B-cell or T-cell lineage precursor cells. Normal maturation for naive B cells includes expression of cell surface antibody or the cells typically undergo **apoptosis,** or programmed cell death. These cells are differentiated from other B cells, such as memory cells, by virtue of cell surface antigen (CD5+ or CD5– and CD27–) and bound antibody (IgM+ and IgD+). Once naive B cells recognize antigen with their cell surface antibody, they accumulate in the lymph nodes, spleen, or other lymphoid tissue. The DNA of these B cells is susceptible to three different types of genetic modification: **receptor editing, somatic hypermutation,** and **class switching** within the germinal center of the lymph node. Germinal centers are microanatomic structures located within lymph nodes that develop with clonal B-cell expansion secondary to antigen stimulation. Under normal circumstances, these genetic changes allow for adaptation of the immune system to the repeated exposure to environmental antigens.

Hodgkin's Lymphoma

The pathophysiology of HL is defined by the presence of the RS cell in a grouping of lymph nodes. The RS cell is a large cell morphologically with a multinucleated structure with pronounced eosinophilic nucleoli.[5] In the affected lymph nodes, the RS cells are contained in a reactive milieu of T lymphocytes, eosinophils, histiocytes, and plasma cells, which makes them difficult to distinguish from these background cells. The natural course of the disease, if left untreated, is less than a 5% probability of surviving 5 years.

RS cells are genetically derived preapoptotic germinal center B cells. There is evidence to suggest that a protein called c-FLIP that inhibits apoptosis garners protection for RS cells. RS cells express cell-surface antigens CD30 and CD15 while lacking other common B-cell antigens such as CD20. RS cells lack the expression of surface immunoglobulin likely owing to the lack of immunoglobulin transcription factors in normal B cells. The overexpression of a proproliferative and antiapoptotic transcription factor NF-κB is believed to contribute to the expansion and survival of RS cells.[6]

HL is classified into disease subtypes based on the number and morphologic appearance of RS cells and the background cellular milieu. These are listed in the WHO classification of lymphoid neoplastic diseases in Table 90–1.[7] Nodular sclerosing HL is the most common form of HL, representing 70% of cases. It is more common in young adults and is marked by the presence of the RS variant cell, the lacunar cell. The second most common form of HL, accounting for approximately 25% of cases, is the mixed-cellularity variant, with others accounting for less than 5% of cases. Factors identified as negative disease prognostic indicators are listed in Table 90–2.[8]

Non-Hodgkin's Lymphoma

The pathophysiology of NHL is governed by numerous environmental and genetic events culminating with a monoclonal population of malignant lymphocytes. B cells represent the cells of origin in excess of 90% of cases of NHL. Figure 90–2 outlines normal B-cell maturation with accompanying cell-surface antigens. ❶ *Evolving data are correlating chromosomal mutations with specific disease subtypes. Cytogenetic abnormalities involving translocations of antigen receptor genes are prevalent in NHL*. These include T-cell receptor genes in T-cell lymphomas and immunoglobulin genes in B-cell lymphomas. The principal defect appears to be an error in the assembly of the regulatory gene segment of an antigen receptor gene, resulting in inappropriate binding to an **oncogene.** This results in dysregulaton of cell growth and proliferation, giving rise to the malignant clone of

TABLE 90–1. WHO Classification of Lymphoid Neoplasms

B-Cell Neoplasms
Precursor B-cell neoplasm
Precursor B-lymphoblastic leukemia/lymphoma
Mature (peripheral) B-cell neoplasms
B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Lymphoplasmacytic lymphoma
Splenic marginal zone B-cell lymphoma (±villous lymphocytes)
Hairy cell leukemia
Plasma cell myeloma/plasmacytoma
Extranodal marginal zone B-cell lymphoma of MALT type
Nodal marginal zone B-cell lymphoma (±monocytoid B cells)
Follicular lymphoma
Mantle-cell lymphoma
Diffuse large B-cell lymphoma
Mediastinal large B-cell lymphoma
Primary effusion lymphoma
Burkitt's lymphoma/Burkitt cell leukemia
T-Cell and NK-Cell Neoplasms
Precursor T-cell neoplasm
Precursor T-lymphoblastic lymphoma/ALL
Mature (peripheral) T-cell neoplasms
T-cell prolymphocytic leukemia
T-cell granular lymphocytic leukemia
Aggressive NK-cell leukemia
Adult T-cell lymphoma/leukemia (HTLV1 positive)
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-type T-cell lymphoma
Hepatosplenic gamma-delta T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides/sezary syndrome
Anaplastic large-cell lymphoma, T or null cell, primary cutaneous type
Peripheral T-Cell lymphoma, not otherwise characterized
Angioimmunoblastic T-cell lymphoma
Anaplastic large-cell lymphoma, T/null cell, primary systemic type
Hodgkin's Lymphoma (Hodgkin's Disease)
Nodular lymphocyte-predominant Hodgkin's lymphoma
Classical Hodgkin's lymphoma
Nodular sclerosis Hodgkin's lymphoma (grades 1 and 2)
Lymphocyte-rich classical Hodgkin's lymphoma
Mixed cellularity Hodgkin's lymphoma
Lymphocyte depletion Hodgkin's lymphoma

TABLE 90–2. Negative Prognostic Factors for Hodgkin's Lymphoma and Non-Hodgkin's Lymphoma

International Prognostic Score—Advanced Hodgkin's Lymphoma
Albumin less than 4 g/dL (40 g/L)
Hemoglobin less than 10.5 g/dL (6.5 mmol/L)
Male sex
Age greater than 45 years
Stage IV disease
White blood cell count greater than or equal to 15,000 mm^3 (15×10^9/L)
Lymphocytopenia [count less than 600 mm^3 (0.6×10^9/L) or less than 8% (0.08) of white blood cell count or both]
International Prognostic Index—Diffuse, Aggressive Non-Hodgkin's Lymphoma
Age greater than 60 years
Stage III/IV disease
Extranodal disease greater than 1 site
ECOG performance status 2 or greater
Serum LDH greater than 1 × normal limit

lymphocytes. Oncogenes that have been identified in different lymphomatous diseases include *c-myc*, a regulator of gene transcription; *bcl-1*, important in the regulation of mitosis; *bcl-2*, a regulator of apoptosis; and *bcl-3*, *NF-κB*, and *bcl-6*, which regulate cell differentiation.[9] Classic translocations for NHL include t(8;14) in Burkitt's lymphoma, t(14;18) in follicular lymphomas, t(11;14) mantle cell lymphoma, and t(11;18)/t(1;14) in mucosal-associated lymphomas (MALT).

❷ *Characterization of the* ***morphology*** *of the lymphocytes, the reactivity of the other cells in the lymph node, and the lymph node architecture is essential in obtaining a diagnosis and predicting disease course.* The nodal presentation of NHL is divided into two main categories: follicular, corresponding with low-grade disease, and diffuse, corresponding with aggressive disease. A follicular disease pattern in the inspected lymph node is indicative of a more indolent or low-grade disease progression that has survival measured in years if left untreated. In contrast, a diffuse pattern of lymph node infiltration is a marker of highly aggressive disease, resulting in death within weeks to months if left untreated. Follicular NHL is the most common indolent sub-type, comprising 22% of NHL cases, where diffuse, large B-cell lymphoma is the most common aggressive histology in 31% of cases. The cells of origin for follicular NHL tend to be more mature, nondividing lymphocytes, whereas aggressive NHL is derived from rapidly dividing lymphoid precursors, such as immunoblasts, lymphoblasts, and centroblasts. B cells at the end of germinal center maturation and small, naive B lymphocytes are transformed neoplastic cells for the indolent NHL subtypes follicular lymphoma and small lymphocytic lymphoma, respectively. Lymphoblastic lymphoma/leukemia is believed to originate from lymphoblasts in which diffuse, large B-cell lymphomas form germinal center centroblasts. A unique feature of the biology of NHL is that follicular low-grade histologies can undergo further malignant transformation, and a segment of malignant lymphocytes transforms further into a diffuse, large B-cell lymphoma population. This syndrome, called *Richter's transformation*, may occur in up to 20% of follicular low-grade lymphoma patients and involves multiple genetic events, including abnormalities of chromosomes 11 and 12 and tumor-suppressor genes.[10]

The classification of NHL has undergone several revisions as the histology, molecular biology, and clinical course of the disease have been better defined. Classification schemes such as the *Working Formulation* categorize disease on aggressiveness into three general categories: low grade—survival estimated in years without treatment; intermediate grade—survival estimated in

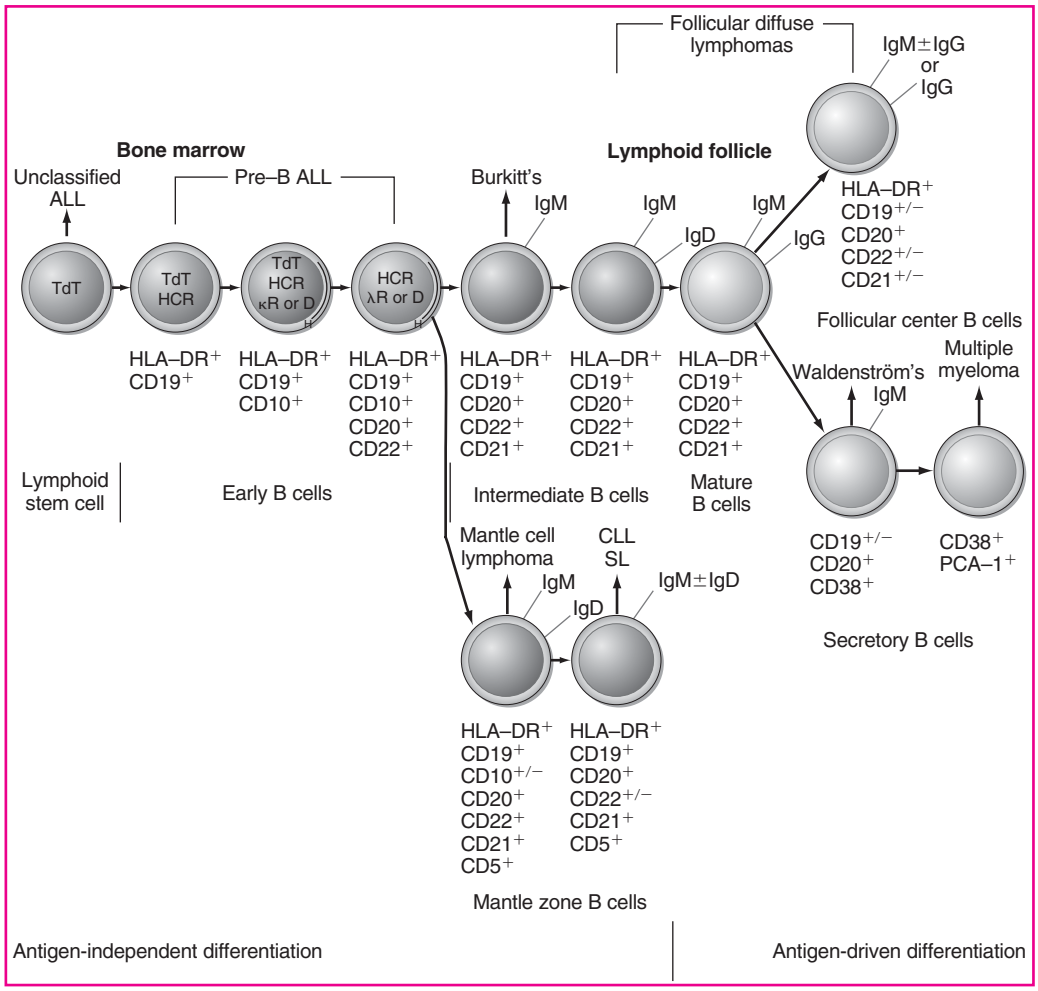


FIGURE 90–2. Pathway of normal B-cell differentiation and relationship to B-cell lymphocytes. (Reproduced from Armitage JO, Longo DL. Malignancies in lymphoid cells. In: Kasper DL, Braunwald E, Fauci AS, et al, (eds.) Harrison's Principles of Internal Medicine. 16th ed. New York: McGraw-Hill; 2005: 544.)



Clinical Presentation and Diagnosis

General

Nonspecific; can range from an asymptomatic patient with a less aggressive lymphoma to a patient that is gravely ill with advanced disease

❸ Symptoms

- Lymphadenopathy, generally in the cervical, axillary, supraclavicular, or inguinal lymph nodes
- Splenomegaly
- Shortness of breath, dry cough, chest pressure (patients with mediastinal mass)
- Gastrointestinal complications (e.g., nausea, vomiting, early satiety, constipation, and diarrhea)
- Back, chest, or abdominal pain

Signs

- Fever
- Night sweats
- Weight loss greater than 10% within last 6 months (These three are known collectively as *B-symptoms*.)
- Pruritus

Laboratory Tests

- LDH
- ESR
- Serum chemistries
- CBC with differential

❹ Other Diagnostic Tests

- Physical examination with careful attention to lymph node inspection
- Imaging: Chest x-ray, chest CT scan, abdominal/pelvic CT scan; PET scan or gallium scan may be used to confirm presence of active disease after treatment.
- Bone marrow biopsy
- *Biopsy of suspected lymph node(s)—either open lymph node biopsy or core biopsy preferred over fine-needle aspiration.*
- *Hematopathology evaluation of biopsy specimen—morphologic inspection, immunohistochemistry for cell-surface antigens to characterize lymphoma cells,* ***cytogenetic analysis***



Patient Encounter, Part 2

PMH
Allegies as a child

FH
Remarkable for colon cancer in maternal grandmother and lung cancer in paternal grandfather

SH
Nonsmoker; social drinker

Meds
Orthocept 1 tablet daily

ROS
As mentioned previously

PE
VSS temp 38.0ºC (100.4ºF)
Labs: WNL, except LDH 2302 units/L (38.4 µkat/L)
Chest x-ray: As mentioned previously
Patient is seen by a hematologist who recommends an open-lung biopsy by a cardiothoracic surgeon. The biopsy is conducted, and pathology assessment shows nodular sclerosing Hodgkin's disease. The hematologist then conducts a staging work-up with computed tomographic (CT) scans of the chest, abdomen, and pelvis and performs a bone marrow biopsy.

• What therapy is appropriate for this patient?

months without treatment; and high grade—survival measured in days to weeks for untreated disease. This scheme is limited in its clinical applicability because the large number of distinct clinical disease entities are not categorized by this classification. The Working Formulation classification of NHL and diseases unclassifiable by that system are presented in Table 90–3. The World Health Organization (WHO) has updated a classification scheme published in 1994 by the International Lymphoma Study Group called the *Revised European American Classification of Lymphoid Neoplasms* (REAL) that broadly categorizes histologic subtypes into B- and T-cell subtypes. This newer classification incorporates immunologic, morphologic, genetic, and clinical attributes of various NHL histologies.

Prognosis with NHL is based on both histology and morphology of the lymphomatous cells. Patients with low-grade lymphomas may remain virtually free of symptoms and able to lead normal lives for many years with minimal intervention, whereas patients with intermediate- and high-grade lymphomas have survival measured in months and weeks, respectively, with untreated disease. Additional prognostic factors present at diagnosis have been identified. Age, presence of B-symptoms, performance status, number of nodal and extranodal sites, lactate dehydrogenase (LDH) concentration, bulky disease (greater than 10 cm), advanced stage, and

TABLE 90–3. Working Formulation for Non-Hodgkin's Lymphoma

Classification	Immunophenotype
Low Grade	
A. Small lymphocytic	100% B cell
B. Follicular, small cleaved cell	100% B cell
C. Follicular, mixed small cleaved cell and large cell	100% B cell
Intermediate Grade	
D. Follicular, large cell	100% B cell
E. Diffuse, small cleaved cell	75% B cell, 20% T cell, 5% null cell
F. Diffuse, mixed small and large cell	75% B cell, 20% T cell, 5% null cell
G. Diffuse, large cell	70% B cell, 20% T cell, 10% null cell
High Grade	
H. Immunoblastic	50% B cell, 50% T cell
I. Lymphoblastic	5% B cell, 95% T cell
J. Diffuse, small noncleaved cell	100% B cell

Lymphomas not included in Working Formulation: mycosis fungoides, mantle cell lymphoma, monocytoid B-cell lymphoma, mucosa-associated lymphoid tissue (MALT), anaplastic large cell lymphoma, angiocentric lymphoma, angioimmunoblastic lymphadenopathy (AILD), Castleman's disease, adult T-cell leukemia/lymphoma.

β_2-microglobulin concentration have been correlated with survival. The *International Index* is a predictive model for aggressive NHL to be treated with doxorubicin-containing chemotherapy regimens.[11] This index is used as a tool for selecting therapy for patients who may warrant a more intense treatment regimen based on known poor prognostic factors.

TREATMENT OF HODGKIN'S LYMPHOMA

Desired Outcome

Staging of HL with a standard staging classification is necessary to guide appropriate treatment with chemotherapy, radiotherapy, or both. The number of involved sites, disease involvement on one or both sides of the diaphragm, localized or disseminated extranodal disease, and B-symptoms are factors in assignment of stage. The Cotswald staging system, a revision of the original Ann Arbor classification, is outlined in Table 90–4.[12]

❺ *The principal goal in treating HL is to cure the patient of the primary malignancy*. HL is a disease sensitive to both radiation and chemotherapy, resulting in an 80% rate of cure with modern therapy. Treatment strategy generally is divided into approaches for early stage I/II localized disease and stage III /IV advanced disease. Regardless of the stage of the disease, all patients are treated with curative intent. Other goals during treatment include:

• Complete resolution of symptoms of disease
• Minimization of acute treatment-related toxicity
• Minimization of long-term treatment-related toxicity

TABLE 90–4. Cotswald Staging Classification for Hodgkin's Disease (1989 Revision of Ann Arbor Staging)

Stage	Description
I	Involvement of a single lymph node region of lymphoid structure (e.g., spleen, thymus, Waldeyer's ring).
II	Involvement of two or more lymph node regions on the same side of the diaphragm. The number of anatomic sites is indicated by a subscript.
III	Involvement of lymph node regions or structure on both sides of the diaphragm.
	III_1: With or without involvement of splenic, hilar, celiac, or portal nodes.
	III_2: Involvement of para-aortic,iliac, or mesenteric.
IV	Involvement of extranodal sites(s) beyond that designated E.
Designations applicable to all stages:	
A	No symptoms
B	Fever, night sweats, and weight loss
X	Bulky disease: greater than 1/3 the width of the mediastinum or greater than 10 cm maximal dimension of nodal mass
E	Involvement of a single extranodal site, contiguous or proximal to a known nodal site
CS	Clinical stage
PS	Pathologic stage

- Provision of high-level supportive care to ameliorate the toxicities of chemotherapy and/or radiation therapy to optimize quality of life during treatment
- Selection of palliative therapy for disease that has become refractory to all curative therapies

Nonpharmacologic Therapy

Patients presenting with stage I/II disease generally are curable with subtotal lymphoid irradiation, which involves treatment of the mantle and paraaortic fields. This therapeutic modality has yielded an overall 90% cure rate, with over a decade of follow-up. However, up to one-third of patients will relapse at the site of original disease presentation. If a patient relapses, then it likely will occur in the first 3 years after therapy has been completed. Fortunately, most of these patients are still curable with salvage chemotherapy.

Standard doses of radiotherapy for HL generally total 3600 cGy to each field in daily fractions of 180 cGy over 4 weeks. Clinically involved areas are given boost doses of 550 to 900 cGy in three to five fractions, resulting in a total dose to the involved area of upwards of 4500 cGy. Radiation may be given as consolidation following completion of a complete course of chemotherapy in patients with advanced HL.[13,14] This treatment typically is reserved for patients who have an unconfirmed response to chemotherapy or who have bulky disease on presentation.

Treatment with these doses of radiotherapy involves toxicity. Both acute and late effects of radiotherapy occur. Acute effects of mantle-field irradiation include nausea, vomiting, anorexia, xerostomia, dysguesia, pharyngitis, dry cough, fatigue, diarrhea, and rash. Prophylaxis with antiemetics such as dexamethasone or prochlorperazine help to prevent or treat nausea. These effects generally are transient and resolve shortly following completion of treatment. Delayed effects from radiotherapy are more concerning in that they may be permanent and present months to years after therapy is complete. Pneumonitis, pericarditis, hypothyroidism, infertility (with pelvic field irradiation), coronary artery disease, deformities in bone and muscle growth in adolescents and children, herpes-zoster reactivation, **Lhermitte's sign,** and secondary malignancies are not uncommon. Patients cured with radiotherapy are at increased risk for breast cancer, lung cancer (particularly in smokers), stomach cancer, melanoma, and non-Hodgkin's lymphoma.

Pharmacologic Therapy

Chemotherapy compared with radiotherapy for stage I or II nonbulky HL has produced equivocal results in major clinical trials.[15] A National Cancer Institute (NCI) trial comparing MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) and radiotherapy showed no overall difference in survival. However, an Italian randomized trial comparing radiotherapy and chemotherapy in early-stage HL showed a significant survival advantage for the radiotherapy arm. This difference has been attributed to the higher salvage rate for patients who relapsed in the radiotherapy arm and received subsequent treatment with salvage chemotherapy. A complete listing of chemotherapy regimens used in HL with drugs, dosing, administration, and treatment interval is presented in Table 90–5.

In an attempt to reduce relapse rate and late toxicity, combined-modality therapy using lower doses of radiation and an abbreviated course of chemotherapy has been evaluated.[16] The goal of decreased relapse rate has been achieved, but no overall survival benefit has been documented. A limitation of this approach is exposing patients to the additive toxicities of chemotherapy. Trials that have investigated this approach typically have incorporated between two and four cycles of a standard regimen for HL, such as ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) with involved-field radiation. At present, combined-modality therapy is considered to be a standard of care for stage I/II HL.

Advanced Disease

Treatment of advanced-stage (stage III–IV) HL is focused on the use of multiagent chemotherapy for six to eight total cycles. MOPP is of historical significance because it was the first chemotherapy regimen to cure HL when it was introduced in the 1960s. However, the significant toxicity, including sterility and secondary leukemia, prompted investigators to evaluate other regimens. ABVD was compared with MOPP or ABVD alternating with MOPP.[17] This pivotal phase III Cancer and Leukemia Group B (CALGB) trial comparing these regimens in 361 patients with stage III or IV HL documented a higher complete response (CR) in the ABVD arms (82% and 83%) versus MOPP (65%). There was increased

TABLE 90–5. Common Treatment Programs in Hodgkin's Lymphoma

MOPP—every 28 days
Mechlorethamine 6 mg/m^2 IV × 1, days 1, 8
Vincristine 1.4 mg/m^2 IV × 1, days 1, 8
Procarbazine 100 mg PO daily, days 1–14
Prednisone 40 mg PO daily, days 1–14

ABVD—every 28 days
Doxorubicin 25 mg/m^2 IV × 1, days 1, 15
Bleomycin 10 units IV × 1, days 1, 15
Vinblastine 6 mg/m^2 × 1, days 1, 15
Dacarbazine 375 mg/m^2 IV, days 1, 15

MOPP/AVD hybrid—every 28 days
Mechlorethamine 6 mg/m^2 IV × 1; day 1
Vincristine 1.4 mg/m^2 IV × 1; day 1
Procarbazine 100 mg PO daily, days 1–7
Prednisone 40 mg PO daily, days 1–14
Doxorubicin 35 mg/m^2 IV × 1; day 8
Bleomycin 10 units IV × 1; day 8
Vinblastine 6 mg IV × 1; day 8

ChlVPP—every 28 days
Chlorambucil 6 mg PO daily, days 1–14
Vinblastine 6 mg/m^2 IV × 1, days 1–8
Procarbazine 100 mg PO daily, days 1–14
Prednisone 40 mg PO daily, days 1–14

BEACOPP (escalated)—every 21 days
Bleomycin 10 mg/m^2 IV, day 8
Etoposide 200 mg/m^2 IV daily, days 1–3
Doxorubicin 35 mg/m^2, day 1
Cyclophosphamide 1200 mg/m^2 IV, day 1
Vincristine 1.4 mg/m^2 IV, day 8
Procarbazine 100 mg/m^2 PO daily, days 1–14
Prednisone 40 mg PO daily, days 1–5
Gemcitabine 1250 mg/m^2 IV × 1; days 1, 8, every 21 days

BCV (high-dose with autologous stem cell transplant)[a]
Carmustine 400 mg/m^2 IV × 1 day
Etoposide 800 mg/m^2 IV daily × 3 days
Cyclophosphamide 1800 mg/m^2 IV daily × 4 days

BEAM (high-dose with autologous stem cell transplant)[a]
Carmustine 300 mg/m^2 IV × 1 day
Etoposide 800 mg/m^2 IV × 1 day
Cytarabine 1600 mg/m^2 IV × 1 day
Melphalan 140 mg/m^2 IV × 1 day

[a]Used for both Hodgkin's lymphoma and non-Hodgkin's lymphoma.

hematologic toxicity in the MOPP arm. A recent update of the data shows the 8-year freedom from progression of 37% in the MOPP arm and about 50% in the ABVD arms. A survival advantage has yet to be demonstrated. ABVD is now considered standard therapy for initial treatment of stage III or IV HL. Further information on ABVD may be found in Table 90–6.

More recently, a German study compared a dose-escalated regimen of BEACOPP (with filgrastim support) with standard-dose bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone, gemcitabine (BEACOPP) and COPP alternating with ABVD (C—cyclophosphamide instead of mechlorethamine for MOPP).[18] The escalated BEACOPP was superior to the other arms in freedom from treatment failure at 5 years and was superior to COPP alternating with ABVD in overall survival at 5 years. The escalated BEACOPP regimen had a higher number of cases of secondary leukemia, and the procarbazine increases the risk of infertility. Currently, this regimen has not been adopted widely in the United States, but considerable interest has been generated in evaluating it in patients with advanced-stage HL with a high number of poor prognostic factors.

Relapse in HL is associated with a significant potential for cure with chemotherapy for both localized and advanced HL. For patients with early-stage HL, the chance of relapse is about 10% to 30%. Advanced-stage HL patients, who have approximately a one-third chance of relapse within the first 3 years of therapy, still retain a chance for cure. Management of relapsed HL can be broadly subcategorized into three different categories: relapse after treatment for early-stage disease, relapse after treatment with chemotherapy for advanced disease, and relapse in patients with advanced disease who do not achieve a remission. For these patients, the definitive therapy is high-dose chemotherapy with autologous stem cell transplant (SCT).[19] This treatment offers a cure rate of approximately 40%.

The role of SCT in HL has evolved from data with conventional four-drug regimens demonstrating that patients with lower dose intensity had a higher rate of relapse. Data comparing high-dose chemotherapy with lower doses of the same regimen yielded a significant benefit in the high-dose arm, leading to early closure of the study. High-dose chemotherapy is given to patients who are in first relapse with encouraging results. A series of 58 patients had a progression-free survival of over 60% with a median follow-up of 2.3 years. The safety profile of autologous SCT continues to improve as improvements in supportive care are realized, and current estimates of mortality from autologous SCT for HL approximate 5%. Morbidity commonly associated with the preparative regimens in HL, aside from infectious and bleeding complications, includes the additive pulmonary toxicity of bleomycin coupled with carmustine in inducing potentially fatal pulmonary pneumonitis.

Patients who are not deemed candidates for high dose chemotherapy with autologous SCT may receive multiagent salvage chemotherapy, such as etoposide methylprednisolone cytarabine cisplatin (ESHAP) or Dexamethasine Cytarabine Cisplatin (DHAP). If less aggressive therapy is desired, patients can be offered palliation with single-agent gemcitabine or vinblastine.[20]



Patient Encounter, Part 3: Creating a Care Plan

Based on the information presented, create a care plan for this patient, including goals of therapy, antineoplastic therapy plan, and necessary supportive care.

TABLE 90–6. Practical Information for ABVD and CHOP

Regimen	Drug Class	Phamacokinetics	Unique Toxicities
ABVD			
Doxorubicin	Anthracycline	Hepatic metabolism	Cardiomyopathy
Bleomycin	Antitumor antibiotic	Renal clearance	Pulmonary fibrosis
Vinblastine	Vinca alkaloid	CYP 3A4/5 metabolism	Neuropathy, constipation
Dacarbazine	Alkylating agent	Hepatic metabolism	Myelosuppression
CHOP			
Cyclophosphamide	Alkylating agent	Prodrug; CYP 3A4/5, 2D6	Hemorrhagic cystitis
Doxorubicin	Anthracycline	Hepatic metabolism	Cardiomyopathy
CYP 3A4/5 metabolism	Vinca alkaloid	CYP 3A4/5	Neuropathy, constipation
Prednisone	Corticosteroid	100% oral bioavailability	Hyperglycemia, osteopenia

TREATMENT OF NON-HODGKIN'S LYMPHOMA

Desired Outcome

Treatment of NHL depends primarily on histologic sub-type (follicular low grade versus diffuse aggressive) and staging (local stage I/II versus advanced stage III/IV) to guide appropriate treatment strategy with observation, chemotherapy, radiotherapy, or chemotherapy and radiation. As with HL, the number of involved sites, disease involvement on one or both sides of the diaphragm, localized or disseminated extranodal disease, and B-symptoms are factors in staging assignment. The Ann Arbor staging system is outlined in Table 90–7.[21]

Treatment goals for NHL depend on the presence of follicular low-grade versus diffuse aggressive disease. For follicular low-grade NHL, the disease is considered to be incurable with standard therapies There is a small prospect for cure using allogeneic SCT owing to the graft-versus-lymphoma effect of donor T cells. Many patients with follicular low-grade NHL are older than 60 years of age, making allogeneic SCT impractical owing to the high treatment-related mortality for older patients.

TABLE 90–7. Ann Arbor Staging of Non-Hodgkin's Lymphoma

Stage	Description
I	Involvement of a single lymph node region (1) or a single extralymphatic organ or site (IE)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm (III) or localized involvement of an extralymphatic organ or site (IIIE) or spleen (IIIS) or both (IIISE)
IV	Diffuse or disseminated involvement of one or more extranodal organs with or without associated lymph node involvement
Designations applicable to all stages:	
A	No symptoms
B	Fever, nights sweats, and weight loss (greater than 10%)

❻ *The treatment goals for low-grade NHL include:*

- *Observation of the disease until the patient exhibits obvious progression that limits functional capacity or is life-threatening for low-grade NHL*
- *Treatment that induces the disease into remission with resolution of disease symptoms and minimal toxicity*
- *Judicious selection of treatment options to avoid long-term toxicity because patients may require several different chemotherapy treatment regimens over a period of years for low-grade NHL*
- *Prevention of infectious complications of treatment*

The treatment aim for patients with aggressive histologies is cure of the malignancy. There are some histologic subtypes that exhibit an aggressive clinical course that are not considered to be curable. These patients are still treated with curative-intent chemotherapy or may be considered for a clinical trial.

Nonpharmacologic Therapy

For patients with low-grade follicular NHL, deferring initiation of therapy until progression of disease is standard. The median survival is 6 to 10 years, with some patients waiting several years before the disease becomes symptomatic, making observation a reasonable front-line therapy for most of these patients. Radiation therapy has a limited role in NHL relative to HL. NHL is a systemic disease, and radiation typically has been reserved for consolidation therapy following chemotherapy in patients presenting with a large extranodal mass.

For early-stage diffuse, aggressive NHL, combined-modality therapy was tested versus a longer course of chemotherapy.[22] Overall survival favored the CHOP/radiation arm for 5 years (82% versus 72%). There was a trend toward increased toxicity, particularly hematologic and cardiac toxicity, in the CHOP alone arm. The results of this trial have established combined-modality therapy as first-line treatment for early-stage NHL. Unique presentations of NHL, such as CNS primary disease, may incorporate radiation into treatment algorithms.[23]

Pharmacologic Therapy

Follicular Low-Grade NHL

The management of low-grade lymphomas is an area of controversy. Chemotherapy such as single-agent oral cyclophosphamide or fludarabine is often offered initially. In patients in whom a more rapid response is desired, multiagent chemotherapy such as cyclophosphamide vincristine prednisone (CVP) or cyclophosphamide doxorubicin vincristine prednisone (CHOP) may be used. None of these therapies is associated with an overall survival benefit, making it impossible to select an unequivocal first-line regimen.[24–26] These regimens are detailed in Table 90–8. Introduction of the monoclonal antibody rituximab has prompted interest in a novel modality of therapy for this disease. Rituximab is a chimeric murine/human monoclonal antibody that binds specifically to the antigen CD20 expressed on pre-B and mature B lymphocytes.[27] NHL of B-cell origin expresses CD20 in greater than 90% of cases. CD20 is believed to play a role in early differentiation and activation of the cell cycle. After the Fab domain of rituximab binds to CD20, the Fc domain acts to recruit complement and other components of the immune system to induce cell-mediated cytotoxicity with subsequent lysis of the bound lymphocytes. Rituximab also may produce apoptosis of the bound lymphocyte with the act of binding to the CD20 receptor. Rituximab has specific affinity for binding to lymphocytes and lymphoid tissue, begins depleting B lymphocytes with the first dose, and results in sustained suppression for 6 to 9 months with as few as three doses. B-cell recovery begins 6 months following administration of the drug. The drug has a half-life of 60 hours with the first dose that increases with subsequent dosing to approximately 150 hours, allowing for weekly dosing. The initial clinical experience with rituximab involved 166 patients with CD20+ low-grade lymphoma treated with four doses of 375 mg/m^2 of rituximab weekly.[28] The overall response rate was 48%, with 6% representing complete responses and the remainder representing partial responses. The median follow-up of 12 months demonstrated a median time to progression of 13 months by intention-to-treat analysis. Most adverse events were related to intolerance of the first infusion with hypotension, fever, chills, nausea, and bronchospasm. These data established the role of rituximab as a viable treatment option in patients with indolent follicular NHL.

Novel strategies for treatment of low-grade lymphomas include the combination of monoclonal antibodies directed against CD20 with a radioactive moiety attached. Two such entities are now approved by the Food and Drug Administration (FDA): ibritumomab-yttrium^{90} (Zevalin) and tositumomab-iodine^{131} (Bexxar). Both agents are active in disease that has become refractory to rituximab. The radiation component necessitates compounding both medications in a nuclear medicine pharmacy. High-dose chemotherapy is being evaluated for low-grade follicular NHL, but its role is currently limited to clinical trials.

TABLE 90–8. Treatment Programs for Low-Grade, Follicular Non-Hodgkin's Lymphomas

Cyclophosphamide 100 mg/m^2 PO daily Fludarabine 25 mg/m^2 IV daily, days 1–5 Rituximab 375 mg/m^2 IV, day 1, given weekly for 4 or 8 weeks
CVP—every 21 days Cyclophosphamide 800 mg/m^2 IV, day 1 Vincristine 1.4 mg/m^2 IV, day 1 Prednisone 100 mg PO daily, days 1–5
rCVP—every 21 days Rituximab 375 mg/m^2 IV, day 1 Cyclophosphamide 800 mg/m^2 IV, day 1 Vincristine 1.4 mg/m^2 IV, day 1 Prednisone 100 mg PO daily, days 1–5
CHOP—every 21 days Cyclophosphamide 750 mg/m^2 IV, day 1 Doxorubicin 50 mg/m^2 IV, day 1 Vincristine 1.4 mg/m^2 IV, day 1 Prednisone 100 mg PO daily, days 1–5
rCHOP—every 21 days Rituximab 375 mg/m^2 IV, day 1 Cyclophosphamide 750 mg/m^2 IV, day 1 Doxorubicin 50 mg/m^2 IV, day 1 Vincristine 1.4 mg/m^2 IV, day 1 Prednisone 100 mg PO daily, days 1–5

Diffuse, Aggressive NHL

? *The mainstay of therapy for diffuse, aggressive NHL has been the administration of anthracycline-based combination chemotherapy, which generally consists of programs of four or more drugs.* Therapy options for intermediate- and high-grade NHL generally are segregated between localized (stage I/II) and disseminated (stage III/IV) disease. As mentioned previously, combined-modality therapy with CHOP and radiation is considered a standard of care for stage I/II disease.

For disseminated disease, the approach has centered on the administration of multiagent chemotherapy. The standard therapy in this disease since the 1970s has been CHOP. This regimen conferred a response of 50% to 60%, with a long-term survival of approximately 30%. However, the 1980s were notable for the development of newer combination drug programs that incorporated increasing numbers of agents with varying schedules. More complex chemotherapy regimens were shown in phase II trials to have higher response rates than CHOP. The CALGB designed a phase III randomized four-arm trial to assess the impact on survival of three more intensive regimens compared with CHOP.[29] This phase III cooperative group trial randomized 899 patients with intermediate- or high-grade (Working Formulation classification) NHL to CHOP or one of the three more intensive advanced-generation regimens just mentioned. There were no significant differences in response rate or overall survival, which was consistent among all subgroups. Severe toxicity and death were higher in the advanced-generation treatment programs relative to CHOP. This pivotal trial has cemented CHOP's position as front-line therapy in diffuse NHL.

The next hypothesis tested was whether combining monoclonal antibody therapy with chemotherapy could increase

activity against diffuse, aggressive NHL. A French study randomized patients 60 to 80 years of age with newly diagnosed diffuse, large B-cell NHL to either CHOP for eight cycles or CHOP plus rituximab for eight cycles.[30] At relatively early follow-up of 2 years, the combination arm had a superior complete response rate (76% versus 63%) and event-free survival (57% versus 38%), with comparable toxicity in each arm. Similar findings in younger patients have been reported recently, making CHOP plus rituximab first-line therapy for advanced-stage diffuse, aggressive NHL (Table 90–9). Alternative approaches that have shown promise are the inclusion of etoposide in the CHOP regimen or shortening the treatment interval from 21 days and supporting the white blood cell count with filgrastim, otherwise known as *dose-dense therapy.*[31]

There are certain histologic subtypes of diffuse, aggressive NHL that respond less well to treatment with conventional regimens such as CHOP. Burkitt's lymphoma, lymphoblastic lymphoma, mantel cell lymphoma, and primary CNS lymphoma are examples of disease that benefit from more intensive therapy. Regimens such as hyper-CVAD, which alternate cycles of hyperfractionated cyclophosphamide, doxorubicin, vincristine, and dexamethasone with high-dose cytarabine and methotrexate, often are substituted for CHOP. Intrathecal therapy with methotrexate is indicated with documented CNS infiltration of tumor or involvement of the sinuses. The recent appreciation of the etiology of *Helicobacter pylori* in the etiology of peptic ulcer disease and the association between colonization and mucosal-associated lymphoma (MALT) has spurred

TABLE 90–9. Treatment Regimens for Diffuse, Aggressive Non-Hodgkin's Lymphomas

CHOP—every 21 days
Cyclophosphamide 750 mg/m^2 IV, day 1
Doxorubicin 50 mg/m^2 IV, day 1
Vincristine 1.4 mg/m^2 IV, day 1
Prednisone 100 mg PO daily, days 1–5

rCHOP—every 21 days
Rituximab 375 mg/m^2 IV, day 1
Cyclophosphamide 750 mg/m^2 IV, day 1
Doxorubicin 50 mg/m^2 IV, day 1
Vincristine 1.4 mg/m^2 IV, day 1
Prednisone 100 mg PO daily, days 1–5

CHOP-14—every 14 days (with filgrastim support days 4–13)
Cyclophosphamide 750 mg/m^2 IV, day 1
Doxorubicin 50 mg/m^2 IV, day 1
Vincristine 1.4 mg/m^2 IV, day 1
Prednisone 100 mg PO daily, days 1–5

CHOEP-21—every 21 days
Cyclophosphamide 750 mg/m^2 IV, day 1
Doxorubicin 50 mg/m^2 IV, day 1
Vincristine 1.4 mg/m^2 IV, day 1
Etoposide 100 mg/m^2 IV daily, days 1–3
Prednisone 100 mg PO daily, days 1–5

m-BACOD—every 21 days
Methotrexate 200 mg/m^2 IV, days 8, 15
Bleomycin 4 mg/m^2 IV, day 1
Doxorubicin 45 mg/m^2, day 1
Cyclophosphamide 600 mg/m^2 IV, day 1
Vincristine 1.4 mg/m^2 IV, day 1
Dexamethasone 6 mg PO daily, days 1–5
Leucovorin 10 mg PO q6hours, 24 hours following methotrexate × 8 doses

ProMACE-CytaBOM—every 28 days
Prednisone 60 mg PO daily, days 1–14
Doxorubicin 25 mg/m^2 IV, day 1
Cyclophosphamide 650 mg/m^2 IV, day 1
Etoposide 120 mg/m^2 IV, day 1
Cytarabine 300 mg/m^2 IV, day 8
Bleomycin 5 units IV, day 8
Vincristine 1.4 mg/m^2 IV, day 8
Methotrexate 120 mg/m^2, day 8
Leucovorin 25 mg/m^2 IV q6hours, 24 hours following methotrexate × 5 doses

MACOP-B
Methotrexate 400 mg/m^2 IV, day 8
Doxorubicin 50 mg/m^2 IV, days 1, 15
Cyclophosphamide 350 mg/m^2 IV, days 1, 15
Vincristine 1.4 mg/m^2 IV, days 8, 15
Prednisone 75 mg PO daily, × 12 weeks
Bleomycin 10 units IV, day 28
Leucovorin 15 mg PO q6hours, 24 hours following methotrexate × 6 doses

Hyper-CVAD
Cyclophosphamide 300 mg/m^2 IV q12hours, days 1–3 (with mesna)
Doxorubicin 50 mg/m^2 IV, day 1
Vincristine 1.4 mg/m^2 IV, days 1, 11
Dexamethasone 40 mg PO qday, days 1–4, 11–14
Methotrexate 15 mg intrathecal, day 2

Cytarabine 30 mg intrathecal, day 2
Hydrocortisone 15 mg intrathecal, day 2
Above drugs given on courses 1, 3, 5, 7
Methotrexate 1000 mg/m^2 IV over 24 hours, day 1
Cytarabine 3000 mg/m^2 IV q12hours, days 2, 3
Leucovorin 25 mg IV × 1, then 25 mg PO q6hours for 7 doses
Methotrexate 15 mg intrathecal, day 2
Above drugs given on courses 2, 4, 6, 8
Relapsed Disease

ESHAP
Etoposide 40 mg/m^2 IV per day continuous infusion, days 1–4
Cisplatin 25 mg/mm^2 IV per day continuous infusion, days 1–4
Cytarabine 2000 mg/m^2 IV × 1, day 5
Methylprednisone 250 mg IV q12hours, days 1–4

DHAP
Dexamethasone 40 mg PO or IV daily, days 1–4
Cisplatin 100 mg/m^2 IV continuous infusion, day 1
Cytarabine 2000 mg/m^2 IV q12hours for 2 doses, day 2

ICE
Etoposide 100 mg/m^2 IV daily, days 1–3
Carboplatin *AUC* 5 (max dose 800 mg) IV, day 2
Ifosfamide 5000 mg/m^2 IV continuous infusion × 1 on day 2 (with 100% replacement with mesna)

the more aggressive treatment of this organism with antibiotics. Generally, 7 to 14 days of combinations of either omeprazole, clarithromycin, and amoxicillin or tetracycline, metronidazole, and bismuth subsalicylate have been shown to provide rates of *H. pylori* clearance near 90%.

With over half of patients expected to relapse with disease, salvage therapy plays a major role in the attempt to cure patients with recurrence. Multiple drug programs such as ESHAP and DHAP can induce a complete response, but the long-term cure rates with these regimens are less than 10%. Further salvage therapy could induce remissions, but with each subsequent relapse, the chance for a CR and the duration of remission decreased. Therefore, the approach of high-dose chemotherapy was attempted with autologous SCT.[32] The best-studied indication for SCT is for patients with intermediate- or high-grade disease that fails to respond to conventional therapy. A 3- to 5-year survival of upwards of 40% is achieved in patients who have good performance and disease that demonstrates a significant response to one or two cycles of salvage chemotherapy. The procedure-related mortality has ranged from 5% to 10% in published reports. However, as with HL, with more broad application of peripheral blood stem cells and improved supportive care, this figure continues to decline. The role of allogeneic bone marrow transplantation (BMT) in this setting is considered investigational at this time owing to the undefined significance of a graft-versus-lymphoma effect and the high treatment-related morbidity and mortality.

Patients with HIV-related lymphoma represent a therapeutic dilemma in that many have high-grade disease of B-cell origin. A common presentation is that of extranodal disease, frequently in the GI tract, CNS, and bone marrow. Therapy for this population thus far has fared poorly, with a median survival of 6 to 12 months, which decreases to 3 months with CNS involvement.[33] It remains to be seen if improved antiretroviral therapy will have an impact on the incidence and treatment options for these patients.

The addition of rituximab to chemotherapy has an adverse effect on outcome in this patient population.

OUTCOME EVALUATION

Treatment success in lymphoma is measured in successive stages, the first being inducing tumor regression and the degree of that regression: complete response (CR) versus partial response (PR) versus stable disease (SD) versus progressive disease (PD). The RECIST criteria, a uniform criteria assessing tumor response, are considered a standard of care. Both HL and NHL may have residual masses following completion of treatment, adding to the difficulty in establishing a definitive remission from treatment. Ongoing clinical trials are evaluating the value of PET scans and gallium scans to rule out whether residual tumor masses following treatment contain viable tumor. PET scans hold the promise of a future role because the 2-fluoro-2deoxyglucose contrast material is taken up more avidly by metabolically active tumor cells relative to fibrosis.

Long-term follow-up monitors patients for continued disease remission or relapse with careful physical examination of the lymph nodes and sites of prior disease involvement and imaging studies. Patients will have routine chest x-rays and CT scans administered to screen for recurrence of disease. Patients require long-term monitoring for toxicities of their primary treatment, either chemotherapy or radiation therapy.

Most patients treated for lymphoma with chemotherapy or radiation notice a regression of palpable lymphadenopathy within days. This is due to the high sensitivity of the rapidly proliferating malignant lymphocytes to chemotherapy and radiotherapy. This necessitates implementation of tumor lysis syndrome precautions with aggressive sodium bicarbonate–containing intravenous fluid resuscitation and allopurinol for patients with moderate to high tumor burdens. Most chemotherapy treatments for lymphoma have a significant risk of infectious complications. Combination chemotherapy for both HL and NHL is associated with rates of severe leukopenia and/or neutropenia ranging from 20% to 100% of patients. Consideration must be given to supportive care with prophylactic antibiotics and myeloid colony-stimulating factors (CSFs). The American Society of Clinical Oncology has published guidelines stating that colony-stimulating factors (CSFs) may be used as primary prevention when the incidence of febrile neutropenia with the chemotherapy is approximately 20% and no other equally effective and less myelosuppresive regimen is available or for secondary prevention where the patient already has experienced febrile neutropenia with the previous cycle of chemotherapy.[34] Effective antiemetic support is currently available that can control chemotherapy-induced nausea and vomiting reasonably well for most standard-dose regimens.[35]

For female survivors of HL who are treated with radiation, there is an increase in the incidence of breast cancer, and baseline mammograms are recommended at the conclusion of treatment.[36] For HL patients, exposure to bleomycin can induce pulmonary fibrosis, which often is subclinical. Patients who relapse and require high-dose chemotherapy and are treated with the drug carmustine in the conditioning regimen are at a higher risk of morbidity and mortality from idiopathic pulmonary syndrome/diffuse alveolar hemorrhage during SCT treatment. These patients are also at risk for exacerbation of underlying bleomycin-induced pulmonary damage if they ever require mechanical ventilation with high oxygen requirements. Combination chemotherapy that contains alkylating agents or etoposide carries the risk of a secondary acute myeloid leukemia or myelodysplastic syndrome. The cumulative dose of doxorubicin used for most lymphoma regimens is unlikely to cause cardiac toxicity with the standard six cycles. Neuropathy with vincristine or vinblastine may necessitate its removal from subsequent cycles if severe. Historically, it is more severe with vincristine. Treatment with fludarabine can harbor the risk of opportunistic infections such as *Pneumocystis carinii* pneumonia (PCP) for months following completion of therapy.

A limitation of rituximab treatment is the severe and potentially fatal infusion-related reactions. To date, eight deaths have

been reported, resulting from the profound hypotension and circulatory collapse seen with the drug, particularly on the first dose. The package labeling recommends premedication with acetaminophen and diphenhydramine before each infusion. For the first infusion, the drug should be administered at 50 mg/hour. The infusion rate may be increased by 50 mg/hour every 30 minutes to a maximum of 400 mg/hour if no infusion-related reactions occur. If infusion-related reactions do occur, the manufacturer recommends stopping the infusion or temporarily slowing it until symptoms resolve. The infusion should be reinstituted at a rate that is one-half the previous rate. For subsequent rituxamab infusions, the rate may commence at 100 mg/hour and be increased at 100 mg/hour increments every 30 minutes for a maximum of 400 mg/hour as tolerated. Other associated toxicities of rituxamab include fever, chills, headache, asthenia, nausea, vomiting, angioedema, bronchospasm, and skin reactions. ❽ *Despite these toxicities, rituximab is an effective treatment option for patients with indolent low-grade NHL as a single agent or in combination with standard chemotherapy regimens for more aggressive NHL histologies.* Radiolabled rituximab causes more myelosuppression than rituximab alone and, similar to combination cytotoxic chemotherapy regimens, has a long-term risk of inducing secondary leukemias.[37]



Patient Care and Monitoring

1. Verify chemotherapy regimen dosages with a standardized reference, and assess for dose adjustment for renal or hepatic dysfunction.
2. Assess appropriateness of supportive care for each chemotherapy regimen, including antiemetics and colony-stimulating factors.
3. Prior to initiation of treatment with chemotherapy, determine if tumor lysis syndrome precautions need to be implemented.
4. Take a thorough medication history with particular attention to over-the-counter and herbal medications.
5. Provide patient education regarding common toxicities associated with chemotherapy, such as nausea/vomiting, mucositis, myelosuppression, and alopecia.
6. For doxorubicin-containing regimens, total the cumulative dosage received by the patient to monitor for cardiac toxicity.
7. For bleomycin-containing regimens, total the cumulative dosage received by the patient to monitor for pulmonary fibrosis.
8. Educate patients regarding short- and long-term complications associated with radiation therapy.
9. Monitor patient for signs of response of tumor to chemotherapy.
10. Provide contact numbers for patient in the event of fever and a response plan if the patient is considered to be at risk for neutropenic fever.

ABBREVIATIONS

bcl-1:	gene important in the regulation of mitosis
bcl-2:	gene that regulates apoptosis
bcl-3:	gene that regulates nuclear transciption factor
bcl-6:	gene that regulates cell differentiation
c-myc:	gene that regulates gene transcription
CALGB:	Cancer and Leukemia Group B (an alliance of cancer centers that conducts national clinical trials in cancer)
CD:	cluster of differentiation
CSFs:	colony-stimulating factors
ESR:	erythroid sedimentation rate
HL:	Hodgkin's lymphoma
IPI:	International Prognostic Index for non-Hodgkin's lymphoma
IPS:	International Prognostic Score for advanced Hodgkin's lymphoma
NHL:	non-Hodgkin's lymphoma
SCT:	stem cell transplant
SWOG:	Southwest Oncology Group (an alliance of cancer centers that conducts national clinical trials in cancer)
NF-κB:	gene that regulates cell differentiation

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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91 Ovarian Cancer

Judith A. Smith



Learning Objectives

Upon completion of the chapter, the reader will be able to

1. Demonstrate understanding of the etiology and risk factors associated with the development of ovarian cancer.
2. Justify the risk and benefits of the surgical and chemoprevention options available for decreasing the potential risk of developing ovarian cancer.
3. Interpret and understand the utility of the screening tests and serologic markers for diagnosing ovarian cancer.
4. Distinguish the non-specific physical signs and symptoms of ovarian cancer.
5. Recommend the appropriate surgical and chemotherapy treatment options for newly diagnosed and relapsed ovarian cancer patients.
6. Compare and contrast chemotherapy options for women with recurrent platinum-resistant ovarian cancer.
7. Compare and contrast the treatment options for management of hot flushes in ovarian cancer patients.
8. Devise a plan for the management of common complications associated with advanced and recurrent ovarian cancer.

Key Concepts

1. Ovarian cancer is a sporadic disease; fewer than 10% of ovarian cancers can be attributed to heredity.
2. Since CA-125 is a non-specific marker, there is no standard recommendation for routine screening for prevention of ovarian cancer.
3. Ovarian cancer is denoted the "silent killer" because of the non-specific signs and symptoms.
4. Although most patients will achieve a complete response initially, more than 50% of cancers will recur within the first 2 years.
5. Surgery is the primary treatment intervention for ovarian cancer.
6. Ovarian cancer is staged surgically using the International Federation of Gynecology and Obstetrics (IFGO) staging algorithm.
7. After initial surgery, the gold standard of care is six cycles of a taxane/platinum-containing regimen for patients with advanced ovarian cancer.
8. Single-agent chemotherapy is standard practice for recurrent platinum-resistant ovarian cancer.
9. Since the efficacy of the agents is similar, selection of an agent for the treatment of recurrent platinum-resistant ovarian cancer depends on residual toxicities, physician preference, and patient convenience.
10. In ovarian cancer patients, small bowel obstruction is a common complication of progressive disease. In general, laxatives should not be used in patients with small bowel obstructions.

Ovarian cancer is relatively uncommon but is the most fatal gynecologic cancer. The primary reason for the high mortality associated with ovarian cancer is the non-specific symptoms and difficulty of early detection or screening that result in patients presenting with advanced disease. Most ovarian cancers are of epithelial origin. Each time ovulation occurs, the epithelium of the ovary is broken, followed by cell repair. The *incessant-ovulation hypothesis* proposes that the increasing number of times the ovary epithelium undergoes cell repair is associated with the increasing risk of mutations and, ultimately, ovarian cancer. Ovarian cancer often is denoted as the "silent killer" because although most patients will achieve a

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Patient Encounter 1, Part 1

A 67-year-old woman with a history of coronary artery disease, diabetes, and gastrointestinal reflux presents to your clinic complaining of persistent flatulence and bloating and the feeling that she is "getting fat." After discussing her symptoms with her, you learn that her reflux symptoms are of recent onset and that her proton pump inhibitor is not "working yet." For the past 3 or 4 months, she also has had irregular bleeding and occasional "cramping," which has been frustrating to her because she thought that ended years ago when she went through menopause. She reports that her menses began when she was 9 years old and lasted all the way until she was 61 years old. She has two sisters in good health and a brother with diabetes. She has been married for 25 years with no children. The physician orders a CA-125 and computed tomographic (CT) scan that both come back positive and suggestive of ovarian cancer.

- What symptoms could be associated with ovarian cancer?
- Does she have any known risk factors?
- What are your treatment options for this patient after surgery?

complete response to primary surgery and chemotherapy, over 50% of the cancers will recur in the first year. Ovarian cancers will **metastasize** often via the lymphatic and blood systems to the liver and/or lungs. Common complications of advanced and progressive ovarian cancer include **ascites** and small bowel obstruction (SBO), which often are associated with end of life.

EPIDEMIOLOGY AND ETIOLOGY

In 2006, there were an estimated 20,180 new cases of ovarian cancer with an associated 15,310 deaths.[1] Ovarian cancer remains the number one gynecologic killer and the fifth leading cause of cancer-related deaths in women. Despite great efforts and extensive research, there has been little change in the mortality rate associated with ovarian cancer over the past three decades. The high mortality associated with ovarian cancer can be attributed to its insidious onset of non-specific symptoms resulting in most patients not presenting until the cancer has progressed to stage III–IV disease.

As with many other disease states, a significant risk factor associated with ovarian cancer is aging. A woman's risk increases from 15.7% to 54% per 100,000 as her age advances from 40 to 79 years, with the mean age at diagnosis being 59 years.[2]

❶ *Ovarian cancer is a sporadic disease; fewer than 10% of ovarian cancers can be attributed to heredity.* Most cases of ovarian cancer occur sporadically, thus making it difficult to screen and prevent. Although heredity accounts for less than 10% of all ovarian cancer cases, when there is a family history, it appears to be an important risk factor in the development of ovarian cancer in some patients.[3] If one family member has a diagnosis of ovarian cancer, the associated risk is about 9%, but this risk increases to greater than 50% if two or more first-degree relatives, i.e., mother and sister, have a diagnosis of ovarian cancer or multiple cases of ovarian and breast cancer.[3] Both *BRCA1* and *BRCA2* mutations have been associated with ovarian cancer. However, *BRCA1* is more prevalent, being associated with 90% of hereditary and 10% of sporadic cases of ovarian cancer.[3] Hereditary breast and ovarian cancer syndrome (HBOC) is one of the two different forms of hereditary ovarian cancer and is associated with germ-line mutations in *BRCA1* and *BRCA2*.[3,4] Hereditary non-polyposis colorectal cancer (HNPCC), or Lynch syndrome, is a familial syndrome with germ-line mutations causing defects in enzymes involved in DNA mismatch repair (MMR) that has been associated with up to 12% of hereditary ovarian cancer cases.[4]

Although it is not clearly defined, hormones and reproductive history are associated with the risk of developing ovarian cancer. **Nulliparity,** infertility, early menarche, and late menopause are associated with an increased risk of ovarian cancer.[5–7]

Ovarian cancer is associated with certain dietary and environmental factors as well. A diet that is high in galactose and animal fat and meat increases the risk of ovarian cancer, whereas a vegetable-rich diet is suggested to decrease risk.[4,8] Although controversial, exogenous factors such as asbestos and talcum powder use on the perineal area also have been suggested to increase the risk of ovarian cancer.[4,8]

Screening and Prevention

Screening

Currently, there is no standard, effective screening tool that is adequately predictive or sensitive for early detection.

Pelvic examinations are effective in detecting obvious tumors with a sensitivity of 67% for detecting all tumors; minimal or microscopic disease cannot be detected on physical examination.[9] Pelvic examinations are non-invasive and well accepted, but they do not usually detect ovarian cancer until it is in an advanced stage. Therefore, routine pelvic examinations will not improve earlier diagnosis or help to decrease overall mortality.[9]

Serum cancer antigen 125 (CA-125) is the most extensively evaluated tumor marker for ovarian cancer. Unfortunately, the CA-125 determination is non-specific, and elevated levels can be associated with a number of other gynecologic and gastrointestinal diseases. CA-125 levels in a woman without ovarian cancer, though, are static or tend to decrease over time, whereas levels associated with malignancy will continue to rise.[10] ❷ *Since CA-125 is a non-specific marker, there is no standard recommendation for routine screening for prevention of ovarian cancer.*

Transvaginal ultrasound (TVUS) is a component of current screening practices. Typically, it is used in combination with CA-125 determination, but it can be used as a single



Patient Encounter 2

A 36-year-old woman who has been in good health presents to your clinic complaining of constipation and abdominal pain. She explains to you that she has been feeling stressed lately because her 40-year-old sister is undergoing chemotherapy for breast cancer, and they just lost there mother to ovarian cancer a few years ago.

- Does she have a hereditary risk factor?
- What screening tools could be used to monitor this patient?
- Identify the treatment options for prevention of ovarian cancer available to this patient?

modality. TVUS releases sonic sound waves that create an image of the ovary to evaluate the size and shape and to detect the presence of cystic or solid masses. Limitations of this technique are lack of specificity and an inability to detect peritoneal cancer or cancer in normal-sized ovaries.[2,10] Most prevention clinics use the multimodality approach to screen high-risk women and recommend yearly ultrasound in combination with a CA-125 blood test every 6 months.

Prevention

Ovulation is considered a hostile event to the ovarian epithelium, making it more susceptible to damage and cancer. Interventions or conditions that limit the number of ovulations in a woman's reproductive history will have a protective effect. For instance, **multiparity** would decrease the number of ovulations.

Chemoprevention

Chemoprevention strategies used for ovarian cancer include oral contraceptives, aspirin and non-steroidal anti-inflammatory agents, and retinoids. The theory that oral contraceptives (OCs) reduce the number of ovulatory events is a basic explanation for its protective effect. Recent data suggest that the mechanism of action is more complex. Recent studies have indicated that progestin-induced apoptosis of the ovarian epithelium is responsible for the chemopreventive effect of OCs. The theory is that cells that have genetic damage but are not yet neoplastic have an increased chance of undergoing apoptosis.[11] OCs decrease the relative risk to less than 0.4% in women who use them for greater than 10 years.[12,13] However, at the same time, OC use has been associated with an increased risk of breast cancer.[12,13] Thus, women with a family history of breast cancer would not be ideal candidates for this preventive measure.

Non-steroidal anti-inflammatory agents, aspirin, and acetaminophen have been suggested for use in the prevention of different cancers, especially hereditary non-polyposis colon cancer.[14] While there have been observational studies linked to a reduction of ovarian carcinoma risk, evidence is still lacking. Potential mechanisms include effects on normal ovulation shed and inhibition of ovulation.[14,15] Other pharmacologic interventions that have been suggested but are still being evaluated include vitamin A, luetin, and other carotenoids.[16–18] The protective effect of these agents is associated with inhibition of cell growth, as well as promotion of cellular differentiation.[17]

Prophylactic Surgery

Surgical strategies are also used in the prevention of ovarian cancer. The goal is to remove healthy, at-risk organs and ultimately reduce the risk of developing cancer. These surgeries include prophylactic **oophorectomy** or **bilateral salpingo-oophorectomy** (BSO) and tubal ligation.

Prophylactic oophorectomy should be considered in any woman with a high risk of developing ovarian cancer.[19] The criteria for defining high risk include any woman with two or more first-degree relatives with epithelial ovarian carcinoma; a family history of multiple occurrences of **non-polyposis** colon cancer, endometrial cancer, and ovarian cancer; and a family history of multiple cases of breast and ovarian cancer.[19] Patients undergoing prophylactic oophorectomy need to be made aware that complete protection is not guaranteed.[13,20] Although a 67% reduction in risk has been shown, a potential 2% to 5% risk of peritoneal **carcinomatosis** remains.[19,21]

Tubal ligation is another procedure that has shown potential for risk reduction. However, it is not recommended as a sole procedure in prophylaxis. Protective effect may be due to limiting exposure of the ovary to environmental carcinogens. A case-control study conducted by Narod and colleagues found that a history of tubal ligation in *BRCA*-positive women was associated with a statistically significant 63% reduction in risk.[22]

Genetic Screening

Genetic screening is another option available for high-risk patients to consider. Patients could be screened for genes such as *BRCA1* and *BRCA2* or other genes such as those associated with HNPCC or HBOC syndrome.[3,22–26] Patient/family counseling and genetic counseling should be available for the patient/family to prepare to deal with the health and psychosocial implications of the genetic test results. Prior to this decision, the potential preventive options should be discussed, such as prophylactic bilateral salpingo-oophorectomy and/or total **hysterectomy.** Patients specifically positive for *BRCA1* or *BRCA2* also may consider a mastectomy.[27] Again, all risk factors and the patient health need to be evaluated, but typically surgery can be held off until after the childbearing years.[28–30]

PATHOPHYSIOLOGY

The three recurrent theories proposed are the incessant-ovulation hypothesis, the pituitary gonadotropin hypothesis, and the chronic inflammatory processes hypothesis.[2,31] The incessant-ovulation hypothesis proposes that the pathogenesis of ovarian

cancer is connected to continual ovulation. Ovulation is considered a "hostile" event to the ovary, perhaps with not enough time for adequate repair. Each time ovulation occurs, the ovary epithelium is disrupted, and cell damage occurs. Thus, repeated ovulations may lead to a greater number of repairs of the ovarian epithelium and increase the possibility of aberrant repairs, mutation, and **carcinogenesis.**[31–34] The pituitary gonadotropin hypothesis associates the disease with elevations in gonadotropin and estrogen levels.[2,31] This leads to an increased number of follicles and therefore an increased risk of malignant changes. There is also some evidence suggesting that chronic inflammatory processes and various environmental carcinogens play a role.[2,13]

The three major pathologic categories of ovarian tumors include sex-cord stromal, germ cell, and epithelial. About 85% to 90% of ovarian cancers are of epithelial origin. Epithelial ovarian tumors are composed of cells that cover the surface of the ovary, such as serous, mucinous, endometrioid, clear cell, and poorly differentiated adenocarcinomas. Germ-cell tumors involve the precursors of ova, with the most common type being dygerminoma, and are diagnosed most commonly in women under 40 years of age; generally, however, they have a better prognosis.[2] Sex-cord stromal tumors are indolent tumors that produce excess estrogen and androgens but also have a better overall prognosis.[2] Although, the histologic type of the tumor is not a significant prognostic factor, it is important to know the histopathologic grade. Undifferentiated tumors are associated with a poorer prognosis than lesions that are considered to be well or moderately differentiated.

Ovarian cancer usually is confined to the abdominal cavity, but spread can occur to the lung, liver, and less commonly, bone or brain. Disease is spread by direct extension, peritoneal seeding, lymphatic dissemination, and blood-borne metastasis. Lymphatic seeding is the most common pathway and frequently causes ascites.

Mechanisms of Resistance

The common mechanisms of drug resistance in ovarian cancer include: (1) alteration of drug inactivation by agents such as glutathione-*S*-transferase (GST), (2) enhanced DNA repair, (3) dysregulation of apoptotic pathways through activation of oncogenes or loss of tumor suppressor gene functions, (4) P-glycoprotein multidrug resistance (Pgp-MDR) that leads to decreased drug accumulation, and (5) steroid xenobiotic receptor (SXR) that leads to enhanced drug metabolism. At this time, our understanding about the mechanism of drug resistance in ovarian cancer is incomplete and limited mostly to in vitro studies. Ongoing improvements in current technology have allowed development of in vivo studies to evaluate mechanisms of drug resistance in ovarian cancer. MDR has been one of the major limitations and is one of the ongoing challenges for the successful therapeutic treatment of recurrent and persistent ovarian cancer.

CLINICAL PRESENTATION AND DIAGNOSIS



Clinical Presentation of Ovarian Cancer

General

❸ *Ovarian cancer often has been denoted as the "silent killer" because of the non-specific signs and symptoms.* By the time symptoms become unrelenting and bothersome, patients have advanced stage disease.

Symptoms

Patients may experience episodes or persistent symptoms of abdominal pain, constipation or diarrhea, flatulence, and urinary frequency.

Signs

The degree of abdominal swelling secondary to fluid accumulation may present like "pregnant abdomen" with irregular vaginal bleeding.

Laboratory Tests

- Cancer antigen 125 (CA-125). The normal level is less than 35 units/mL (35 kU/L). This test is associated with a lack of specificity. CA-125 can be elevated in a number of other states, such as different phases of the menstrual cycle, endometriosis, and non-gynecologic cancers. It is important to rule out other cancers associated with the abdominal cavity.
- *Carcinoembryonic antigen (CEA).* CEA is a marker for colon cancer. Normal value is less than 2.5 ng/mL (2.5 mcg/L).
- *CA19-9.* This is a marker for many gastrointestinal tumors such as cholangiocarcinomas.

Chemistries with Liver Function Tests (LFTs)

LFTs and serum creatinine may be suggestive of extent of disease. Most of this information is needed to determine if a patient is a surgical candidate. Labs should be within normal limits.

Complete Blood Count (CBC)

Abnormalities in CBC are not associated with ovarian cancer, but this information is needed to determine if the patient is a surgical candidate. Labs should be within normal limits.

Other Diagnostic Tests

To characterize local disease, one or both of the following are completed:

- Transvaginal ultrasound
- Abdominal ultrasound

To evaluate extent of disease, only one of the following is completed:

- Compute tomographic (CT) scan
- Magnetic resonance imaging (MRI)
- Positron-emission tomographic (PET) scan

Chest x-ray is also often done as part of clearance for surgery.

TREATMENT

Desired Outcomes

Health care providers use a multimodality approach including surgery and chemotherapy in the initial treatment of ovarian cancer with a curative intent. ❹ *Although most patients will achieve a complete response initially, more than 50% of cancers will recur within the first 2 years.*[2,35] Complete response to treatment is defined as no evidence of disease can be detected by physical examination or diagnostic tests, and patient has a normalized CA-125 value.

The histology of the disease is a prognostic factor. For instance, clear-cell and undifferentiated tumors do not respond as well to chemotherapy.[2] The extent of residual disease and tumor grade are also predictive of response to chemotherapy and overall survival.[2] There are other prognostic factors that may predict how well a patient will respond to adjuvant chemotherapy.

Generally, younger patients with a better performance status tolerate chemotherapy better than elderly patients. Caucasian women tend to have a worse prognosis and response to therapy compared with other ethnic backgrounds.[2,4,5]

The treatment goals shift when a patient presents with recurrent ovarian cancer. The desired outcomes focus on relief of symptoms such as pain or discomfort from ascites, slowing of disease progression, and prevention of serious complications such as small bowel obstructions. When a patient relapses, the prognostic factors are similar to those after initial surgery, except that the amount of time that has lapsed since the completion of chemotherapy should be considered to determine if drug resistance is emerging in the tumor. For example, recurrent platinum-sensitive ovarian cancer patients generally have a better prognosis than platinum-resistant patients.

Nonpharmacologic Therapy

❺ *Surgery is the primary treatment intervention for ovarian cancer.*[36–40] A total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO; Fig. 91–1), **omentumectomy,** and lymphonectomy (or lymph node dissection) is the standard initial surgical treatment of ovarian cancer.[36,38] The objective of the surgery is to debulk the patient until less than 1 cm of residual disease remains. Residual disease of less than 1 cm correlates with better complete response rates to chemotherapy and better overall survival compared with patients with bulky residual disease (less than or equal to 1 cm).[39,40] Indeed, the size of residual tumor mass after primary surgery is found to be the most important prognostic factor in patients with advanced ovarian cancer.[40]

A thorough exploratory **laparotomy** is essential for the accurate staging of patients.[36–38] ❻ *Ovarian cancer is staged surgically using the International Federation of Gynecology and Obstetrics (IFGO) staging algorithm* (Fig. 91–2). For certain patients with limited-stage disease, surgery may be curative.

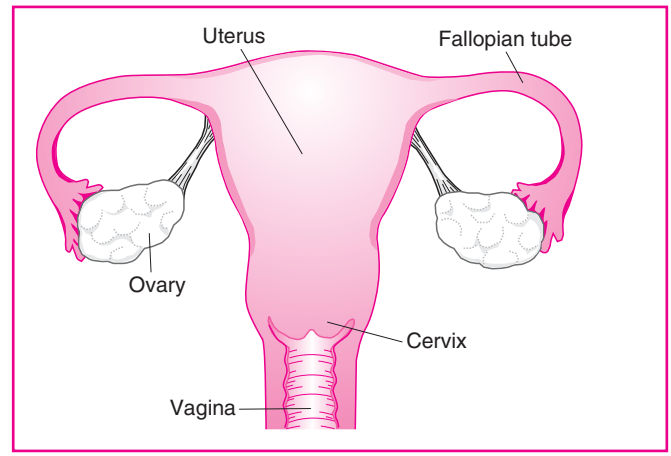


FIGURE 91–1. Diagram of female reproductive tract (uterus, fallopian tubes, ovaries, vagina). Dashed-line box outlines what is removed during the total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO).

Other surgical procedures have been evaluated to improve overall survival. Interval debulking that is completed after two to three cycles of chemotherapy has not translated into an improved survival benefit. Often debated, the benefit of the second-look laparotomy to evaluate residual disease after completing chemotherapy remains controversial because it has been difficult to establish any impact on patient overall survival. It has questionable benefit because although approximately 40% of patients with advanced disease will have a negative second look, 50% still relapse.[2] The role of **laparoscopic** surgery is somewhat controversial as initial surgery but is considered more often for debulking of recurrent or advanced disease when the intent is palliative rather than curative.[39]

Debulking surgery is intended to relieve symptoms associated with complications such as small bowel obstructions and to help improve the patient's quality of life but does not have a curative intent.

Pharmacologic Therapy

First-Line Chemotherapy

❼ *After initial surgery, the gold standard of care is six cycles of a taxane/platinum-containing regimen for patients with advanced ovarian cancer.*[41–43] Patients with limited disease will have observation alone after surgery (Fig. 91–3). Most often, paclitaxel is the taxane agent used in combination with carboplatin as the preferred platinum agent.[41–43] Depending on the patient's preexisting comorbidities and how well the patient tolerates chemotherapy regimens, substitution with docetaxel or cisplatin may be considered. The route of administration also should be discussed. Most often, intravenous (IV) administration will be used; however, in some patients, **intraperitoneal** (IP) administration may have an advantage in terms of overall survival[44]

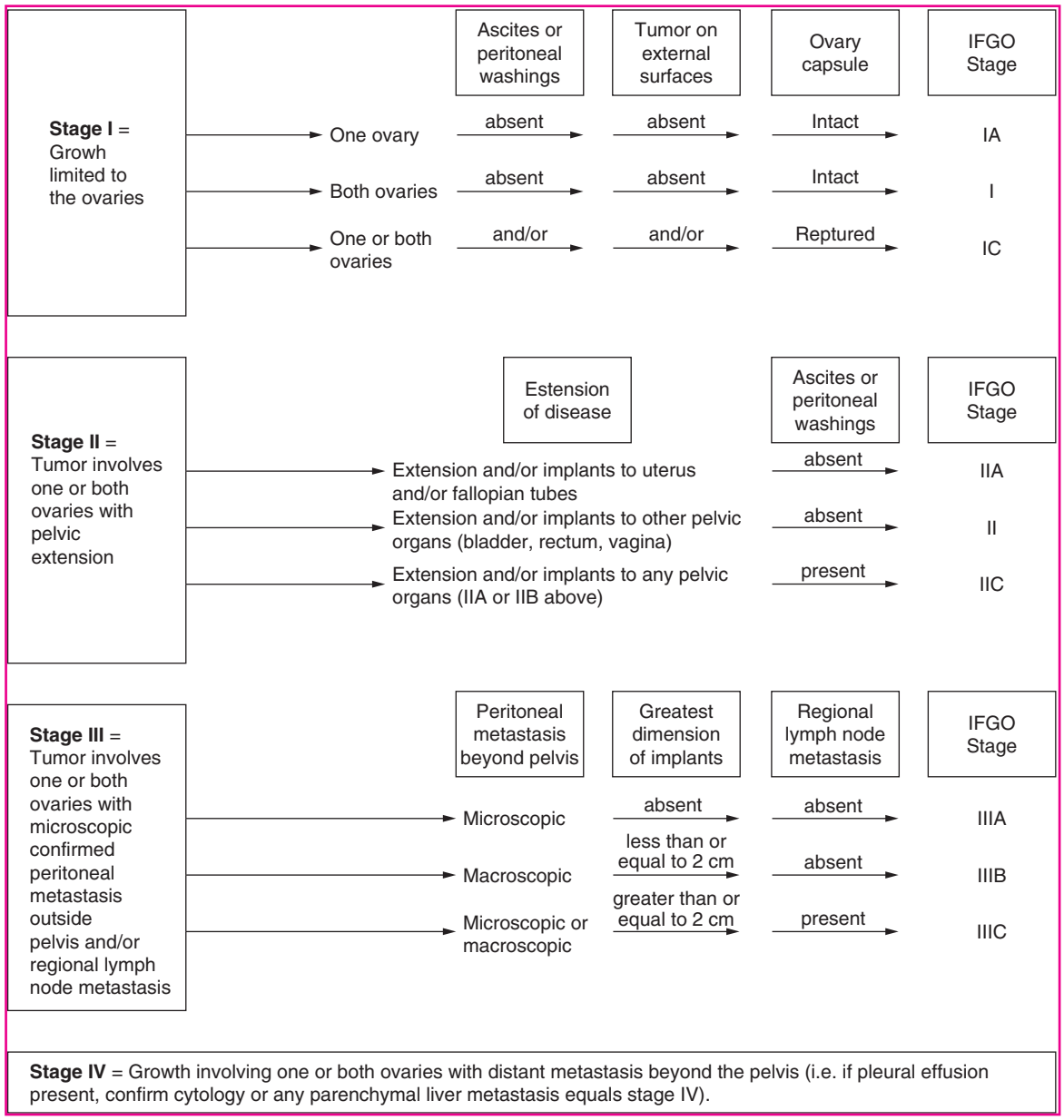


FIGURE 91–2. International Federation of Gynecology and Obstetrics (IFGO) staging algorithm.

(Table 91–1). Close monitoring of organ function, nausea and vomiting, myelosuppression, and neuropathies is necessary for all taxane/platinum regimens (Table 91–2).

Neoadjuvant Chemotherapy

In patients who are deemed poor surgical candidates or patients with a bulky or significant tumor burden, neoadjuvant chemotherapy would be the first-line treatment.[35] For patients who are poor surgical candidates because of significant comorbidities, a combination of taxane and a platinum agent will be administered every 3 to 4 weeks as tolerated with the intent to relieve symptoms and slow progression of the disease. In some cases, especially elderly patients, single-agent carboplatin will be used as palliative treatment instead. Chemotherapy alone has not been curative for patients with advanced ovarian cancer.[35]

In patients with bulky disease or a significant tumor burden, neoadjuvant chemotherapy can be used to decrease tumor burden to increase the likelihood of optimal tumor debulking during surgery.[35] Typically, three cycles of the standard combination taxane/platinum regimen is administered once every 3 weeks. After surgery, the patient will receive another three to six cycles depending on response to chemotherapy.

Consolidation Chemotherapy

Consolidation chemotherapy is the addition of cycles of the taxane/platinum regimen or the addition of single-agent platinum or a single taxane after completion of first-line chemotherapy.[45] If the tumor has a partial response to first-line chemotherapy evident by a significant decline in CA-125 by more than 50% of the preoperative level and/or

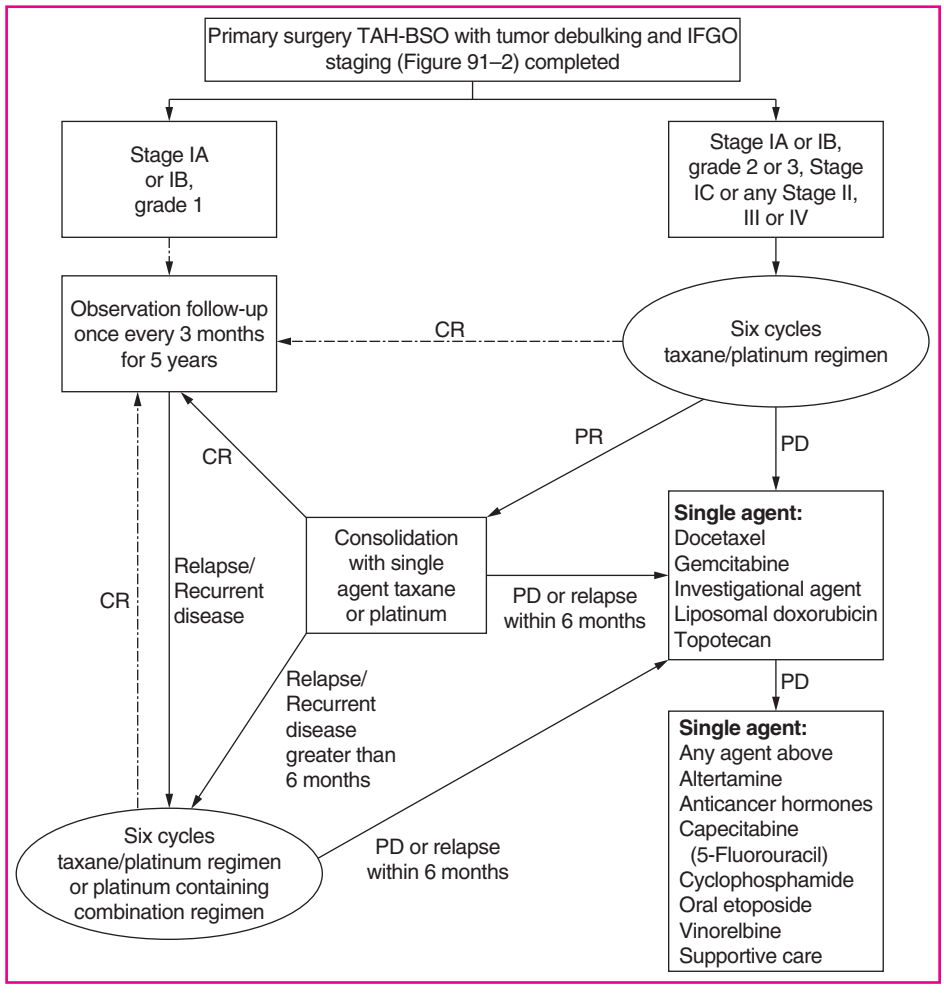


FIGURE 91–3. Summary of chemotherapy treatment algorithm for epithelial ovarian cancer. CR, complete response; PR, partial response; PD, progressive disease.

TABLE 91–1. Summary of First-Line Chemotherapy Regimens for Advanced Ovarian Cancer

Gold standard first-line chemotherapy after initial surgery for treatment of ovarian cancer.

Paclitaxel 175 mg/m^2 IV infused over 3 hours + carboplatin AUC = 5 IV infused over 1 hour. Regimen is given once every 21 days × six cycles.

Alternative first-line regimen: Addition of IP therapy. Patient selection is critical: Must have optimally debulked disease (less than or equal to 2 cm), no significant comorbidities, younger patients tolerate better.

Day 1: Paclitaxel 135 mg/m^2 IV infused over 24 hours + day 2: cisplatin 100 mg/m^2 IP infused over 1 hour + day 8: Paclitaxel 60 mg/m^2 IP infused over 1 hour. Regimen is given once every 21 days × six cycles.

Alternative first-line regimen: Substitution of cisplatin in place of carboplatin. Consider for patients experiencing difficulty with maintaining platelet counts.

Paclitaxel 135 mg/m^2 IV infused over 24 hours + day 2: cisplatin 75 mg/m^2 IV infused over 4 hours. Regimen is given once every 21 days × six cycles.

Alternative first-line regimen: Substitution of docetaxel in place of paclitaxel. Consider for patients with preexisting or increased risk of neuropathies.

Docetaxel 75 mg/m^2 IV infused over 1 hours + carboplatin AUC = 5 IV infused over 1 hour. Regimen is given once every 21 days × six cycles.

tumor regression/decrease in size, then the cancer still is considered taxane/platinum-sensitive. Additional cycles of chemotherapy are given until complete response is achieved (see Fig. 91–3).

Recurrent Chemotherapy

In the recurrent setting, the first question to address is whether or not the ovarian cancer is platinum-sensitive or platinum-resistant. If it has been less than 6 months or the disease progresses while receiving a platinum-based regimen, the cancer is considered to be platinum-resistant (see Fig. 91–3). These parameters are also used to determine taxane sensitivity or resistance. However, patients resistant to paclitaxel still may respond to docetaxel.[46] If the treatment goal is palliative care, then often single-agent therapy will be used, whereas curative care typically is an aggressive combination regimen (see Fig. 91–3).

Platinum-Sensitive

In patients who experienced a complete response to first-line chemotherapy and have had greater than a 6-month platinum-free interval, retreatment with a platinum-containing regimen is appropriate. Current National Comprehensive Cancer Network (NCCN) guidelines recommend the combination of carboplatin

TABLE 91–2. Summary of Chemotherapy Agents Used for First-Line Treatment of Advanced Ovarian Cancer

Mechanism of action of first-line agents:
Platinum analogs: Produce intra- and interstrand cross-links and DNA adducts to disrupt DNA replication
Taxane agents: Stabilize microtubules and prevent de-polymerization of tubulin

Agent	Common Adverse Effects	Monitoring/Comments
Paclitaxel	Peripheral neuropathy (DLT), nausea/vomiting, alopecia, hypersensitivity reactions	Use caution with any elevation in AST (SGOT). Give proper dosing for liver dysfunction. Premedicate: dexamethasone, diphenhydramine, and cimetidine.
Docetaxel	Neutropenia (DLT), hyperlacrimation, fluid retention, nail disorders, myelosuppression	Use with caution in liver dysfunction. Do not give if biliary tract is obstructed. Premedicate: dexamethasone.
Carboplatin	Myelosuppression (DLT), nephrotoxicity, nausea/vomiting, electrolyte wasting, diarrhea, stomatitis, hypersensitivity reactions	Prehydration not required. Give proper dosing for renal dysfunction. Premedicate: dexamethasone, diphenhydramine, and cimetidine.
Cisplatin	Neurotoxicity (DLT), nausea/vomiting, ototoxicity, nephrotoxicity, myelosuppression, electrolyte wasting, diarrhea	Prehydration required. Do not use if ScCr greater than 1.5 mg/dL or BUN greater than 25. Give proper dosing for renal dysfunction.

DLT, dose-limiting toxicity.

with either gemcitabine or paclitaxel for the treatment of platinum-sensitive recurrent ovarian cancer with a curative intent.[44] However, in patients unable to tolerate additional combination chemotherapy regimens, carboplatin alone or any one of the second-line agents would be appropriate[47] (Table 91–1).

Platinum-Resistant

Recurrent or persistent ovarian cancer after platinum-based regimens has a discouraging prognosis. Second-line agents have not been successful to date, but any active agent that has not been used during initial treatment is available for use. ❽ *Single-agent chemotherapy is standard practice for recurrent platinum-resistant ovarian cancer.* Active agents include altretamine (formerly hexamethylmelamine), anastrozole, capecitabine (5-fluorouracil), cyclophosphamide, docetaxel, gemcitabine, liposomal doxorubicin, oral etoposide, vinorelbine, and topotecan or investigational agents (Fig. 91–3). ❾ *Since the efficacy of the agents is similar, selection of an agent for treatment of recurrent platinum-resistant ovarian cancer depends on residual toxicities, physician preference, and patient convenience.* Table 91–3 gives a short summary of the adverse effects and monitoring parameters for chemotherapy agents commonly used for the treatment of recurrent ovarian cancer.



Patient Encounter 1, Part 2: One Year Later after Initial Diagnosis

This 67-year-old patient was optimally debulked and completed six cycles of paclitaxel/carboplatin after her surgery. Her CA-125 normalized (12 U/mL, 12 kU/L) on completion of her chemotherapy treatment, and her CT scan was negative. This patient returns to your clinic for her first 3-month follow-up appointment. Her CA-125 is (45 U/mL, 45 kU/L), and she reports some mild bloating. CT scan report states mild fluid accumulation in the pelvic cavity.

- List the possible chemotherapy treatment options for this patient
- Discuss the side-effect profile and administration schedule of each agent and how this information would help in selection of her next chemotherapy regimen
- What is the goal of treatment for this patient?

OUTCOME EVALUATION

Overall survival is affected by the success of the initial surgery to debulk the tumor to less than 1 cm of disease and response to first-line chemotherapy. The CA-125 level should be monitored with each cycle, and at least a 50% reduction in CA-125 after four cycles of taxane/platinum chemotherapy is related to an improved prognosis. Patients who achieve a complete response should have follow-up examinations every 3 months, including CA-125 determination, physical examination, pelvic examination, and appropriate diagnostic scans (e.g., CT scan, MRI, or PET scan) and should be evaluated for the detection of disease. Evaluate patients for resolution of any residual chemotherapy-related side effects, including neuropathies, nephrotoxicity, ototoxicity, myelosuppression, and nausea/vomiting.

In the progressive disease or recurrent setting, CA-125 levels still should be monitored with each cycle, but no change in therapy is recommended until after a minimum of three cycles of chemotherapy. In addition, appropriate diagnostic scans (e.g., CT scan, MRI, or PET scan) should be evaluated once every three cycles. Patients also should have routine physical examinations with each cycle of chemotherapy to evaluate for any physical

TABLE 91–3. Summary of Chemotherapy Agents Used for Second-Line Treatment of Progressive and Recurrent Platinum-Resistant Ovarian Cancer

Agent	Dose	Response Rate(%)	Common Adverse Effects	Monitoring/Comments
Docetaxel	75 mg/m^2 IV over 1 hour repeat every 21–28 days *vs.*	22%	Neutropenia (DLT), hyperlacrimation, fluid retention, nail disorders, myelosuppression	1. Premedicate: dexamethasone. 2. Use with caution in liver dysfunction. 3. Do not give if biliary tract is obstructed.
	30–40 mg/m^2 IV over 1 hour once every week	NR		
Gemcitabine	800 mg/m^2 IV infused over 30 minutes once a week on days 1, 8, & 15, followed by 1 week of rest	13.9%–27%	Myelosuppression (DLT), flulike symptoms, headache, somnolence, nausea/vomiting, stomatitis, diarrhea, constipation, rash	
Liposomal Doxorubicin	40 mg/m^2 IV infused over 3 hours cycles 1 & 2 and then infused over 1 hour thereafter; repeat every 28 days	12.3%–18%	Myelosuppression, stomatitis, mucositis, alopecia, flushing, shortness of breath, hypotension, headaches, cardiotoxicity, hand-foot syndrome	1. Give proper dosing for liver dysfunction. 2. Do not give if total bilirubin is greater than 5 mg/dL.
Topotecan	1.5 mg/m^2 IV infused over 30 minutes on days 1, 2, 3, 4, & 5; repeat every 21 days *or*	6.5%–17%	Myelosuppression (DLT), nausea/vomiting, diarrhea, Stomatitis, abdominal pain, alopecia, SGOT/SGPT elevation	1. Give proper dosing for renal dysfunction
	4 mg/m^2 IV infused over 30 minutes once a week for 3 consecutive weeks, followed by 1 week rest	31%		
Altretamine (Hexalen™)	260 mg/m^2 PO daily for 14–21 days; repeat every 28 days	9.7%	Nausea/vomiting, diarrhea, abdominal cramping, myelosuppression	1. Monitor for potential CYP450 drug interactions.
Capecitabine	1800–2500 mg/m^2 PO as divided dose twice for 14 consecutive days, followed by 1 week of rest	29%	Myelosuppression, hand-foot syndrome, nausea/vomiting, edema, stomatitis, diarrhea, cardiotoxicity, rash	1. Monitor for PPE and recommend regular use of lotions on hands and feet.
Cyclophos-phamide	750 mg/m^2 IV over 30 minutes	NR	Nausea/vomiting, nephrotoxicity, myelosuppression, cardiotoxicity, alopecia, hemorrhagic cystitis	1. Monitor for potential CYP450 drug interactions. 2. Monitor for any signs of blood in urine.
Etoposide	50 mg/m^2 per day PO in divided doses given daily for 3 consecutive weeks, followed by 1 week of rest	18%	Myelosuppression, nausea/vomiting, anorexia, alopecia, headache, fever, hypotension	1. Give proper dosing for liver dysfunction. 2. Do not give if total bilirubin is greater than 5 mg/dL. 3. Give proper dosing for renal dysfunction.
Letrozole	2.5 mg once daily	15%	Headache, nausea, dyspepsia, skin rash	1. No protective effect on bone; recommend calcium supplementation.
Tamoxifen	20 mg PO twice a day continuously until progressive disease	10%	Thrombocytopenia, anemia, thromboembolism, hot flashes, decreased libido, nausea/vomiting	1. Protective effect on bone and lipids. 2. Increased risk for endometrial cancer.
Vinorelbine	30 mg/m^2 IV infused over 15 minutes on days 1 and 8; repeat every 21 days	29%	Constipation, neutropenia, anemia, thrombocytopenia, neurotoxicity	1. Consider bowel regimen to prevent constipation.

NR, not reported.

toxicity associated with the chemotherapy, such as neuropathies, fluid retention, PPE, myelosuppresion, or nausea/vomiting.

Unfortunately, patients eventually will progress through all chemotherapy options, and then supportive-care measures should be provided to maintain patient comfort and quality of life. Develop a plan for treatment of common complications of advanced/progressive ovarian cancer, including ascites, uncontrollable pain, and SBO. Caution should be used in the removal of ascites because of the potential complications associated with rapid fluid shifts. Liberal use of opioids to control

pain is appropriate as ovarian cancer patients cope with progressive disease and approach end of life. Appropriate bowel regimens with laxatives and stool softeners should be used to prevent constipation. However, when a patient with a well-controlled bowel regimen presents with new onset of constipation, additional work-up is required prior to altering the bowel regimen. ⑩ *In ovarian cancer patients, small bowel obstruction is a common complication of progressive disease. In general, laxatives should not be used in patients with small bowel obstructions.* Prior to treating constipation, the patient should have a physical examination and abdominal x-ray to rule out SBO. Often, palliative surgery is required to correct SBO and alleviate patient pain. Patients should not eat any solids or liquids until resolution of the SBO. If inoperable SBO exists, then parenteral nutrition can be considered, but it should be weighed against ultimate treatment objectives. Overall, providing any measures needed to maintain patient comfort is the priority for patients with progressive ovarian cancer.



Patient Care and Monitoring

1. Assess patient history of non-specific symptoms to determine if patient should be evaluated by a gynecologist.
2. Determine if patient is at high risk for development of ovarian cancer, and make appropriate recommendations for screening and prevention.
3. Evaluate patient comorbidities and medications to determine if additional work-up is necessary prior to tumor debulking surgery. Do any medications need to be stopped or changed prior to surgery (e.g., aspirin, warfarin, or non-steroidal anti-inflammatory agents)?
4. Develop a plan for preventing and treating nausea and vomiting in patients receiving emetogenic chemotherapy.
5. Monitor the patient for signs of hypersensitivity reactions to taxane or platinum chemotherapy regimens.
6. Monitor appropriate labs to determine
   - Changes in organ function: adjust chemotherapy doses as indicated.
   - Electrolyte wasting: replace and supplement electrolytes intravenously or orally as indicated.
7. Provide appropriate patient education on respective chemotherapy agents that will be given for treatment of recurrent ovarian cancer.
   - What the chemotherapy is and how this agent works.
   - Explain plan for monitoring response to treatment.
   - What side effects to expect during chemotherapy
   - Precautions to take to prevent infection when neutropenic.
   - Monitor for signs/symptoms of infection.
   - When to contact the physician/clinic between cycles of chemotherapy
   - Drug or food interactions to avoid with chemotherapy.

ABBREVIATIONS

AUC:	area under the curve
BRCA1:	*breast cancer activator gene 1*
BRCA2:	*breast cancer activator gene 2*
BSO:	bilateral salpingo-oophorectomy
CA-19:	cancer antigen 19
CA-125:	cancer antigen 125
CEA:	carcinoembryonic antigen
CR:	complete response
DLT:	dose-limiting toxicity
GFR:	glomerular filtration rate
HBOC:	hereditary breast ovarian cancer
HNPCC:	hereditary non-polyposis colorectal cancer
IFGO:	International Federation of Gynecology and Obstetrics
NCCN:	National Comprehensive Cancer Network
NR:	not reported
PD:	progressive disease
PR:	partial response
SBO:	small bowel obstruction
Topo I:	topoisomerase I
Topo II:	topoisomerase II

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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92 Acute Leukemias

Nancy Heideman



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Compare the classification systems for acute lymphocytic leukemia (ALL) and acute nonlymphocytic leukemia (ANLL).
2. Describe the pathogenesis of acute leukemia.
3. Identify the prognostic factors for acute lymphocytic leukemia (ALL).
4. Explain the purpose of induction, consolidation, and maintenance phases for acute leukemia.
5. Explain the role of central nervous system (CNS) preventive therapy for acute leukemia.
6. Explain the treatment complications associated with therapy for acute leukemia.
7. Recognize the late effects of the treatment for long-term survivors of acute leukemias.

Key Concepts

❶ The acute leukemias are hematologic malignancies of bone marrow precursors characterized by excessive production of immature hematopoietic cells. This proliferation results in a large number of immature cells (blasts) appearing in the peripheral blood and bone marrow causing failure of normal hematopoiesis.

❷ Acute leukemias are classified according to their cell of origin. Acute lymphocytic leukemia (ALL) arises from the lymphoid line. Acute nonlymphocytic leukemia (ANLL) or acute myelogenous leukemia (AML) arises from the myeloid line.

❸ Children with acute lymphocytic leukemia (ALL) are classified according to their risk of relapse. Risk assessment is an important factor in the selection of treatment. The goal is to match treatment to risk and minimize over- or undertreatment.

❹ The initial treatment for acute leukemias is called ***induction.*** The purpose of induction is to induce a **remission**, a lack of identifiable leukemic cells in the bone marrow or peripheral blood with light microscopy. This definition may change as more sensitive techniques come into play.

❺ The current induction therapy for acute lymphocytic leukemia (ALL) typically consists of vincristine, asparaginase, and a steroid (prednisone or dexamethasone). An anthracycline is added for higher-risk patients.

❻ The current induction therapy for acute myelogenous leukemia (AML) usually consists of a combination of cytarabine and daunorubicin, with the frequent addition of a steroid and/or an antimetabolite such as 6-thioguanine. The risk of infection is so high during this period that patients receive antibiotic and fungal prophylaxis.

❼ Because the risk of central nervous system (CNS) involvement is high, regardless of cerebrospinal fluid (CSF) cytology, all patients with acute lymphocytic leukemia (ALL) receive intrathecal prophylaxis.

❽ Although survival in pediatric cancers has improved dramatically over the last 35 years, 50% to 60% of cancer survivors are estimated to have at least one chronic or late-occurring complication of treatment.

❶ *The acute leukemias are diseases of bone marrow resulting from aberrant proliferation of hematopoietic precursors. The hallmark of these malignancies is the leukemic blast cell, a visibly immature and abnormal cell in the peripheral blood that often replaces the bone marrow and interferes with normal hematopoiesis.* These blast cells proliferate in the marrow and inhibit normal cellular elements, resulting in anemia, neutropenia, and thrombocytopenia. Leukemia also may infiltrate other organs, including the liver, spleen, bone, skin, lymph nodes, and central nervous system (CNS). Virtually anywhere there is blood flow, the potential for extramedullary (outside the bone marrow) leukemia exists.

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❷ *Acute leukemias are categorized according to the cell of origin. Acute lymphocytic leukemia (ALL) arises from the precursor lymphoid cells. Acute myelogenous leukemia (AML), also called acute nonlymphocytic leukemia (ANLL), arises from the precursor myeloid cells.* As a result of the treatment of acute leukemias, especially ALL, the number of survivors has increased dramatically in the last 30 or more years.[1] ❸ *Risk-based treatment strategies have been developed that attempt to match the aggressiveness of therapy with the presumed risk of relapse and death.* This approach is based on the identification of multiple **phenotypic** and biologic risk factors. If left untreated, most patients with acute leukemia will die of their disease within 2 to 3 months.

EPIDEMIOLOGY AND ETIOLOGY

Epidemiology

Leukemia is a relatively uncommon disease overall. The current overall age-adjusted annual incidence of acute leukemia in the United States is 10 per 100,000. Of the estimated 1.4 million new cancers diagnosised in 2005, only 1% to 2% were acute leukemia,[2,3] with 4000 cases of ALL and about 12,000 cases of AML. Interesting age-related patterns of disease exist in ALL and AML. The average age of diagnosis for AML is about 65 years, whereas the average age for ALL is 10 years. This is a result of an increasing incidence of AML with age from about 1.8 per 100,000 in childhood to a peak of 17.7 per 100,000 adults 65 years of age and older.[4] ALL occurs in only about 20% of adult acute leukemia.[5] ALL is the most common malignancy of childhood; the peak incidence is in the 2- to 5-year range.[6]

In the pediatric population, leukemia is a common disease, accounting for almost one-third of all childhood malignancies. ALL accounts for 75% to 80% of all cases of childhood leukemia, whereas AML accounts for no more than 20%. Males generally are affected more often than females in all but the infant age group, and its incidence is higher in Caucasians than among other racial groups. The incidence of AML in children is bimodal: It peaks at 2 years of age, decreases steadily thereafter to age 9 years, and then peaks again at around age 16.[3]

The 5-year **event-free survival** rate for ALL is nearly 80% in children and approximately 40% for adults.[1] The success rate for children with ALL is attributed to risk-directed therapy and enrollment in clinical trials. For patients with AML younger than 20 years of age, the 5-year survival is 50%.[6] Patients with AML older than age 60 generally have a poorer prognosis of less than 20%.

Etiology

The cause of the acute leukemias is unknown; multiple influences related to genetics, socioeconomics, infection, environment, hematopoietic development, and chance all may play a role.[3] Table 92–1 lists the major conditions that have been implicated in the acute leukemias. In most cases, however, there is no explanation for the development of leukemia.



Patient Encounter, Part 1

RH is a 7-year-old girl who presents to her pediatrician with a 1-week history of runny nose and fever. Her mom has noted a lot of bruising on her lower exytremities. Physical examination reveals splenomegaly, multiple petechiae, and pallor. A complete blood count reveals a normochromic, normocytic anemia with a hemoglobin of 6 g/dL (60 g/L, 3.6 mmol/L; normal 11.7–15.7 g/dL, 117–150 g/L, 7.3–9.7 mmol/L), hematocrit of 18% (0.18; normal 35%–47%, or 0.35–0.47), and white blood cell (WBC) count of $2.6 \times 10^3/\mu L$ ($2.6 \times 10^9/\mu L$). The differential on the WBC count reveals 75% (0.75) lymphocytes (normal 20%–40%, or 0.2–0.4), 20% (0.2) neutrophils (normal 55%–62%, or 0.55–0.62), and 5% (0.05) lymphoblasts (normal 0%). Based on this information, a bone marrow aspirate and biopsy are performed, which reveal 85% (0.85) lymphoblasts and a DNA index of 1.17. A lumbar puncture is also performed, which shows no evidence of leukemia.

- What information is suggestive of acute lymphocytic leukemia?
- What are the prognostic factors for RH?
- What is the goal of induction therapy?

TABLE 92–1. Clinical Conditions Associated with an Increased Frequency of Acute Leukemias

Drugs	**Chemical**
Alkylating agents	Benzene
Epidophyllotoxins	**Radiation**
Genetic Conditions	Ionizing radiation
Down's syndrome	**Virus**
Bloom's syndrome	Epstein-Barr virus
Fanconi's anemia	Human T-lymphocyte virus (HTLV-1 and HTLV-2)
Klinefelter's syndrome	**Social Habits**
Ataxia telangiectasia	Cigarette smoking
Langerhans cell histiocytosis	Maternal marijuana use
Shwachman's syndrome	Maternal ethanol use
Severe combined immunodeficiency syndrome	
Kostmann's syndrome	
Neurofibromatosis type 1	
Familial monosomy 7	
Diamond-Blackfan anemia	

Adapted from Leather HL, Bickert B. Acute leukemias. In: DiPiro JT, Talbert RL, Yee GC, et al., (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 2458–2511.

The influence of genetics in leukemia is supported by several observations. For example, among identical twins, the occurrence of ALL is associated with a 20% to 25% chance of the disease developing in the other twin within 1 year. In fraternal twins, there is a fourfold increase in the risk of leukemia compared with the normal population. Additionally, leukemia is known to be increased in several chromosomally abnormal populations. Patients with Down's syndrome have a 20 times increased risk of developing leukemia compared with the rest of the population. Patients with Klinefelter's syndrome and Bloom's syndrome also have an increased incidence of leukemias.[7]

Even though exposure to environmental agents such as agricultural chemicals, pesticides, and radiation has been associated with leukemia, none of these agents is linked conclusively with the development of leukemia. An increased frequency of ALL is associated with higher socioeconomic status. It is postulated that less social contact in early infancy and thus a late exposure to some common infectious agents may have some impact.[7] In most individual instances, there is no reasonable or obvious explanation for the development of leukemia.

Risk factors for the development of AML include exposure to environmental toxins, Hispanic ethnicity, and genetics.[6] Of greater concern is the increased prevalence of AML as a secondary malignancy, resulting from chemotherapy and radiation treatment for other cancers. Alkylating agents, such as ifosfamide and cyclophosphamide, and topoisomerase inhibitors, such as etoposide, are linked to an increased risk of **myelodysplastic syndrome** (MDS) and AML.[8]

PATHOPHYSIOLOGY

Hematopoiesis is defined as the development and maturation of blood cells and their precursors. In utero, hematopoiesis may occur in the liver, spleen, and bone marrow. However, after birth, it occurs exclusively in the bone marrow. All blood cells are generated from a common hematopoietic precursor, or *stem cell.* These stem cells are self-renewing and pluripotent and thus are able to commit to any one of the different lines of maturation that give rise to platelet-producing megakaryocytes, lymphoid, erythroid, and myeloid cells. The myeloid cell line produces monocytes, basophils, neutrophils, and eosinophils, whereas the lymphoid stem cell differentiates to form circulating B and T lymphocytes. In contrast to the ordered development of normal cells, the development of leukemia seems to represent an arrest in differentiation at an early phase in the continuum of stem cell to mature cell.[1]

Both AML and ALL are presumed to arise from clonal expansion of a single "arrested" cell. As these cells expand, they acquire one and often more chromosomal aberration, including translocations, inversions, deletions, point mutations, and amplifications.[3] An example is the t(9;22) translocation, which underlies the *BCR-ABL* fusion protein. The normal *ABL* gene encodes a growth-promoting protein kinase whose activity is tightly controlled. By contrast, the translocation and fusion of the *BCR* and *ABL* gene sequences produce a kinase that leads to uncontrolled proliferation, survival, and self-renewal of cells. Imatinib is a tyrosine kinase inhibitor that inhibits the activity of *ABL.* It has shown great success given the pathogenic role of *BCR-ABL* tyrosine kinase in chronic myelogenous leukemia (CML). Imatinib also has shown activity in patients with acute lymphoblastic leukemia in patients who are *BCR-ABL*-positive.[3]

AML represents a group of disorders in which both failure to differentiate and overproliferation in the stem cell compartment produce an overabundance of nonfunctional cells termed myeloblasts. While the specific cause for this biologic abnormality is unknown, an understanding of the genetic influence of leukemia is leading to a wide variety of targeted therapies.[9]

In AML, there is a substantial difference in clinical and biologic features, as well as in response to and tolerance of therapy, by age group. In the elderly, trilineage leukemic involvement is common, indicating that the cell of origin is probably a stem or very early progenitor cell. In the younger population, a more differentiated progenitor becomes malignant, permitting maturation of some granulocytic and erythroid populations. These two forms of AML show different patterns of resistance to chemotherapy, with resistance more frequent in the older adults with AML.[6]

For patients with myelodysplastic syndrome or AML as a secondary neoplasm, there are a number of key features characteristic of the leukemia. Alkylator-related secondary leukemias after Hodgkin's disease usually have a myelodysplastic prodrome and a monosomy 5 or monosomy 7. Secondary ANLL with the use of epipodophyllotoxin (etoposide) demonstrates mainly M4 or M5 morphology and exhibits translocations within the *MLL* gene with 11q23 chromosomal alterations.[8]

Leukemia Classification

For all newly diagnosed patients with leukemia, an aspirate of the liquid marrow and a bone marrow core biopsy are obtained.[5] Morphologic and cytochemical analysis of these samples distinguishes three subtypes of ALL (L1, L2, and L3) and eight subtypes of AML (M0–M7) as classified by the French-American-British (FAB) scheme. See Tables 92–2 and 92–3 for the FAB classification of acute myelogenous leukemia and acute lymphocytic leukemia.

Classification methods for leukemia have evolved from simple schemes that were largely phenotypic and considered only age, gender, WBC count, and blast morphology to now-complex methods that include biologic features such as cell-surface receptor features and cytogenetics.

TABLE 92–2. Morphologic (FAB) Classification of Acute Myelogenous Leukemia

Sub-type		Frequency of FAB Sub-type[a] Adults (%)	Children less than 2 years (%)	Children less than 2 years (%)
M0	Acute myeloblastic leukemia, without maturation	5	Low	Low
M1	Acute myeloblastic leukemia with minimal maturation	15	17	25
M2	Acute myeloblastic with maturation	25		27
M3	Acute promyelocytic leukemia	10		5
M4	Acute myelomonocytic leukemia	25	30	26
M5a	Acute monoblastic leukemia, poorly differentiated	5	52	16
M5b	Acute monoblastic leukemia, well differentiated	5		
M6	Acute erythroleukemia	5		2
M7	Acute megakaryoblastic leukemia	10		5–7

[a]Percentages should be compared vertically and not horizontally. FAB, French-American-British.
Adapted from Leather HL, Bickert B. Acute Leukemias. In: DiPiro JT, Talbert RL, Yee GC, et al., (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 2458–2511.

Markers on the cell surface or membrane of the lymphoblast can be used to classify ALL. Among the early classification system was the FAB scheme, which was based purely on morphology and cytochemistry. This system considered nuclear appearance and degree of differentiation. This is no longer used, and the current classification of acute leukemias is based on features that can be identified only by immunologic and molecular analyses.[3]

Immunophenotyping by **flow cytometry** has taken on an increasingly important role in the diagnosis of leukemia. Owing to the ease of application, sensitivity, and quantifiable results, flow cytometry is the preferred method for lineage assignment.[7] This approach takes advantage of the development of monoclonal antibodies (MABs) to cell-surface antigens that are differentially expressed during hematopoietic differentiation. The antigens are referred to as antibody *cluster determinants* (CDs) that define cells at various stages of development and can easily separate ALL from AML and T-cell from pre-B-cell ALL.[5] The combined approach of using blast cell morphology and immunophenotype has facilitated diagnosis and delivery of specific treatments for the major subtypes of acute leukemia. The detailed information offered by flow cytometry and recognition of several prognostic cytogenetic features has combined to more narrowly predict prognosis and develop risk-directed therapies in ALL and AML. Common immunophenotypic markers seen in AML and ALL are provided in Table 92–4

TABLE 92–3. Morphologic (FAB) Classification and Immunophenotype of Acute Lymphocytic Leukemia

Sub-type	Cell of Origin	Frequency of FAB Sub-type[a] Adults (%)	Children (%)
L1	Early pre-B cell Pre-B cell B cell T cell	30	85
L2	Early pre-B cell Pre-B cell B cell T cell	60	14
L3	B cell	10	1

[a]Percentages should be compared vertically and not horizontally. FAB, French-American-British.
Adapted from Leather HL, Bickert B. Acute Leukemias. In: DiPiro JT, Talbert RL, Yee GC, et al., (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 2458–2511.

CLINICAL PRESENTATION



Clinical Presentation of Acute Myelogenous Leukemia[3,6,10]

General

Patients may have symptoms of AML for 1 to 3 months prior to presentation. These include fatigue, fever, and pallor**,** but patients generally are in no obvious distress.

Symptoms

- The patient may present with weakness, malaise, bleeding, and weight loss.
- Neutropenic patients are often febrile and highly susceptible to infection.
- Anemia usually presents as pallor, tiredness, and general fatigue.
- Patients with thrombocytopenia usually present with bruising, petechiae, and ecchymosis.
- Chloromas (localized leukemic deposits named after their color) may be seen, especially in the periorbital regions and as skin infiltrates.
- Gum hypertrophy is indicative of AML M4 and AML M5 subtypes.
- Disseminated intravascular coagulation is common in AML M3 and is associated with generalized bleeding or hemorrhage.
- Lymphadenopathy, massive **hepatosplenomegaly**, and bone pain are not as common in AML as in ALL.

Signs

- Temperature may be elevated secondary to a low WBC count.
- Petechiae and bleeding are indicative of thrombocytopenia.

Laboratory Tests

- Complete blood count with differential is performed.
- The anemia is usually **normochromic** and **normocytic.**
- Approximately 50% of children present with platelet counts of less than $50 \times 10^3/\mu L$ ($50 \times 10^9/L$).
- The WBC count may be normal, decreased, or high. About 20% of patients have WBC counts of over $100 \times 10^3/\mu L$ ($100 \times 10^9/L$), which places them at risk for **leukostasis.**
- Uric acid is increased in approximately 50% of patients secondary to rapid cellular turnover.
- *Electrolytes:* Potassium and phosphorus are often elevated. Calcium is usually low.
- *Coagulation disorders:* Elevated prothrombin time, partial thromboplastin time, D-dimers; hypofibrinogenemia

Other Diagnostic Tests

Flow cytometric evaluation of bone marrow and peripheral blood to characterize the type of leukemia, as well as to detect specific chromosomal rearrangements. The bone marrow at diagnosis usually is hypercellular, with normal hematopoiesis being replaced by leukemic blasts. The presence of greater than 20% blasts in the bone marrow is diagnostic for AML.

- At diagnosis, a lumbar puncture is performed to determine if CNS leukemia is present.

Prognostic Factors

❸*The survival of patients with leukemia has improved markedly in the last 30 years. This is a result of intensive classification and risk assessment that is a prerequisite in the selection of treatment aimed at ensuring that patients are neither over- nor undertreated.*[11] *Risk-adapted therapy tailors treatment based on the predicted risk of relapse.* Age, WBC count, leukemic cell **genotype,** and response to induction therapy are used commonly in risk classification, each possessing different and sometimes overlapping prognostic significance.[3] On the basis of these prognostic variables, patients are assigned to one of three risk groups (e.g., standard-, high-, or very high-risk groups) that determine the aggressiveness of treatment.

TABLE 92–4. Common Immunophenotypes in Acute Leukemia

Leukemia	Common Immunophenotypes
Acute myeloid leukemia	CD13, CD15, CD33, CD14, CD64, and C-KIT
B-cell acute lymphoblastic leukemia	CD19, CD20, CD10, and CD22
T-cell acute lymphoblastic leukemia	CD2, CD3, CD4, CD5, and CD7

Adapted from Leather HL, Bickert B. Acute Leukemias. In: DiPiro JT, Talbert RL, Yee GC, et al., (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 2458–2511.

Prognostic Factors in Acute Lymphocytic Leukemia

In both children and adults with ALL, clinical trials have identified several risk factors that correlate with outcome (Table 92–5). Prognostic features include age, WBC count, cytogenetic abnormalities, ploidy, leukemic cell immunophenotype, and degree of initial response to therapy.[7] When these factors are combined, they predict groups of patients with varying degrees of risk for treatment failure.



Clinical Presentation of Acute Lymphocytic Leukemia[3,6,10]

General

Typically, patients have symptoms for 1 to 3 months before presentation. These include fatigue, fever, and pallor, but patients generally are in no obvious distress.

Symptoms

- The patient may present with weakness, malaise, bleeding, and weight loss.
- Neutropenic patients are often febrile and highly susceptible to infection.
- Anemia usually presents as pallor, tiredness, and general fatigue.
- Patients with thrombocytopenia usually present with bruising, petechiae, and ecchymosis.
- Patients often present with bone pain secondary to expansion of the marrow cavity from leukemic infiltration.
- CNS involvement is common at diagnosis.

Signs

- Temperature may be elevated secondary to a low WBC count.
- Petechiae and bleeding are indicative of thrombocytopenia.
- Patients may present with organ involvement, such as peripheral adenopathy, hepatomegaly, and **splenomegaly.**
- T-lineage ALL may present with a mediastinal mass.

Laboratory Tests

- Complete blood count with differential is performed.
- The anemia is usually normochromic and normocytic. Approximately 50% of children present with platelet counts of less than $50 \times 10^3/\mu L$ ($50 \times 10^9/L$). The WBC count may be normal, decreased, or high. About 20% of patients have WBC counts over $100 \times 10^3/\mu L$ ($100 \times 10^9/L$), which places them at risk for leukostasis.
- Uric acid is increased in approximately 50% of patients secondary to rapid cellular turnover.
- *Electrolytes:* Potassium and phosphorus often are elevated. Calcium usually is low.
- *Coagulation disorders:* Elevated prothrombin time, partial thromboplastin time, D-dimers; hypofibrinogenemia.

Other Laboratory Tests

Flow cytometric evaluation of bone marrow and peripheral blood is performed to characterize the type of leukemia as well as to detect specific chromosomal rearrangements. The bone marrow at diagnosis usually is hypercellular, with normal hematopoiesis being replaced by leukemic blasts. At diagnosis, a lumbar puncture is performed to determine if CNS leukemia is present.

In adults, there is a steady decline in the rate of complete remission (CR) following initial induction therapy with increasing age. While induction treatment produces 95% CR in children, it decreases to 40% to 60% in patients older than 60 years of age. The prognostic implication is due in part to decreased tolerance of stringent induction/consolidation regimens in older patients, but it is mostly due to biologic differences, particularly the presence of Philadelphia chromosome (Ph^+) or t(9;22), which confers higher-risk disease.[5] *BCR-ABL* fusions are strongly associated with chemoresistant leukemia in all age groups but are much more prevalent in adults with ALL than in children (30% versus less than 5%).[10]

TABLE 92–5. Prognostic Factors in Acute Lymphocytic Leukemia

	Risk for Leukemic Relapse	
Factor	**Low**	**High**
Morphology	L1	L2, L3
Immunologic phenotype	Early pre-B cell	Null cell, T cell, pre-B cell, B cell
WBC count at diagnosis	Less than $10 \times 10^3/\mu L$ ($10 \times 10^9/L$)	Greater than $50 \times 10^3/\mu L$ ($50 \times 10^9/L$)
Platelets	Greater than $100 \times 10^3/\mu L$ ($100 \times 10^9/L$)	Less than $30 \times 10^3/\mu L$ ($30 \times 10^9/L$)
Patient age	3–7 years	Less than 1 year or greater than 10 years
Cytogenetics	Normal karyotype	t(9;22); t(4;11); –7; +8
Myeloid markers	Absent	Present
CNS leukemia	Absent	Present
Node/liver/spleen enlargement	Absent	Massive
Mediastinal mass	Absent	Present
Time to remission	Less than 4 weeks	Greater than 4 weeks

CNS, central nervous system; WBC, white blood cell.
Adapted from Leather HL, Bickert B. Acute Leukemias. In: DiPiro JT, Talbert RL, Yee GC, et al., (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 2458–2511.

TABLE 92–6. Risk Category According to Cytogenetic Abnormalities Present

	Risk Category		
Disease	**Good Risk**	**Intermediate Risk**	**High Risk**
AML	t(8;21)(q22;q22); inv(16); t(15;17); t(9;11) trisomy 21	Normal karyotype; trisomy 8; 11q23; del(7q); del(9q); trisomy 22	Complex karyoptype; –5; –7; del (5q); inv(3P)
Probability of relapse	Less than or equal to 25%	50%	Greater than 70%
4-Year survival	Greater than or equal to 70%	40–50%	Less than or equal to 20%
ALL	Hyperdiploidy; t(10;14); or 6q		t(9;22); t(8;14); t(4;11); t(1;9)

Adapted from Leather HL, Bickert B. Acute Leukemias. In: DiPiro JT, Talbert RL, Yee GC, et al., (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 2458–2511.

Like age, the WBC count at presentation is a reliable indicator of CR rate and outcome. WBC count is indicative of tumor burden, although the underlying biologic mechanisms that account for the unfavorable outcomes associated with an elevated WBC count are unclear. Patients with WBC counts of less than $50 \times 10^3/\mu L$ ($50 \times 10^9/L$) are considered standard risk, and a higher WBC count at presentation is associated with higher risk of treatment failure (Table 92–6).

Specific chromosomal abnormalities in leukemic cells also possess prognostic significance. Blast cells with a translocation of parts of chromosome 12 and 21 (the *TEL-AML1* fusion) or trisomies of 4, 10, and 17 are considered to have favorable genetic features.[3] The presence of specific translocations between chromosome 9 and 22 (Philadelphia chromosome, or Ph^+) is a high-risk feature. Other cytogenetic abnormalities, such as translocation of the *MLL* gene that occurs primarily in infant ALL, exist with varying degrees of prognostic significance.

The DNA content of blast cells, hyper-, hypo-, or diploid, corresponding to increased, decreased, or normal chromosome numbers, has been considered prognostic. Lower-risk patients with hyperdiploidy (greater than 50 chromosomes) generally are between the ages of 1 and 9 years, whereas the higher-risk patients with normal diploidy (50 chromosomes) generally are older.

Patients with cell-surface markers indicating that the blasts are early in the B-cell lineage (CD markers) are standard risk, whereas those with mature B-cell and T-cell blasts are considered high risk.

Patients completing induction treatment and in apparent remission still harbor malignant cells in their bone marrow, even though they are disease-free by peripheral blood and bone marrow morphology. These residual leukemic cells are below the limits of detection using standard morphologic examination. Measurement of this population of cells has become an increasingly significant prognostic factor and a determinant of the aggressiveness of postinduction therapy. Thus flow cytometric analysis for the determination of minimal residual disease (MRD) has become increasingly important.[12] Several studies in children, in whom ALL is common, have evaluated disease levels at the end of induction and correlated these values with event-free survival (EFS). For example, a patient with no detectable MRD at the end of induction has an EFS greater than 90% at 3 years. Conversely, a patient with a high MRD (1%) has a 3-year EFS of only about 25%.[13] Assessment of MRD is also emerging as an important indicator of disease recurrence in the adult population.

Prognostic Factors in Acute Myelogenous Leukemia

The major prognostic factors in newly diagnosed AML are age, sub-type (FAB M2), and chromosome status. Older adults with AML (greater than 60 years), in comparison with younger patients with the same disease, have a dismal prognosis and represent a distinct population in terms of disease biology, treatment-related complications, and overall survival. These older patients have a higher incidence of unfavorable chromosomal abnormalities, such as aberrations of chromosomes 5, 7, or 8, and fewer abnormalities that are associated with a more favorable outcome, such as t(8;21) or inv(16) (see Table 92–6).[9]

Even though chromosomal abnormalities correlate with prognosis in adult AML, they appear to have less influence on outcome. Among children, the male gender, platelet count of less than $20 \times 10^3/\mu L$ ($20 \times 10^9/L$), hepatomegaly, more than 15% bone marrow blasts on day 14 of induction, myelodysplastic syndrome (MDS), and FAB sub-type M5 all were associated with lower CR rates. The absence of these features and abnormal chromosome 16 were associated with more favorable outcomes.[6]

TREATMENT

Desired Outcome

The primary objective in treating patients with acute leukemia is to achieve a complete and continuous remission (CCR). **Remission** is defined as the absence of all clinical evidence of



Patient Encounter, Part 2

RH is admitted to the pediatric oncology service. She is started on allopurinol and intravenous fluids with sodium bicarbonate to prevent tumor lysis syndrome. According to her risk status, she will receive a three-drug induction with vincristine, dexamethasone, and pegylated asparaginase. She also will receive intrathecal (IT) chemotherapy for CNS prophylaxis with methotrexate, cytarabine, and hydrocortisone.

- What is the role of CNS prophylaxis?

leukemia with the restoration of normal hematopoiesis. For both ALL and AML, remission induction is achieved with the use of highly myelosuppresive chemotherapy that induces a state of bone marrow aplasia.[10] Following this period, hematopoiesis is restored. Failure to achieve remission in the first 7 to 14 days of therapy is highly predictive of disease recurrence.

Pharmacologic Therapy

Acute Lymphoblastic Leukemia (ALL)

The treatment for ALL consists of three main elements: remission induction, intensification (**consolidation**), and continuation (maintenance) phases of treatment.[3] Therapy to eradicate subclinical CNS leukemia is also an integral part of therapy for ALL (Table 92–7).

Remission Induction

❹*The primary objective of treatment is to eliminate all morphologic evidence of disease and restore normal hematopoiesis.*[15] ❺*Induction consists of a standard three-drug regimen: glucocorticoid (prednisone or dexamethasone), vincristine, and asparaginase or pegylated asparaginase. For patients with high-risk ALL, daunorubicin is added to the standard three-drug regimen.* Since adults are considered to be at high risk, their induction regimens include anthracycline (daunorubicin or doxorubicin).[5] Dexamethasone is replacing prednisone in some standard-risk protocols owing to its longer half-life and better CNS penetration.[6,16] Even though dexamethasone possesses more favorable pharmacologic characteristics than prednisone, its use may be associated with more life-threatening infections and septic deaths.[16]

Intensification (Consolidation)

After completion of induction and restoration of normal hematopoiesis, patients begin intensification (consolidation). The goal of intensification is to administer dose-intensive chemotherapy in an effort to further reduce the burden of



Patient Encounter, Part 3

RH had a bone marrow aspiration performed on days 15 and 29 that showed morphologic remission. The MRD on day 29 was less than 0.1%. RH completed her induction therapy and started intensification therapy.

- What is the significance of MRD?
- What is the purpose of intensification therapy?

residual leukemic cells.[12] It is in this and subsequent treatment phases that the presence of MRD is reduced by increasing the aggressiveness of the drug regimen. Several regimens use agents and schedules designed to minimize the development of drug cross-resistance. Studies have demonstrated that this phase of treatment has proven to be an effective strategy in the prevention of relapse in children with ALL, but its benefits in adults are less clear.

❸ *In children, the intensity of the consolidation treatment is now determined not only by the child's risk classification but also by the rate of cytoreduction during induction.*[5] Patients who respond slowly to induction therapy (as determined by bone marrow examination early in induction) are at higher risk of relapse and are treated on more aggressive regimens.

The Berlin-Frankfurt-Munster (BFM) Study Group introduced a treatment element called *delayed intensification* (or *reinduction*) *therapy.* This therapy consisted of repetition of the initial remission induction therapy administered approximately 3 months after remission. Most institutions have adopted this regimen.[12]

Intensification regimens may vary in their aggressiveness and the drugs they use depending on the patient's risk group and immunophenotype. For example, the use of very-high-dose methotrexate (5 g/m^2) appears to improve outcome in patients with T-cell ALL. The use of intensive asparaginase treatment in T-cell ALL patients also has improved outcome significantly.[12]

Continuation (Maintenance)

The purpose of maintenance therapy is to further eliminate leukemic cells and produce an enduring CCR. The two most important agents in maintenance chemotherapy are a combination of oral methotrexate and 6-mercaptopurine. Improved outcome has been associated with increasing 6-mercaptopurine dosages to the limits of individual tolerance based on absolute neutrophil count. The use of 6-mercaptopurine at doses that cause neutropenia has been associated with increased rates of infection, an inability to deliver planned therapy, and a higher relapse rate. 6-Mercaptopurine is metabolized by thiopurine methyltransferase (TPMT). TPMT deficiency is inherited as an autosomal recessive trait, with 89% to 94% of Caucasians having high activity, 6% to 11% having intermediate activity, and

TABLE 92–7. Representative Chemotherapy Regimens for Adult Acute Lymphocytic Leukemia

Remission Induction		CNS Prophylaxis		Consolidation		Maintenance
Drug and Dose	**Days**	**Prophylaxis**	**Days**	**Drug and Dose**	**Days**	**Drug, Dose, and Timing**
German or Hoelzer Regimen (Adult)[d]						
PRED (Oral) 60 mg/m^2	1–28	Cranial irradiation		DEX (Oral) 10 mg/m^2	1–28	MP (Oral) 60 mg/m^2 daily and
VCR (IV) 1.5 mg/m^{2a}	1, 8, 15, 22	MTX (IT) 10 mg/m^{2b}	31, 38, 45, 52	VCR (IV) 1.5 mg/m^{2a}	1, 8, 15, 22	MTX (Oral/IV) 20 mg/m^2 weekly,
DNR (IV) 25 mg/m^2	1, 8, 15, 22			DOX (IV) 25 mg/m^2	1, 8, 15, 22	weeks 10–18 and 29–130
ASP (IV) 5,000 units/m^2	1–14			CTX (IV) 650 mg/m^{2c}	29	
CTX (IV) 650 mg/m^{2c}	29, 43, 57			Ara-C (IV) 75 mg/m^2	31–34, 38–41	
Ara-C (IV) 75 mg/m^2	31–34, 38–41, 45–48, 52–55			TG (Oral) 60 mg/m^2	29–42	
MP (Oral) 60 mg/m^2	29–57					
CALGB 8811 (Adult)[e]				**Course II: Early intensification**		**Course V**
Course I				MTX (IT) 15 mg	1	VCR (IV) 2 mg day 1 monthly
CTX (IV) 1,200 mg/m^2	1			CTX (IV) 1,000 mg/m^2	1	PRED (Oral) 60 mg/m^2
DNR (IV) 45 mg/m^2	1, 2, 3			MP (Oral) 60 mg/m^2	1–14	days 1–5 monthly
VCR (IV) 2 mg	1, 8, 15, 22			Ara-C (SC) 75 mg/m^2	1–4, 8–11	MTX (Oral) 20 mg/m^2 days
PRED (Oral) 60 mg/m^2	1–21			VCR (IV) 2 mg	15, 22	1, 8, 15, 22 monthly MP
ASP (SC) 6,000 U/m^2	5, 8, 11, 15, 18, 22			ASP (SC) 6,000 units/m^2	15, 18, 22, 25	(Oral) 60 mg/m^2 days 1–28 monthly
Induction chemotherapy for patients greater than or equal to 60 year old, use:						
CTX (IV) 800 mg/m^2	1					
DNR (IV) 30 mg/m^2	1–3					
PRED (Oral) 60 mg/m^2	1–7					
	Course III			**Course IV: Late intensification**		
		Cranial irradiation		DOX (IV) 30 mg/m^2	1, 8, 15	
		MTX (IT) 15 mg	1, 8, 15, 22, 29	VCR (IV) 2 mg	1, 8, 15	
		MP (Oral) 60 mg/m^2	1–70	DEX (Oral) 10 mg/m^2	1–14	
		MTX (Oral) 20 mg/m^2	36, 43, 50, 57, 64	CTX (IV) 1,000 mg/m^2	29	
				TG (Oral) 60 mg/m^2	29–42	
				Ara-C (SC) 75 mg/m^2	29–32, 36–39	

C, cytarabine; ASP, asparaginase; CALGB, Cancer and Leukemia Group B; CNS, central nervous system; CTX, cyclophosphamide; DEX, dexamethasone; DNR, daunorubicin; DOX, doxorubicin; IT, intrathecal; captopurine; MTX, methotrexate; PRED, prednisone; TG, thioguanine; VCR, vincristine.

[a] Maximum single dose, 2 mg.

[b] Maximum single dose, 15 mg.

[c] Maximum single dose, 1,000 mg.

[d] Adapted from Leather HL, Bickert B. Acute Leukemias. In: DiPiro JT, Talbert RL, Yee GC, et al., (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 2458–2511.



Patient Encounter, Part 4: Creating a Care Plan

After completion of induction and intensification therapy, RH will begin maintenance therapy for 2.5 years.

- Which agents are used in maintenance therapy?
- Why is maintenance therapy of such a long duration?
- Create a care plan to include (1) monitoring parameters during maintenance therapy, (2) a list of drug-related problems to access toxicity during maintenance therapy, and (3) goals of maintenance therapy.

0.3% having very low or no activity. This deficiency is explained largely by three polymorphisms in the *TPMT* gene (**2*, **3A*, and **3C*) that also have a profound influence on 6-mercaptopurine tolerance and dose intensity in children with ALL. While these polymorphisms are rare, they are certainly important, with case reports of toxic deaths attributed to 6-mercaptopurine dating back several decades.

Children who were homozygous for one of the alleles require 6-mercaptopurine dose reductions of 91%, whereas heterozygotes require a dose reduction of approximately 50%. Children with dose reductions had equivalent overall survival when compared with children receiving full-dose 6-mercaptopurine, suggesting that TPMT polymorphisms are important for drug metabolism and toxicity but play no role in the pathogenesis of ALL. TPMT screening is recommended for children starting therapy with 6-mercaptopurine, with empirical dose reductions for those with genotypes associated with a deficiency. The addition of intermittent "pulses" of vincristine and a steroid (usually dexamethasone) to the antimetabolite backbone improves outcome and is encouraged in most modern continuation regimens.[12]

The optimal duration of maintenance therapy in both children and adults is unknown, but most regimens are given for 2 to 3 years; extension of the regimen beyond 3 years has not shown any additional benefit.

Central Nervous System Prophylaxis

❼ *CNS prophylaxis is necessary in any treatment regimen for ALL. At diagnosis, the incidence of CNS disease is less than 10%, but it increases to 50% to 75% after 1 year in patients without CNS prophylaxis.*[3] *The justification for CNS prohylaxis is based on two clinical findings. First, many chemotherapeutic agents do not cross the blood-brain barrier easily. Second, the CNS is a frequent sanctuary for leukemia, and undetectable leukemic cells are present in the CNS in many patients at the time of diagnosis.*[6]

CNS prophylaxis relies on intrathecal chemotherapy (e.g., methotrexate, cytarabine, and corticosteroids), systemic chemotherapy with dexamethasone and high-dose methotrexate, and craniospinal irradiation (XRT) in selected high-risk patients.[11] Even though XRT is the most effective modality, its use is associated with learning disabilities, growth retardation, secondary brain tumors, and other complications. Thus intrathecal therapy largely has replaced cranial irradiation for all except patients at very high risk of CNS relapse.

The treatment of CNS leukemia has had a remarkable impact on the overall survival for childhood ALL. While also effective at reducing the incidence of CNS relapse in adults, CNS prophylaxis has not shown measurable effects on overall survival.[10]

Acute Lymphocytic Leukemia in Infants

Infants account for approximately 5% of all children with ALL, and they experience the worst prognosis of any group of children with the disease. These patients have several poor prognostic features at diagnosis, including hyperleukocytosis, hepatomegaly, splenomegaly, and CNS leukemia.[6] The bone marrow of infants at day 14 usually shows poor response to therapy. Infants with ALL have increased frequencies of cytogenetic abnormalities; 60% to 70% have a translocation that involves the *MLL* gene located at 11q23. The 11q23 breakpoint abnormality, t(4,11), is the most common structural karyotypic abnormality in infants with ALL. In vitro, blasts from infants with ALL showed greater drug resistance to prednisolone and L-asparaginase than those from older patients, although they are more sensitive to cytarabine.[12] Based on this information, several studies are testing the efficacy of intensified chemotherapy that includes high-dose cytarabine. Another achievement is the prevention of CNS relapse using intrathecal cytarabine in conjunction with high-dose systemic cytarabine. This combination has eliminated the need for cranial irradiation in this young population. Even with major advances in cure rates for the general pediatric ALL population, where survival is 80% or more, the long-term EFS of infants is only about 40% (Tables 92–8, 92–9).

Acute Lymphocytic Leukemia in the Elderly

The proportion of ALL in patients older than age 60 years constitutes between 16% and 31% of all adult leukemias. Treatment of adults largely has followed the conventional chemotherapeutic regimes used in childhood ALL. However, the intensification regimens common in childhood are not suitable for this population because of their associated toxicities in older patients. The adverse prognostic factor, the Philadelphia chromosome, occurs in 15% to 30% of adults and thus is more common in the over 60 age group.[17] Based on the experience achieved in CML, the use of imatinib, a potent inhibitor of the Ph^+-associated *BCR-ABL* tyrosine kinase, is becoming a common practice for these older adults. Results show that the combination of imatinib with conventional chemotherapy has improved remission rates compared with the use of conventional chemotherapy alone,

TABLE 92–8. Representative Chemotherapy Regimens for Pediatric Acute Lymphocytic Leukemia

Induction (1 month)
Intrathecal cytarabine on day 0
Prednisone 40 mg/m^2 per day or dexamethasone 6 mg/m^2 per day orally for 28 days
Vincristine 1.5 mg/m^2 per dose (max 2 mg) IV weekly for 4 doses
Pegaspargase 2,500 units/m^2 per dose IM for 1 dose or asparaginase 6,000 units/m^2 per dose IM Mon, Weds, and Fri for 6 doses
Intrathecal methotrexate weekly for 2–4 doses
Consolidation (1 month)
Mercaptopurine 50–75 mg/m^2 per dose orally at bedtime for 28 days
Vincristine 1.5 mg/m^2 per dose (max 2 mg) IV on day 0
Intrathecal methotrexate weekly for 1–3 doses
Patients with CNS or testicular disease may receive radiation
Interim maintenance (1 or 2 cycles) (2 months)
Methotrexate 20 mg/m^2 per dose orally at bedtime weekly
Mercaptopurine 75 mg/m^2 per dose orally daily on days 0–49
Vincristine 1.5 mg/m^2 per dose (max 2 mg) IV on days 0 and 28
Dexamethasone 6 mg/m^2 per day orally on days 0–4 and 28–32
Delayed intensification (1 or 2 cycles) (2 months)
Dexamethasone 10 mg/m^2 per day orally on days 0–6 and 14–20
Vincristine 1.5 mg/m^2 per dose (max 2 mg) IV weekly for 3 doses
Pegaspargase 2,500 units/m^2 per doses IM for 1 dose
Doxorubicin 25 mg/m^2 per dose IV on days 0, 7, and 14
Cyclophosphamide 1,000 mg/m^2 per dose IV on day 28
Thioguanine 60 mg/m^2 per dose orally at bedtime on days 28–41
Cytarabine 75 mg/m^2 per dose SC or IV on days 28–31 and 35–38
Intrathecal methotrexate on days 0 and 28
Consolidation option 2(3-week intervals for 6 courses on weeks 5–24)
Mercaptopurine 50 mg/m^2 per dose orally at bedtime
Prednisone 40 mg/m^2 per day for 7 days on weeks 8 and 17
Vincristine 1.5 mg/m^2 per dose (max 2 mg) IV on the first day of weeks 8, 9, 17, and 18
Methotrexate 200 mg/m^2 per dose IV + 800 mg/m^2 dose over 24 hours on day 1 of weeks 7, 10, 13, 16, 19, and 22
Intrathecal methotrexate on weeks 5, 6, 9, 12, 15, and 18
Late intensification (weeks 25–52)
Methotrexate 20 mg/m^2 per dose IM weekly or 25 mg/m^2 per dose orally every 6 hours for 4 doses every other week
Mercaptopurine 75 mg/m^2 per dose orally at bedtime
Prednisone 40 mg/m^2 per day orally for 7 days on weeks 25 and 41
Vincristine 1.4 mg/m^{2}w per dose (max 2 mg) IV on the first day of weeks 25, 26, 41, and 42
Intrathecal methotrexate on day 1 of weeks 25, 33, 41, and 49
Maintenance (12-week cycles)
Methotrexate 20 mg/m^2 per dose orally at bedtime or IM weekly with dose escalation as tolerated
Mercaptopurine 75 mg/m^2 per dose orally at bedtime on days 0–83
Vincristine 1.5 mg/m^2 per dose (max 2 mg) IV on days 0, 28, and 56
Dexamethasone 6 mg/m^2 per day orally on days 0–4, 28–32, and 56–60
Intrathecal methotrexate on day 0

Adapted from Leather HL, Bickert B. Acute Leukemias. In: DiPiro JT, Talbert RL, Yee GC, et al., (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 2458–2511.

although the effect on long-term disease-free survival is unclear. Improving the outcomes of these elderly patients with ALL continues to be a challenge.

Treatment: Acute Myelogenous Leukemia

As with ALL, the primary aim in treating patients with AML is to induce remission and thereafter prevent relapse. Treatment of AML is conventionally divided into two phases: induction and postremission. Despite several strategies to increase the intensity of therapy, the overall survival rate has reached a plateau at 50% to 60%, suggesting that further intensification of therapy will not improve survival rates greatly.[11]

Remission Induction

The goal of induction chemotherapy in AML is essentially identical to that in ALL: "Empty" the bone marrow of all hematopoietic precursors, and allow repopulation with normal cells. ❻*The combination of an anthracycline (e.g., daunorubicin, doxorubicin, or idarubicin) and the antimetabolite cytarabine forms*

TABLE 92–9. Chemotherapy for the Acute Leukemias

Agent/Major Uses	Class/Mechanism	Major Side Effects	Drug Interactions
Asparaginase (L-asparaginase; Elspar) Pegaspargase (Oncospar)[b] ALL	Antitumor enzyme, hydrolyzes L-asparagine in bloodstream, depriving tumor cells of the essential amino acid; results in inhibition of protein, DNA, and RNA synthesis and cell proliferation; derived from *Escharichia coli*	Hypersensitivity reactions (fever, hypotension, rash, dyspnea in 25%), much lower risk with polyethylene gycol form; low emetogenic potential; pancreatitis; decreased synthesis of proteins, clotting factors; CNS: lethargy	Increased toxicity has been noted when given concurrently with vincristine and prednisone. Decreased metabolism when used with cyclophosphamide. Increased hepatotoxicity when used with mercaptopurine.
Cylarabine (Ara-C; cytosine arabinoside; Cytosar U)[d] ANLL; ALL; Lymphomatous meningitis; NHL; MDS High-dose ara-C (HDAC) liposomal cytarabine (Depocyt) for intrathecal use for lymphomatous meningitis	Antipyrimidine antimetabolite; inhibits DNA polymerase with inhibition of DNA strand elongation and replication; activated in tumor cells in triphosphate form; competes with conversion of cytidine to deoxycytidine nucleotides, further blocking polymerization of DNA; leads to production of short DNS strands; cell-cycle specific (S phase): acts only on proliferating cells.	Myelosuppression; alopecia; moderate emetogen; worse with high dose (greater than 1 g/m^2) or IT administration; diarrhea; mucositis; flu-like syndrome with fever and arthralgias; rash often followed by desquamation on palms and soles *HDAC toxicities;* cerebellar direct neurotoxicity:ataxia, slurred speech, nystagmus; conjunctivitis (drug is excreted into tears and blocks corneal DNA synthesis)	Possible increased toxicity when given concurrently with alkylating agents, radiation, purine analogs, and methotrexate.
Daunorubicin (daunomycin, Dauno, Creubidine)[c] Liposomal daunorubicin (DaunoXome) ANLL; ALL; KS (liposomal)	Antitumor antibiotic; topoisomerase II inhibitor; DNA intercalator; free-radical formation (thought to be related to cardiac toxicity and tissue injury)	Myelosuppression (dose-related); mucositis (worse with continuous infusion); moderate emetogenic potential; alopecia; vesicant: severe extravasation injury; cardiac toxicities: *acute*—not related to cumulative dose; arrhythmias, pericarditis; chronic—cumulative injury to myocardium (total dose greater than 550 mg/m^2; lower total cumulative doses cause damage to myocardium in children (e.g., 350 mg/m^2)	
Etoposide (VP-16; Vepesid), Etoposide phosphate (Etopophos)[d] Testicular cancer; SCLC; NSCLC; ANLL; KS; HD; NHL; BMT preparative chemotherapy; gastric cancer	Plant alkaloid, epipodophyllotoxin; inhibits DNA binding activity of topoisomerase II, resulting in multiple DNA double-strand breaks	Myelosuppression; moderately emetogenic: may be worse with oral and high-dose regimens; alopecia; mucositis; hypotension: infusion rate-related; etoposide phosphate can be given IV push without hypotension risk; hypersensitivity reactions: especially common in children	Substrate of P-450 3A4 Cyclosporine may increase levels of etoposide.
Gemtuzumab ozogamicin (Mylotarg)[i]	Humanized anti-CD33 antibody linked to calicheamicin, a potent toxin; binding to the CD33 receptor results in internalization of the antibody-antigen complex; calicheamicin is then released intracellularly and exerts cytotoxicity by causing DNA double-strand breaks, resulting in cell death	Infusion reactions: fevers, chills, nausea, vomiting, hypotension, dyspnea; myelosuppression may be severe and prolonged; tumor lysis syndrome: WBCs should be reduced to less than 30,000/mm^3 prior to administration if possible, to decrease risk; increased liver function tests and bilirubin, hepatic veno-occlusive disease	

(Continued)

TABLE 92–9. Chemotherapy for the Acute Leukemias (*Continued*)

Agent/Major Uses	Class/Mechanism	Major Side Effects	Drug Interactions
Imatinib mesylate (Gleevec, STI 571)[d] CML (adults and pediatrics) ; GIST; Ph+ ALL	Tyrosine kinase inhibitor; relatively specific for the tyrosine kinase coded for by the *bcr-abl* translocation in CML patients	Moderate emetogenic potential: take with meals and a full glass of water; edema; periorbital edema is characteristic; pleural effusions, ascites, or pulmonary edema also occur; rash; diarrhea; neutropenia, thrombocytopenia (sometimes difficult to distinguish from CML-induced cytopenias); increased liver function tests	Drug interactions are minimal. Substrate of P450 3A4 Serum concentrations of imatinib may be increased by drugs which inhibit CYP3A4.
6-Mercaptopurine (Purinethol; 6-MP)[c] ALL	Antipurine antimetabolite; purine analog; inhibits DNA, RNA, protein synthesis; metabolized by xanthine oxidase	Myelosuppression: mild, anorexia, low emetoginic potential; dry skin rash, photosensivity; hepatotoxicity: jaundice and hyperbilirubinemia occur after 1–2 months of therapy and may be dose-limiting	Allopurinol can increase levels of mercaptopurine. Aminosalicylates may inhibit TPMT.
Methotrexate (MTX) ALL CNS leukemia (IT) Breast cancer NHL Osteosarcoma Head and neck cancer Bladder cancer Rheumatoid arthritis	Folic acid antagonist; inhibits dihydrofolate reductase (DHFR); blocks reduction of folate to tetrahydrofolate; inhibits de novo purine synthesis; results in arrest of DNA, RNA, and protein synthesis Leucovorin provides reduced folate to bypass the metabolic block	Myelosuppression: can be prevented with leucovorin rescue Mucositis: can be prevented with leucovorin Renal dysfunction: (high dose regimens) caused by precipitation of drug in renal tubules; hydration (3 L/m^2/day) and alkalinization of urine	Salicylates, sulfonamides, probenecid, and high dose penicillin may decrease clearance of methotrexate.
Vincristine (VCR, Oncovin)[b] ALL; HD; NHL; multiple myeloma; breast cancer; SCLC, KS; brain tumors; soft tissue sarcomas; osteosarcomas; neuroblastoma; Wilms' tumor	Antimicrotubule agent/vinca alkaloid; derived from periwinkle plant; disrupts formation of microtubules	Peripheral neuropathy: primary dose-limiting toxicity; motor sensory, autonomic, and cranial nerves may all be affected (paresthesias, ileus, urinary retention, facial palsies); may be irreversible; mild emetogen; SIADH; vesicant: extravasation injury	Vincristine levels may be increased when given with drugs that inhibit cytochrome P450 3A enzyme (itraconazole).

Adapted from McManus Balmer C, Wells Valley A, Iannucci A. Cancer Treatment and Chemotherapy. In: DiPiro JT, Talbert RL, Yee GC, et al., (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 2458–2511.

the backbone of AML induction therapy. The most common induction regimen (7 + 3) combines daunorubicin for 3 days with cytarabine on days 1 to 7. The remission rate for this combination is approximately 80% in children and younger adults but declines to 40% to 50% in patients older than 60 years of age.[6] Despite studies that have used alternative anthracyclines or substituted high-dose for conventional-dose cytarabine and added etoposide and/or thioguanine, the 7 + 3 regimen remains the standard induction regimen.

Postremission Therapy

Once an initial remission is achieved, further intensive therapy is imperative to prevent relapse. Induction therapy fails to provide adequate cell kill, and leukemia cells survive the initial treatment. Three options available for patients include high-dose chemotherapy, allogeneic bone marrow transplantation from an HLA-matched related or unrelated donor, and autologous bone marrow transplantation.[8]

Postremission Chemotherapy

Several cycles of intensive postremission chemotherapy combining non-cross-resistant agents given every 4 to 6 weeks improves disease-free survival. One of three cytarabine-based regimens has been used in current treatment programs, either alone or in combination with L-asparaginase, mitoxantrone, or etoposide. The following dosing schedule is used: 100 mg/m^2 per day for 5 days by continuous infusion (standard arm), 400 mg/m^2 per day for 5 days by continuous infusion (intermediate-dose arm),

or 3 g/m^2 twice daily over 3 hours on days 1, 3, and 5 (high-dose arm). The higher-dose regimen for cytarabine can be tolerated only by younger patients (less than 60 years of age). While the optimal number of courses remains to be determined, at least three are probably required.[11]

Gemtuzumab ozogamicin is a monoclonal antibody that binds to the CD-33 antigen. Almost all AML cells express this antigen. Phase I and II trials using this agent have shown some success, and current studies using this agent alone or with chemotherapy for the treatment of AML are ongoing.[18]

Allogeneic Hematopoietic Stem Cell Transplantation

Allogeneic hematopoietic stem cell transplantation (HSCT) has been used in the treatment of pediatric AML in first complete remission. In most clinical trials, the availability of HLA-matched sibling donors determined whether patients underwent HSCT as postremission treatment. To facilitate this process, it is important to obtain HLA typing on all younger patients with AML and siblings shortly after diagnosis. Patients who do not have an HLA-matched sibling will proceed to postremission therapy.

In HSCT, very high doses of chemotherapy with or without total-body radiation (TBI) are given in an attempt to potentiate leukemia cell kill. Hematopoiesis is restored by the infusion of stem cells harvested from an HLA-compatible donor, thereby rescuing the patient from the consequences of total aplasia.[13] It is the most effective antileukemic therapy currently available.

Transplantations from nonidentical sources have many complications, including graft-versus-host disease (GVHD), delayed or incomplete engraftment, and an increased likelihood of opportunistic infections that increase morbidity and mortality substantially. An immunologic effect of the donor marrow on residual host leukemic cells may translate into antileukemic activity, however, as indicated by the lower relapse rates in patients with GVHD. The graft-versus-leukemia (GVL) also accounts for the success of allogeneic HSCT.

Transplant-related mortality following matched-sibling allogeneic HSCT is 20% to 30% in most series. Complications from transplantation increase with age; therefore, patients older than 60 years of age are uncommonly considered to receive an allogeneic HSCT. Since the average age of AML patients is 65 years, it is obvious that most patients with this disease are not candidates for this form of therapy.

HSCT in first remission is often recommended for patients with a matched-sibling donor because of the lower relapse rate with transplant versus postremission chemotherapy. However, only 30% of patients will have an HLA-matched sibling. Some types of AML patients may be curable with conventional-dose chemotherapy alone. Thus indiscriminate use of allogeneic HSCT could reduce the rate and quality of survival in these individuals.

Autologous Hematopoietic Stem Cell Transplantation

Since the majority of AML patients lack a HLA-identical donor, investigators began to consider the use of the patient's own bone marrow, obtained while in CR, as a source of hematopoietic regeneration. However, relapse continues to be a problem secondary to the presence of residual disease in the graft. The **disease-free survival** for patients undergoing autologous bone marrow transplantation in first remission has been reported at 40% to 60%, with a relapse rate of 30% to 50%. Thus few investigators recommend the use of autologous transplantation, because it failed to improve outcome substantially versus standard postremission chemotherapy.[3,10]

CNS Therapy

The prevalence of CNS disease at diagnosis of AML ranges from 5% to 30% in various treatment series. Features associated with the risk of CNS leukemia include hyperleukocytosis, monocytic or myelomonocytic leukemia (FAB M4 or M5), and young age. In most cases, intrathecal cytarabine with or without methotrexate and systemic high-dose cytarabine provide adequate CNS prophylaxis.[3] Results from studies have shown that patients with CNS disease at diagnosis can be cured with intrathecal therapy alone without the use of cranial irradiation.[11]

Acute Myelogenous Leukemia in Infants

AML in infants younger than 12 months shows clinical and biologic characteristics different from AML in older children. The phenotype is more commonly monoblastic or myelomonoblastic (M4, M5), and the patients usually present with hyperleukocytosis. Extramedullary involvement is common, often involving skin and other organs. As in infant ALL, there is a high incidence of translocations involving the *MLL* gene in infant AML. The number of infant AML trials reported is limited, but the EFS is similar to that of older children with AML. This is in marked contrast to the outcomes for infants with ALL, for whom the EFS is much lower than in older children (Tables 92–8, 92–9).[19]

Acute Myelogenous Leukemia in the Elderly

AML is the most common leukemia in the elderly. In comparison with younger patients with the same disease, older adults have a poor prognosis and represent a distinct population with regard to disease biology. Older adults have a lower incidence of favorable chromosomal aberrations and a higher incidence of unfavorable aberrations.[9]

In older adults, AML is either more likely to arise from a proximal bone marrow stem cell disorder, such as myelodysplastic syndrome (MDS), or present as a secondary leukemia resulting from treatment with prior chemotherapy or radiation for an earlier malignancy. These forms of AML are notoriously less responsive to chemotherapy and thus have a lower CR rate and EFS.[20]

Older adults are not as tolerant of or as responsive to remission induction and consolidation chemotherapy as younger patients. Younger adults treated with a standard induction regimen of an anthracycline and cytarabine have approximately 70% probability of attaining a CR, whereas patients older than 60 years of age have only a 38% to 62% probability. Further, long-term survival for patients older than 60 years is only 5% to 15% compared with 30% DFS for younger adults.[9]

Treatment of Relapsed Leukemias

Relapse is the recurrence of leukemic cells at any site after remission has been achieved. Most relapses occur during treatment or within the first 2 years of its completion. The bone marrow is the most frequent site of relapse in both ALL and AML and accounts for 90% or more of relapses. Extramedullary relapse, such as the CNS and the testes, while once common, has decreased to 5% or less because of effective prophylaxis.[21]

Bone marrow relapse predicts a poor outcome for most patients. In either ALL or AML, the duration of the second remission depends on the duration of the first remission. Factors predicting a relapse and poor prognosis for children with ALL are short initial remission, T-cell immunophenotype, high leukocyte count at relapse, t(9;22), and other high-risk features. Once a patient has obtained a second remission with conventional chemotherapy, allogeneic HSCT is the therapy of choice. For patients without an HLA-matched sibling, matched unrelated marrow or cord blood transplantation may be a reasonable alternative. The combination of myeloablative high-dose chemotherapy and the graft-versus-leukemia effect is thought to offer the best chance of survival in either AML or ALL.

Complications of Treatment

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is an oncologic emergency that is characterized by metabolic abnormalities resulting from the death of blast cells and the release of large amounts of purines, pyrimidines, and intracellular potassium and phosphorus. Uric acid, the ultimate breakdown product of purines, is poorly soluble in plasma and urine. Deposition of uric acid and calcium phosphate crystals in the renal tubules can lead to acute renal failure. Many patients with acute leukemia, especially those with a high tumor burden, are at risk for TLS during the first few days of chemotherapy. Measures to prevent TLS include aggressive hydration, alkalinization to help solubulize uric acid, allopurinol, and on some occasions, the use of rasburicase. Rasburicase is an enzyme that catalyzes the oxidation of uric acid to allantoins, which are more soluble and excreted more easily than uric acid.[22] Given its high cost, rasburicase generally is restricted to patients with a high WBC count (greater than $50 \times 10^3/\mu L$, $50 \times 10^9/L$) and uric acid levels greater than 8 g/dL (476 μmol/L).

Infection

Infection is a primary cause of death in acute leukemia patients. The majority of chemotherapy used to treat ALL and AML can cause severe myelosupression, placing the patient at risk for sepsis from otherwise normal bacteria. It is important to recognize that symptoms and signs of infection may be absent in a severely immunosuppressed or neutropenic patient. Fever (greater than 38.3°C, 100.9°F) in a neutropenic patient is a medical emergency. Following chemotherapy, the period of neutropenia usually reaches its nadir approximately 14 days after the beginning of a course of chemotherapy and usually lasts another 7 to 14 days. In a newly diagnosed leukemic, the period of neutropenia may persist until remission is obtained. The most common sites of infection include the gastrointestinal tract and vascular access devices.[6]

Because the progression of infection in neutropenic patients can be rapid, empirical antibiotic therapy should be administered quickly to such patients once fever is documented. Currently, the most commonly used initial antibiotic agent is cefipime, a fourth-generation cephalosporin that has good antipseudomonal coverage as well as adequate coverage against *viridans* streptococci and pneumococci.[23]

❻ *The therapy for AML is extremely myelosuppressive. Children with AML have a 10% to 20% induction mortality rate secondary to infection and bleeding complications.* Therefore, patients receiving induction therapy usually are hospitalized for the first 4 to 6 weeks of therapy. The induction therapy for ALL is less myelosuppressive; therefore, these patients recover their counts quicker and usually do not require prolonged hospitalizations.[6]

Trimethoprim-sulmethoxazole is started in all patients with acute leukemia for the prevention of *Pneumocystis carrinii* pneumonia. Patients normally continue this therapy for 6 months after completion of treatment. The use of additional antibiotic prophylaxis is not encouraged in all patients with leukemia because of concerns for antibiotic resistance.

Secondary Malignancies

In children, secondary malignancies are a risk of the successful treatment for cancer. The chemotherapy agents used, especially alkylating agents and topoisomerase II inhibitors, predispose the patient to secondary hematopoietic neoplasms. As the aggressiveness of treatment and the number of survivors of ALL increase, the risk of secondary neoplasms also may rise. There are two different types of second malignancies: acute leukemia, which generally is myeloid in orgin (or myelodysplastic syndrome), and solid tumors. The latency period between treatment and the development of a secondary leukemia is often several years, with leukemia being the earlier and solid tumors being the later of such events.

Secondary neoplasms induced by epipodophyllotoxins are characterized by balanced chromosomal translocations and short latency periods (2–4 years). The risk of this leukemia is related to schedule (dose intensity) and the concomitant use of other agents (L-asparaginase, alkylating agents, and possibly antimetabolites). The prognosis for topoisomerase II inhibitor–related secondary leukemia is extremely poor. Only about 10% of these patients survive after chemotherapy, and only 20% survive after HSCT. The incidence of second cancers attributed to alkylators peaks 4 to 6 years after exposure and plateaus after 10 to 15 years. Higher cumulative doses and older age at the time of treatment are risk factors for this type of cancer.[24]

Ionizing radiation therapy is also a cause of secondary malignancies. These secondary tumors generally develop within or adjacent to the previous radiation field. These cancers often have

a prolonged latency, typically 15 to 30 years, but shorter latencies (5–14 years) are known. Higher doses of radiation and younger age are associated with an increased risk of secondary malignancy.

Unlike children, adults may have other factors that predispose them to secondary malignancies. Lifestyle choices such as tobacco use, alcohol use, and diet have been implicated in influencing the development of secondary neoplasms in the adult population.

Now that 80% or more of children survive their primary cancers, the incidence of secondary neoplasms may increase. Recognizing this potential, many treatment regimens for children are being modified appropriately to reduce exposure to alkylators, topoisomerase inhibitors, and radiation. Late effects clinics screen for secondary malignancies and other disease and treatment-related disabilities that accompany childhood cancer. Similar screening and educational opportunities are not currently established in adult survivors.

Late Effects

❽ *With increased success in pediatric clinical trials, the overall survival rate for pediatric cancers has increased significantly over the last 35 years. For certain disease states, the overall survival rate for specific pediatric malignancies is now up to 80%. Unfortunately, the consequences of success are that approximately two-thirds of childhood cancer survivors have at least one chronic or late-occurring complication of treatment.* Long-term follow-up of survivors treated decades ago also has revealed very late sequelae.[24]

In leukemia, the intensified use of methotrexate and glucocorticoids is responsible for causing an increased frequency of neurotoxicity and, in older children and adults, avascular necrosis of bone. High cumulative doses of anthracyclines can cause cardiomyopathy. Cranial irradiation causes neuropsychologic deficits and endocrine abnormalities that lead to obesity, short stature, precocious puberty, and osteoporosis.[3] As newer and more intensive treatments enter clinical trials, close observation for long-term side effects will assume even greater importance.[24]

Supportive Care

Because of the need for repeated venous access, a central venous catheter or infusion port is placed prior to starting treatment. These devices are useful not only for delivery of chemotherapy but also to support patients during periods of myelosuppression. Infection and bleeding complications are the primary cause of mortality in patients with leukemia.

Platelet transfusions are used to prevent hemorrhage. Patients with uncomplicated thrombocytopenia can be transfused when the platelet count falls below 10,000/μL (10×10^9/L). Patients who are either highly febrile or actively bleeding may require transfusions at higher levels. Red blood cell transfusions generally are not necessary for a hemoglobin concentration greater than 8 g/dL (80 g/L, 4.96 mmol/L).

There is much controversy regarding the routine use of colony-stimulating factors (e.g., G-CSF and GM-CSF) in neutropenic patients. Even though several clinical trials have shown the time to absolute neutrophil count (ANC) recovery is increased with a colony-stimulating factor, none have demonstrated that CSFs stastistically influence infection-related mortality. At present, the use of colony-stimulating factors (G-CSF most commonly) generally is limited to those chemotherapy regimens that place the patient at highest risk for prolonged neutropenia.[6]

OUTCOME EVALUATION

Developing strategies for the treatment and monitoring of acute leukemias begins with risk stratification. Knowing the likely risk determines the aggressiveness and length of therapy. First to monitor for is remission status following the induction phase of treatment. Failure to obtain morphologic bone marrow remission by day 28 is a bad prognostic sign that dictates further induction treatment. For those with morphologic remission, quantification of submicroscopic residual disease (MRD) is being used increasingly as a prognostic factor.

It is important to develop a plan to educate patients and families about their drugs and doses. If modifications are necessary secondary to toxicity or inadequate response, establish a plan for treatment change. Remember that individual patients often do not fit the "average" patient profile, and dose modifications frequently are needed. The practitioner should be familiar with dosing ranges, WBC count, and other parameters that indicate "appropriate" treatment response. Based on response to prior phases of treatment, the clinician should recognize potential toxicities in subsequent phases of treatment with the same or different drugs at similar or different doses.



Patient Care and Monitoring

1. Evaluate the patient for response to therapy during induction, consolidation, and maintenance by following hematologic indices closely.
2. Review the treatment plan closely with the patient.
3. Educate the patient on potential adverse reactions and drug interactions.
4. Stress the importance of medication compliance.
5. Provide patient education regarding disease state and drug therapy:

- Possible complications of leukemia, especially infectious.
- Potential side effects of drug therapy that may occur
- Warning signs to report to the physician (e.g., temperature, bruising, or bleeding).

6. Based on WBC counts during ALL maintenance, is the patient receiving the appropriate dose of mercaptopurine?
7. Provide education regarding the long-term sequelae associated with the treatment for the acute leukemias.

ABBREVIATIONS

ALL:	acute lymphocytic leukemia
AML:	acute myeloid leukemia
BFM:	Berlin-Frankfurt-Munster
CR:	complete remission
CSF:	colony-stimulating factor
DFS:	disease-free survival
EFS:	event-free survival
FAB:	French-American-British classification system
G-CSF:	granulocyte colony-stimulating factor
GM-CSF:	granulocyte-macrophage colony-stimulating factor
GVHD:	graft-versus-host disease
GVL:	graft-versus-leukemia (effect)
HLA:	human leukocyte antigen
HSCT:	hematopoietic stem cell transplantation
MDS:	myelodysplastic syndrome
MRD:	minimal residual disease
MUD:	matched unrelated donor
OS:	overall survival
Ph^+:	Philadelphia chromosome
WBC:	white blood cell
WHO:	World Health Organization

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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93 Chronic Leukemias and Multiple Myeloma

Amy M. Pick and Timothy R. McGuire



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Explain the role of the Philadelphia chromosome in the pathophysiology of chronic myelogenous leukemia (CML).
2. Describe the natural history of chronic myelogenous leukemia (CML).
3. Identify the clinical signs and symptoms associated with chronic myelogenous leukemia (CML).
4. Discuss treatment options for chronic myelogenous leukemia (CML) with special emphasis on imatinib.
5. Describe the clinical course of chronic lymphocytic leukemia (CLL).
6. Describe patients who may be observed without treatment and those who receive aggressive treatment for chronic lymphocytic leukemia (CLL).
7. Discuss the various treatment options available for chronic lymphocytic leukemia (CLL).
8. Describe the clinical presentation of multiple myeloma.
9. Discuss treatment options available for multiple myeloma.

Key Concepts

❶ A chromosomal translocation, the Philadelphia chromosome, is responsible for chronic myelogenous leukemia (CML).
❷ The Philadelphia chromosome results in the formation of an abnormal fusion gene, *BCR-ABL*, that encodes an overly active tyrosine kinase.
❸ Allogeneic stem cell transplantation is the only curative treatment for chronic myelogenous leukemia (CML).
❹ Imatinib is a tyrosine kinase inhibitor that produces high complete response rates and is first-line treatment for chronic myelogenous leukemia (CML).
❺ Chronic lymphocytic leukemia (CLL) can have a variable disease course, but most patients survive many years.
❻ Chemotherapy does not improve overall survival in early-stage chronic lymphocytic leukemia (CLL).
❼ Fludarabine-based chemotherapy is used increasingly as first-line therapy for younger patients with chronic lymphocytic leukemia (CLL).
❽ Chronic lymphocytic leukemia (CLL) patients who receive fludarabine-based combination chemotherapy and rituximab may have long-term disease-free survival.
❾ Myeloma is a plasma cell cancer associated with bone disease that can be improved by bisphosphonates.
❿ Autologous transplant either as a single or double transplant offers younger patients with myeloma longer disease-free survival.

CHRONIC LEUKEMIA

Chronic leukemia consists of a number of disorders, including chronic myelogenous leukemia (CML) and chronic lymphocytic leukemia (CLL).

CHRONIC MYELOGENOUS LEUKEMIA

CML is a hematologic cancer that results from an abnormal proliferation of an early myeloid **progenitor** cell.[1] The clinical course of CML has three phases: chronic phase, accelerated

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TABLE 93–1. Clinical Course of CML

Phase	Characteristics	Median Duration (with Treatment)
Chronic	Elevated WBC count Responsive to treatment	4–6 years[a]
Accelerated	Elevated WBC count Unresponsive to treatment Increased symptoms	6–9 months
Blast	Disease transformation to acute leukemia	3–6 month survival

[a]Prior to imatinib therapy

phase, and **blast** crisis. Chemotherapy can be used to control CML in the chronic phase, but as the disease progresses, the cancer may no longer respond to treatment. Blast crisis resembles acute leukemia, and immediate aggressive treatment is required. Table 93–1 describes each of the phases of CML.

Epidemiology and Etiology

It is estimated that 4570 new cases of CML were diagnosed in 2007, accounting for 15% of all adult leukemias.[2] The incidence of CML increases with age, with the median age of diagnosis in the fifth decade of life.[3] In most newly diagnosed cases, the etiology cannot be determined, but high doses of ionizing radiation and exposure to solvents such as benzene are recognized risk factors.

Pathophysiology

Cell of Origin

CML arises from a defect in an early progenitor cell. Several cell lines may be affected, including myeloid, erythroid, megakaryocyte, and rarely, lymphoid lineages. These cells remain functional in chronic-phase CML, which is why patients in this phase are at low risk for developing infectious complications.

Ph Chromosome

❶ *The Philadelphia chromosome (Ph) results from a translocation between chromosomes 9 and 22, leaving a shortened chromosome 22.* ❷ *The Ph results in the formation of an abnormal fusion gene between the breakpoint cluster region and the Abelson protooncogene (BCR-ABL) that encodes an overly active tyrosine kinase. The loss of control of tyrosine kinase activity causes abnormal cellular proliferation and inhibition of apoptosis.*[3,4] Molecular tools such as reverse transcriptase polymerase chain reaction (RT-PCR) and fluorescence in situ hybridization (FISH) are used in the detection and monitoring of CML.[3]

Clinical Presentation and Diagnosis



Clinical Presentation

Signs and Symptoms

- Approximately 50% of patients are asymptomatic at diagnosis.[5]
- Symptoms may include fatigue, fever, weight loss, and bleeding.
- Organomegaly consisting of splenomegaly and hepatomegaly is common.

Diagnostic Procedures

- Peripheral blood smear
- Bone marrow biopsy (required for diagnosis)
- Cytogenetic studies
- Molecular testing (RT-PCR and FISH)

Laboratory Findings

- Peripheral blood smear
  - Leukocytosis (WBC count greater than $100 \times 10^3/\mu L$, or $100 \times 10^9/L$)
  - Thrombocytosis (approximately 50% of patients in chronic phase)
  - Anemia
  - Presence of blasts
- Bone marrow
  - Hypercellularity with presence of blasts
  - Presence of Ph

Poor Prognostic Factors (Sokal Risk Model)[6]

- Older age
- Splenomegaly
- High percent blasts in the blood
- High platelet count

Treatment

Desired Outcome

The primary goal in the treatment of CML is to eradicate the Ph-positive clones. Elimination of the Ph is termed *cytogenetic complete remission.* If treatment produces RT-PCR-negative disease, this is termed *molecular complete remission* and indicates a several-log reduction over cytogenetic complete remission. An early goal of therapy is to achieve *hematologic complete remission* or to normalize peripheral blood.

General Approach to Treatment

There have been significant advances in the treatment of CML. The success of therapy depends in part on the clinical phase of the disease. Nearly all patients with CML are treated initially with imatinib. Hydroxyurea may be used after diagnosis to rapidly reduce high white blood cell (WBC) counts and to prevent complications associated with large numbers of circulating neutrophils. Imatinib also can reduce peripheral WBC counts over

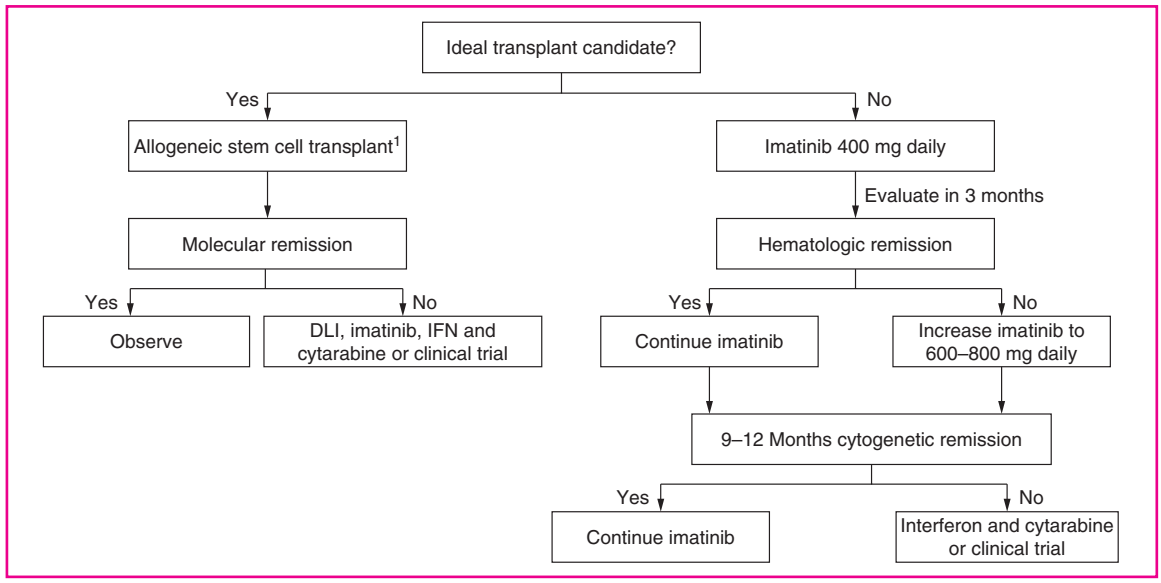


FIGURE 93–1. Algorithm for primary therapy in newly diagnosed CML patients. DLI, donor lymphocyte infusion; IFN, interferon.
[1]Nearly all patients will have had a course of imatinib prior to transplant.

several weeks; thus many patients are started on imatinib alone. Interferon-alfa is not used in newly diagnosed patients and is used largely in patients who do not respond to imatinib therapy. **Allogeneic** stem cell transplantation is the only curative therapy for CML and is used in younger patients with a matched donor. Figure 93–1 illustrates one common method of clinically managing CML patients.

Nonpharmacologic Therapy

Allogeneic Stem Cell Transplantation

❸ *Allogeneic stem cell transplantation is the only curative treatment option for CML.*[5] It is an option for younger patients (younger than 50 years of age) in chronic-phase CML who have an HLA-matched donor. Cure rates are superior when patients are transplanted in chronic phase within the first year of diagnosis and may be as high as 70%.[5,12] Unfortunately, only 30% to 40% of patients will be candidates for transplantation. There are significant risks associated with allogeneic transplantation, with a 10% to 20% early mortality (100 days).[12] Patients also may have a significant decline in quality of life from chronic **graft-versus-host disease** and other long-term complications associated with allogeneic stem cell transplantation. For those patients who do not achieve a molecular complete remission or have a relapse after transplantation, the infusion of donor lymphocytes usually will place the patient back into a durable remission.

Pharmacologic Therapy

Imatinib Mesylate (Gleevec®)

The treatment of CML has experienced a dramatic change since the introduction of imatinib. ❹ *Imatinib mesylate (STI-571; Gleevec®) is a tyrosine kinase inhibitor used as first-line therapy in the majority of patients with CML.* As a potent tyrosine kinase inhibitor, imatinib inhibits phosphorylation of various proteins involved in cell proliferation. Imatinib works by binding to the ATP-binding pocket of *BCR-ABL*.[7] The drug induces complete hematologic responses in more than 95% of patients and complete cytogenetic responses in about 80% of patients in chronic phase.[8] Most patients have traces of the disease when measured by RT-PCR and are not cured of their disease.

As expected in more aggressive disease, lower response rates are reported in the accelerated phase and blast crisis.[9,10] The clinical dosing of imatinib depends on the phase, with 400 mg/day used in chronic phase and 600 to 800 mg/day in accelerated phase and blast crisis (see Table 93–2). Therapy with imatinib generally is well tolerated. Common side effects include **myelosuppression** (phase and dose related), rash, nausea, edema, fatigue, arthralgias, myalgias, and headaches. Imatinib is metabolized by cytochrome CYP3A4, and possible drug interactions include those agents which inhibit or induce CYP3A4, such as erythromycin, ketoconazole, and phenytoin.[11]

Interferon-Alfa and Cytarabine

Prior to the introduction of imatinib, the combination of interferon-alfa and low dose cytarabine was the nontransplant treatment of choice for patients in chronic phase CML. The precise mechanism of action of interferon-alfa remains unknown. The addition of cytarabine to interferon-alfa improves the response compared with interferon alone. This combination produces cytogenetic response rates of 30%, much lower than imatinib.[13] One of the major drawbacks, in addition to the low response rates, is interferon's toxicity,

TABLE 93–2. Drugs Used in CML

Drug	Adverse Effects	Comments
Imatinib mesylate (Gleevec, STI 571)	Neutropenia, thrombocytopenia, rash, nausea, edema, fatigue, arthralgias, myalgias, headache, increased liver function tests	Dose range: 400–800 mg orally per day depending on phase Take with meals and a full glass of water Drug interactions: Metabolized by CYP450 3A4 (e.g., cyclosporine, erythromycin, itraconazole, phenytoin, St. John's wort)
Interferon-alfa (Intron A, Roferon-A, IFN)	Flulike symptoms: fever, chills, myalgias; fatigue; depression; insomnia; thrombocytopenia	Premedicate with acetaminophen or a NSAID to lessen flulike symptoms. Dose is given subcutaneously or intramuscularly daily.

including flulike symptoms, depression, and thrombocytopenia. Today, interferon-alfa and cytarabine remain an alternative therapy for patients who do not respond to imatinib and are not candidates for stem cell transplantation.

Outcome Evaluation

Successful treatment for CML depends on the elimination of the Ph. Allogeneic transplant offers a cure for the minority of patients who have a matched donor and are young enough to tolerate transplant. Nearly all newly diagnosed CML patients are placed on imatinib. If patients fail to obtain a cytogenetic response within 9 to 12 months, dose escalation of imatinib or a switch to alternative therapies is recommended.[14] Patients who do not respond to imatinib and cannot be transplanted should be encouraged to enroll in investigational trials. Some patients will not respond to imatinib and will progress to blast crisis, where they will receive treatment for acute leukemia.



Patient Encounter 1

A 40-year-old woman well known to you comes into your pharmacy complaining of fatigue. You suggest she see her doctor to have some blood work done. A complete blood count (CBC) shows the following:

- Total WBC count: 158 × 10^3/μL (158 × 10^9/L), 20% (0.20) blasts, 70% (0.70) segs, 10% (0.10) lymphs
- HgB/Hct: 9 g/dL (5.6 mmol/L), 32% (0.32)
- Platelets: 650 × 10^3/μL (650 × 10^9/L)
- Bone marrow biopsy: Hypercellular; FISH is positive for Ph.

- What is the treatment of choice for this chronic-phase CML patient?
- How would you evaluate response to therapy?
- If this patient has suboptimal response to initial therapy, what would you recommend?

CHRONIC LYMPHOCYTIC LEUKEMIA

CLL is a cancer that results in the accumulation of functionally incompetent lymphocytes.[15] CLL is considered an indolent, incurable disease in which treatment should be initiated when patients have symptoms. However, some patients have aggressive disease and need to be treated with intensive therapy.

Epidemiology and Etiology

CLL is the most common type of leukemia diagnosed in adults. It is estimated that in 2007, 15,340 new cases were diagnosed in the United States.[2] Median age at diagnosis is the sixth decade, with the incidence increasing with age. The etiology of CLL is unknown, but hereditary factors may have a role, with family members of CLL patients having a two- to sevenfold increased risk of CLL.[3]

Pathophysiology

Cell of Origin

CLL is characterized by small, relatively incompetent B lymphocytes that accumulate in the blood and bone marrow over time. The exact cell of origin is controversial but has been described as an antigen-activated B lymphocyte.[3]

Clinical Course

❺ *CLL can have a variable clinical course, with survival ranging from months to decades.* Low-risk disease is asymptomatic, and median survivals exceed 10 years; intermediate risk is associated with lymphadenopathy and has median survivals of about 7 years; and high-risk patients with anemia have median survivals of only 3 years.[16,17] The typical low-risk patient is an elderly person without symptoms who is diagnosed on routine blood draw. The typical high-risk patient is middle-aged, and symptoms have brought the patient to his or her physician.

Clinical Presentation and Diagnosis



Clinical Presentation

Signs and Symptoms
- Fatigue, chills, bleeding, and lymphadenopathy
- Chronic infections owing to immature lymphocytes
- Organomegaly consisting of splenomegaly and hepatomegaly

Diagnostic Procedures
- Peripheral blood smear
- Bone marrow biopsy
- Cytogenetic studies
- Molecular testing

Laboratory Findings
- Peripheral blood
  - Leukocytosis
  - Anemia
  - Thrombocytopenia
  - **Hypogammaglobulinemia**
  - Bone marrow: Must have at least 30% lymphocytes.

Poor Prognostic Factors
- Lymphocytosis with accompanying
  - Anemia [hemoglobin less than 11 g/dL (110 g/L, 6.8 mmol/L)]
  - Thrombocytopenia (platelets less than 100×10^3 /μL, 110 g/L or 100×10^9/L)
- *ZAP-70* mutation

Prognostic Factors

Two staging systems, Rai's and Binet's, have been developed to help practitioners determine the overall prognosis of patients with CLL. They are comparable systems and useful when broadly determining good, intermediate, and poor prognostic disease.[16,17] These systems are less useful in accurately determining prognosis in an individual patient. Increasingly, molecular characteristics of the disease such as cytogenetics and ***ZAP-70* expression** are being used to predict likely clinical course.[18]

Treatment

Desired Outcome

The primary goals in the treatment of CLL are to provide palliation of symptoms and to improve overall survival. Since the current treatments for CLL are not curative, reduction in tumor burden and improvement in disease symptoms are reasonable end points, particularly in older patients. A response to therapy can be evaluated by a resolution of lymphadenopathy and organomegaly, normalization of peripheral blood counts, and elimination of lymphoblasts in the bone marrow.

Nonpharmacologic Therapy

❻ *Chemotherapy does not improve overall survival in early-stage CLL.* In addition, deferring therapy until a patient becomes symptomatic does not alter overall survival.[19,20] For this reason, the notion of "watch and wait" is considered reasonable for older patients with indolent disease.

Stem Cell Transplantation

Stem cell transplantation is an option for younger patients. Currently, allogeneic transplant offers longer disease-free remissions than **autologous** transplantation, but neither has demonstrated the ability to cure patients.[30] Several factors must be considered before allogeneic transplantation. The lack of a donor, older age, and poor performance status make transplant an uncommon procedure in this population. In addition, early mortality after allogeneic transplant can be as high as 40% in CLL.[31] Reduced-intensity allogeneic transplant may reduce this high early mortality, but it is unclear whether it will produce long-term disease-free survival.

Pharmacologic Therapy

Single-Agent Chemotherapy

The treatment for CLL has changed with the development of the purine analog fludarabine (Fludara®) (see Table 93–3). Historically, chlorambucil (Leukeran®), an alkylating agent, was considered standard treatment for CLL. ❼ *Today, fludarabine-based chemotherapy is used as first-line therapy for younger patients with CLL.* Randomized clinical trials have shown that fludarabine is superior to chlorambucil in achieving higher response rates and producing a longer duration of response (CR 20% versus 4%, respectively).[20] Fludarabine is effective in previously untreated patients, as well as in patients who have chlorambucil-resistant disease.[21]

The most commonly used dose for fludarabine is 20 mg/m^2 intravenously daily for 5 consecutive days, whereas chlorambucil can be taken daily as an oral tablet with the dose ranging from 4 to 10 mg/day.[21] Fludarabine is associated with more toxicities than chlorambucil, including myelosuppression and prolonged immunosuppression.[19] Resulting infectious complications may occur during the periods of prolonged immunosuppression. The ease of administration and limited side effects make chlorambucil a practical option for symptomatic elderly patients who require palliative therapy.

Monoclonal Antibodies

Rituximab (Rituxan®) Rituximab is a chimeric monoclonal antibody directed against the CD20 molecule on B lymphocytes.[21] Similar to other B-cell malignancies, CLL

TABLE 93–3. Drugs Used in CLL

Drug	Adverse Effects	Comments
Alemtuzumab (Campath)	Infusion-reactions: fever, chills, nausea, vomiting; rash hypotension; prolonged immunosuppression (resulting in infectious complications)	Antiviral and PCP prophylaxis should be initiated during treatment. Premedicate with acetaminophen, diphenhydramine, with or without a steroid to alleviate infusion-related reactions. Subcutaneous dosing may lessen acute toxicity. Initially 3 mg/day as a 2-hour infusion, increase to 10 mg/day, then 30 mg/day as tolerated.
Chlorambucil (Leukeran)	Myelosuppression; allergic reactions (skin rash); secondary malignancies	Take on an empty stomach because food decreases absorption. Dose range: 4–10 mg PO daily.
Fludarabine (Fludara)	Myelosuppression; prolonged immunosuppression resulting in secondary infectious complications; edema; neurotoxicity	Dose: 20 mg/m^2 IV daily for 5 days.
Rituximab (Rituxan)	Infusion reactions: fever, chills, rigors, hypotension	Premedicate with acetaminophen, diphenhydramine, with or without a steroid to alleviate infusion-related reactions. Rate of infusion should be increased gradually to minimize reactions.

expresses CD20 surface markers. Rituximab alone can induce partial responses in untreated and previously treated CLL patients.[22,23] Dose-escalation studies suggest that higher doses are required than those used in non-Hodgkin's lymphoma; however, the typical 375 mg/m^2 dose is still used commonly.[24] The higher doses which may be used in CLL is probably a combined effect of lower CD20 expression and higher concentrations of soluble CD20 than in non-Hodgkin's lymphoma.[25] Combination therapies with rituximab result in higher complete responses than rituximab alone.[26] The most commonly observed side effects of rituximab include infusion reactions consisting of fever, chills, hypotension, nausea, vomiting, and headache.[23] Premedication with diphenhydramine and acetaminophen is recommended to minimize infusion reactions.

Alemtuzumab (Campath®) Alemtuzumab is a humanized monoclonal antibody directed against CD52.[27] CD52 is expressed on the majority of B and T lymphocytes. Alemtuzumab is FDA approved as a single agent for the treatment of CLL in patients who have failed alkylating agents and fludarabine. It is being evaluated in combination with other CLL therapies. Infusion-related reactions can be significant and typically occur with the initial dose and lessen in severity with subsequent doses. To limit acute allergic reactions, subcutaneous administration may be given instead of intravenous dosing. Premedication with oral antihistamines and acetaminophen is recommended. Since alemtuzumab also suppresses T cells, prolonged immunosuppression is a major toxicity. Infectious complications may occur from the reactivation of cytomegalovirus and herpes virus and from infection with *Pneumocystis*. Patients should receive trimethoprim-sulfamethoxazole and famciclovir or valacyclovir to prevent these infections.[21,27]

Combination Therapy

❽ *Combination therapy may provide improvement in long-term disease-free survival.* The combination of fludarabine, cyclophosphamide, and rituximab improves CR rates compared with fludarabine alone (70% versus 20%) but at the expense of increased infections.[28,29] Combinations of fludarabine and alemtuzumab are also being investigated, with the hope of improving overall survival.[21]

Outcome Evaluation

Successful treatment in the older CLL patient depends on the reduction of malignant lymphocytes. Treatment often begins when a patient becomes symptomatic. A desirable response to therapy includes a reduction in lymphocytes, decrease in stage of the disease, and resolution of symptoms. Since CLL is not a curable disease, palliation of symptoms is a reasonable goal in older patients, and aggressive therapies are reserved for younger patients with high-risk CLL.

MULTIPLE MYELOMA

❾ *Multiple myeloma is a malignancy of* ***plasma cells*** *that is characterized by an abnormal production of a monoclonal protein. Features of the disease include bone lesions, anemia, and*



Patient Encounter 2

A 72 year-old man presents to his primary care physician for his yearly check-up. He reports feeling fine over the past year. A physical examination appears normal, but the patient had an abnormal WBC count of $20 \times 10^3/\mu L$ ($20 \times 10^9/L$) with 80% (0.80) lymphocytes. The bone marrow examination reports 60% (0.60) lymphocytes, and the diagnosis of CLL is made.

- What treatment approach do you recommend?
- Would your treatment options change if the patient becomes symptomatic? If so, what are your new options?

renal insufficiency.[32] Multiple myeloma is an incurable disease; however, advancements in the treatment of myeloma have extended survival significantly.

Epidemiology and Etiology

Multiple myeloma is the second most common hematologic malignancy. It is estimated that approximately 19,900 new cases of multiple myeloma were reported in 2007, accounting for 1% to 2% of all cancers.[2] The median age at diagnosis is 68 years, but a small percentage of those diagnosed are under age 45. The incidence of myeloma is highest in African Americans and lowest in Asians, and the disease occurs more frequently in men than in women.[32] The etiology of multiple myeloma is unknown.

Pathophysiology

The pathogenesis of multiple myeloma is poorly understood but must be distinguished from a condition called *monoclonal gammopathy of unknown significance* (MGUS), which is characterized by a monoclonal immunoglobulin without malignant plasma cells. Yearly, about 1% of patients with MGUS will develop multiple myeloma. The pathophysiology of multiple myeloma involves complex bone marrow microenvironment and cytokine interactions. Interleukin 6, tumor necrosis factor, vascular endothelial growth factor, and stroma-derived factor 1 support the establishment and proliferation of myeloma cells.[32,33] It is the understanding of these interactions that has led to the newer agents used in the treatment of multiple myeloma.

Clinical Presentation and Diagnosis



Clinical Presentation

Signs and Symptoms
- Fatigue (anemia)
- Bone pain (fractures, lytic lesions)
- Recurrent infections
- Renal failure

Diagnostic Procedures
- Peripheral blood smear
- Serum protein electrophoresis and immunofixation
- Urine protein electrophoresis and immunofixation
- Radiologic evaluation (MRI, bone densitometry)
- Bone marrow biopsy (required for diagnosis)
- Cytogenetic studies
- Molecular testing

Laboratory Findings
- Peripheral blood
  - Monoclonal protein in serum (usually IgG or IgA)
  - High β_2-microglobulin
  - Low platelets and hemoglobin
  - High creatinine, urea, LDH, C-reactive protein, and calcium
- Urinalysis: **Bence-Jones protein**
- Bone marrow
  - Plasma cells (greater than or equal to 10%)
  - Abnormal cytogenetics
- Other findings: Bone lesions, fractures, osteoporosis

Poor Prognostic Factors
- High serum β_2-microglobulin and low serum albumin
- Elevated C-reactive protein
- Elevated LDH
- IgA isotype
- Low platelet count
- Chromosome 13 deletions and other cytogenetic abnormalities

Prognostic Factors

Prognostic factors include tumor load and patient performance status. High β_2-microglobulinemia, high lactate dehydrogenase (LDH), and extensive plasma cell infiltration of the bone marrow are all poor prognostic factors and are indicative of high tumor load. The older-aged patient, renal impairment, and other comorbidities also predict for poorer outcome.[34] Increasingly, chromosomal changes are being used to predict the high-risk patient, with perhaps the most important being deletion of the long arm of chromosome 13.[33]

Treatment

Desired Outcome

The primary goal in the treatment of multiple myeloma is to decrease tumor burden and minimize complications associated with the disease. A "watch and wait" approach is an option for asymptomatic patients who have no lytic lesions in the bone. Once symptoms occur, treatment is required. Chemotherapy can be used to reduce tumor burden in patients with symptomatic disease, but increasingly, immunomodulators such as thalidomide and dexamethasone are initial therapy. Almost all patients will become refractory to initial treatment and will require the use of salvage therapies such as bortezomib. Autologous stem cell transplantation prolongs overall survival in patients who can tolerate high-dose chemotherapy and may be the treatment of choice for many patients.

Nonpharmacologic Therapy

⓾ *Autologous stem cell transplantation results in higher response rates and extends overall survival compared with those who receive conventional therapy such as vincristine, doxorubicin, and dexamethasone (VAD).* Since overall median survival is prolonged from 42 to 54 months, stem cell transplant should be considered in all patients who can tolerate high-dose chemotherapy.[40] High-dose melphalan is the most common preparative regimen. Two sequential transplants (tandem transplants) improve overall survival in patients who do not have a good response after one transplant.[41] The use of maintenance therapy after autologous transplantation with thalidomide or bortezomib is under investigation.

Pharmacologic Therapy

Conventional-Dose Chemotherapy

Patients who present with symptomatic disease will be started on therapy. Two regimens used are VAD and melphalan and prednisone (MP). VAD like chemotherapy regimens are used most often in transplant candidates because it avoids the alkylating agent melphalan, thus minimizing damage to the stem cell compartment. These two regimens produce equivalent response rates of approximately 50% to 70% in previously untreated patients with myeloma (see Table 93–4).[35,36]

Corticosteroids

High-dose dexamethasone (40 mg/day) is an option for patients who cannot tolerate chemotherapy or have few high-risk features. Response rates are approximately 40% to 50% in previously untreated patients.[37] Advantages of this regimen include ease of administration and lack of hematologic adverse effects.

Thalidomide (Thalomid®)

Thalidomide as monotherapy or combination therapy is beneficial in the treatment of multiple myeloma. The precise mechanism of action of thalidomide is unknown, but its antimyeloma activity may be due to its **antiangiogenic** and

TABLE 93–4. Drugs Used in Multiple Myeloma

Drug	Adverse Effects	Comments
Bortezomib (Velcade)	Constipation, decreased appetite, asthenia, fatigue, fever, thrombocytopenia, dose-related, reversible peripheral neuropathy	Dose: 1.3 mg/m^2 IV bolus twice weekly for two weeks; week 3 off; repeat
Dexamethasone	Hyperglycemia, edema, adrenal cortical insufficiency	Dose given orally once daily
Doxorubicin (Adriamycin)	Myelosuppression, alopecia, cumulative dose-limiting toxicity, myocardium damage	Given in combination with vincristine and dexamethasone (VAD)
Lenalidomide (Revlimid)	Possible birth defects (since analogue of thalidomide), neutropenia, thrombocytopenia, deep vein thrombosis, pulmonary embolism, pruritis, fatigue	Dose is 10 mg orally taken with water once daily Women of childbearing age must use two forms of contraception Pregnancy test must be taken before and during use
Melphalan (Alkeran)	Myelosuppression, secondary malignancies, pulmonary fibrosis, sterility, alopecia	Dose of 0.15 mg/kg for 7 days given orally once daily, repeated every 4–6 weeks IV formulation used for stem cell transplantation
Thalidomide (Thalomid)	Severe birth defects, peripheral neuropathy, deep vein thrombosis, somnolence, constipation	Start at 50 mg by mouth daily and titrate to a maximum of 800 mg; doses are taken nightly Women of childbearing age must use two forms of contraception Pregnancy test must be taken before and during use
Vincristine (Oncovin)	Dose limiting toxicity: peripheral neuropathies, paresthesias, constipation, alopecia	Given in combination with doxorubicin and dexamethasone (VAD)

anticytokine properties.[33] Thalidomide may be given in combination with dexamethasone, resulting in greater response rates than when given alone. Thalidomide and steroid combinations produce responses in 60% to 80% of previously untreated patients.[37] Common side effects of thalidomide therapy include somnolence, constipation, peripheral neuropathy, and deep vein thrombosis. Prophylactic anticoagulation should be considered to prevent deep vein thrombosis associated with thalidomide therapy. There are substantial teratogenic effects of thalidomide if used during pregnancy.[33]

Bortezomib (Velcade®)

Bortezomib is a member of a new class of agents known as **proteosome** inhibitors. Proteosome inhibitors induce myeloma cell death by modulating ***NF-κB*** products, including inflammatory cytokines and adhesion molecules that support myeloma cell growth. Approved for the treatment of relapsed disease, bortezomib has been shown to produce response rates of 35% in heavily pretreated individuals.[38] Side effects of bortezomib include fatigue, nausea, peripheral neuropathy, and hematologic effects.[33] Currently, the investigation of bortezomib in untreated patients is underway, with preliminary results indicating about an 80% response when it is used in combination with steroids, thalidomide, or cytotoxic agents.[39]

Lenalidomide (Revlimid®)

Lenalidomide is an immunomodulating agent related to thalidomide that was recently approved for the treatment of patients with multiple myeloma and myelodysplastic syndrome (MDS). Lenalidomide lacks the common side effects of thalidomide, such as constipation and peripheral neuropathy. Interim analyses of two phase III trials show that lenalidomide in combination with dexamethasone produces higher response rates than dexamethasone alone in relapsed and refractory myeloma. Adverse effects of lenalidomide include diarrhea, nausea, muscle cramps, hematologic side effects and deep vein thrombosis.[42]

Bisphosphonates

❾ *Bone disease is a common manifestation of multiple myeloma. Bisphosphonates should be initiated in symptomatic patients with bone lesions to slow osteopenia and reduce the fracture risk associated with the disease.* Pamidronate and zolendronic acid have equivalent efficacy in the management of osteolytic lesions, but because of relative ease of administration, zolendronic acid is used most frequently.[43] The use of zolendronic acid decreases pain and bone-related complications and improves quality of life. The suggestion that bisphosphonates have direct antimyeloma activity, based on the ability to inhibit *NF-κB* signaling, remains controversial. Recent cases of osteonecrosis of the jaw have been a major concern. Risk factors are unclear, but osteonecrosis of the jaw is more common in patients receiving intravenous administration of bisphosphonates and having dental procedures performed. It is recommended that patients have dental restoration work done prior to starting bisphosphonate therapy.[43]

WALDENSTRÖM'S MACROGLOBULINEMIA

Waldenström's macroglobulinemia is a rare immunoglobulin disorder that is associated with non-Hodgkin's lymphoma. Approximately 4 per 1 million individuals are affected with the disease. Waldenström's is characterized by an elevation of serum IgM and involvement of the lymph nodes, bone marrow, and spleen. Patients typically are asymptomatic at the time of diagnosis, with the disease being discovered by routine laboratory examination. Similar to indolent lymphomas, the "watch and wait" approach is employed for asymptomatic patients. Symptomatic patients experience anemia, fatigue, hepatosplenomegaly, lymphadenopathy, and hyperviscosity syndrome. When these symptoms arise, treatment is necessary, with the goal being palliation. Systemic therapy includes alkylating agents, nucleoside analogs, and rituximab. These treatment options have similar efficacy. Treatment often is continued until a desired response (reduction in symptoms) is achieved. **Plasmapheresis** may be required in addition to systemic therapies in the treatment of hyperviscosity syndrome.[44]

Outcome Evaluation

Newly diagnosed, asymptomatic patients may be observed without treatment. This asymptomatic period may last for months to a couple years. All patients with multiple myeloma will become symptomatic, and once this occurs, treatment is required. First-line treatment may be one of several therapies, including VAD, thalidomide plus steroids, and autologous transplant. Nearly all patients will progress at some point, and second-line therapy usually will include bortezomib. All patients who have bone lesions should receive monthly bisphosphonates, with the hope of reducing pain and fractures.



Patient Encounter 3

A 50-year-old male presents with fatigue and back pain. A CBC reveals the following: hemoglobin 8.7 g/dL (87 g/L, 5.4 mmol/L), platelets $128 \times 10^3/\mu L$ ($128 \times 10^9/L$), corrected calcium 11.8 mg/dL (2.95 mmol/L), serum creatinine 1.4 mg/dL (124 μmol/L), and serum IgG 3500 mg/dL (35 g/L; normal 620–1500 mg/dL, or 6.2–15 g/L). A subsequent bone marrow biopsy confirms multiple myeloma.

- Given this information, identify treatment options.
- Discuss whether this patient is a candidate for autologous stem cell transplantation.



Patient Care and Monitoring

CML

1. Patients are placed on imatinib at the time of diagnosis. Patients should be monitored for a dose-dependent myelosuppression, GI intolerance, edema, and rash. Drug interactions with CYP450 3A4 inducers are clinically important and should be monitored.
2. An increase in imatinib dose may be required if patients have no hematologic response at 3 months or no complete cytogenetic response at 9 to 12 months.
3. Early in the diagnosis, patients should be evaluated for allogeneic stem cell transplantation. Ideal candidates include younger patients in chronic-phase CML who have an HLA-matched related or unrelated donor.

CLL

1. Observation is reasonable if the patient is asymptomatic.
2. Monitor WBC count, and watch for infection if patients are receiving chemotherapy.
3. Watch for infusion reactions with rituximab and alemtuzumab. Premedicate with acetaminophen and diphenhydramine to prevent these reactions.
4. Prophylactic trimethoprim-sulfamethoxazole is recommended for all patients receiving alemtuzumab.

Multiple Myeloma

1. During chemotherapy, monitor myeloma monoclonal protein in urine and serum, renal function, hemoglobin, and platelets.
2. Bisphosphonates should be initiated in patients with lytic bone lesions. Renal function must be monitored. Patients may need pain medication for bone pain.
3. If a reduction in myeloma protein is not seen on one chemotherapy regimen, another regimen should be used.
4. Evaluate the patient for adverse effects, including peripheral neuropathy and deep vein thrombosis. Prophylactic anticoagulation therapy should be considered in thalidomide or lenalidomide based therapy.

ABBREVIATIONS

CLL:	chronic lymphocytic leukemia
CML:	chronic myelogenous leukemia
CR:	complete response
FISH:	fluorescence in situ hybridization
HLA:	human leukocyte antigen
MGUS:	monoclonal gammopathy of undetermined significance
MP:	melphalan-prednisone
Ph:	Philadelphia chromosome
RT-PCR:	reverse-transcriptase polymerase chain reaction
VAD:	vincristine-doxorubicin-dexamethasone
WBC:	white blood cell

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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94 Skin Cancer

Trinh Pham



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Identify the risk factors associated with skin cancer.
2. Describe the common signs and symptoms of skin cancer and identify the features of a mole that are suspicious for melanoma.
3. Identify the key features in the different stages of melanoma and their correlation with prognosis.
4. Explain the goals of therapy for the treatment of nonmelanoma and melanoma skin cancer.
5. Devise a plan of lifestyle modifications for the prevention of skin cancer.
6. Discuss the pros and cons of interferon-α therapy for melanoma, and formulate a monitoring plan for patients receiving interferon-α.
7. Discuss the pros and cons of interleukin 2 therapy for melanoma, and formulate a monitoring plan for patients receiving interleukin 2.
8. Discuss the different treatment options for melanoma with brain metastasis.
9. Discuss the role of temozolomide in the treatment of stage IV melanoma with or without central nervous system (CNS) metastasis.
10. Discuss the different treatment options for nonmelanoma skin cancer.

Key Concepts

❶ Exposure to ultraviolet radiation from the sun is recognized as one of the primary triggers for skin cancer development.

❷ Staging of malignant melanoma is important to determine prognosis, categorize patients with regard to metastatic potential and survival probability, and aid in clinical decision making.

❸ Determination of lymph node status is important in melanoma staging because it is an independent prognostic factor, and it provides the oncologist with guidance for therapy decisions.

❹ Surgery is the primary treatment modality for nonmelanoma and melanoma skin cancer.

❺ Stage IIB, IIC, and III melanoma are considered to be high risk because of their potential for recurrence and distant metastasis. The primary treatment modality is surgical excision of the tumor and a lymphadenectomy for patients with positive lymph nodes.

❻ Interferon-α2b is approved by the Food and Drug Administration (FDA) as adjuvant therapy for high-risk melanoma. It is controversial if it should be offered to every patient at high risk for recurrence.

❼ Stage IV melanoma is not curable, and the primary goal of therapy is local control of the disease and relief of identifiable symptoms.

❽ Interleukin 2 therapy is approved by the Food and Drug Administration (FDA) for the treatment of metastatic melanoma, and it is a reasonable option for patients with this stage of the disease.

❾ Combination chemotherapy or biochemotherapy increases toxicity significantly without offering overall survival benefit; thus they are not standard of care for stage IV melanoma.

❿ Brain metastasis is common in melanoma, and treatment options for brain metastasis include surgery, radiation, and chemotherapy. The choice of therapy depends on the number of metastatic lesions, accessibility of the lesions for surgery, the presence of neurologic symptoms, and the status of extracranial disease.

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Skin cancer is the most prevalent of all malignancies occurring in humans, and in the United States it accounts for more than 50% of all cancers.[1] The most common cutaneous malignancies are basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and malignant melanoma (MM). BCC and SCC are categorized as nonmelanoma skin cancer. Worldwide, the incidence of nonmelanoma skin cancer (NMSC) and MM is increasing at a rate of 3% to 8% per year in fair-skinned Caucasian populations.[2] The mortality rate for MM is on the rise in North America, Australia, and New Zealand at pace of 2% to 4% annually.[2] Ultraviolet (UV) radiation exposure is the leading environmental factor causing skin cancer.[3] This is a modifiable risk factor, and prevention of skin cancer development is possible through a sun protection regimen that includes wearing protective clothing, avoidance of prolonged, intense sun exposure, and regular application of sunscreen. If skin cancer is detected in its early stage, survival is improved, and the disease is curable. Therefore, campaigns for primary and secondary prevention of skin cancer are important in combating this tumor. NMSC and MM differ with regard to prognosis, metastatic potential, mortality, curability and treatment options. This chapter will review the pathogenesis and risk factors for the development of skin cancer and provide current data on the recommendations for the prevention and treatment of both NMSC and MM.



Patient Encounter, Part 1

KM is a 71-year-old man being evaluated in the dermatology clinic for a recent change in a mole on his shoulder. The mole has been on his shoulder for as long as he can remember. A year ago it began to itch, and his wife noted that it seemed to be getting darker in color. On physical examination, it is noted that the primary lesion is a nodule, the border is ragged and irregular, and it is brown, black, and white in color. There is no oozing, bleeding, or crusting around the lesion. A couple of years ago, he had a complete excision of an in situ melanoma on his back.

KM has light-brown hair, blue eyes, and fair skin. He has a history of numerous severe blistering sunburns in his childhood. As a teenager and young adult, he spent many hours outdoors as a construction worker and a lifeguard. He lives with his wife in Denver, Colorado, and they enjoy outdoor activities such as hiking, skiing, and canoeing. He does not have a family history of melanoma.

- What are KM's risk factors for malignant melanoma?
- What information is suggestive of malignant melanoma?
- What should be done to confirm the diagnosis of malignant melanoma?
- How is the stage of the melanoma determined?
- What primary prevention measures are recommended to prevent skin cancer?

EPIDEMIOLOGY AND ETIOLOGY

Nonmelanoma Skin Cancer

NMSC accounts for nearly half of all newly diagnosed cancers in the United States each year, and it is estimated that more than 1 million cases will be diagnosed in 2006.[1] The true prevalence of NMSC may be underestimated because it is treated in outpatient settings, and no formal reporting to cancer registries is required.[4] BCC is the most common form of NMSC in Caucasians and comprises 75% of newly diagnosed NMSC. SCC accounts for 20% of NMSC.[4] NMSCs occur at a lower incidence in darker-skinned people or in descendants of African, Asian, and Mediterranean countries. In African Americans, the most common form of NMSC is SCC.[5] The majority of NMSCs are curable, and the mortality rate is low; cure rates approach 98%, and the overall 5-year survival rate is greater than 95%.[5] **Metastasis** occurs in less than 0.1% of BCCs compared with an average of 3.6% of SCCs. Seventy-five percent of all NMSC deaths are attributed to SCC.[5] NMSC is associated with considerable morbidity owing to functional and cosmetic deformity. In addition, it is an economic burden to the health care system because costs associated with NMSC treatment are estimated at approximately US$426 million per year.[6]

Malignant Melanoma

Malignant melanoma is ranked as the fifth most common cancer among men and sixth most common cancer in women.[1] In 2006, it is estimated that 62,190 new cases of invasive melanoma will be diagnosed. MM is a major public health problem of significant worldwide concern because of its dramatic rise in incidence and mortality. In the United States in 1935, the lifetime risk of melanoma was estimated at 1 in 1500; in 2002, the lifetime risk was 1 in 68 persons.[2] In Australia, the country with the highest incidence of melanoma in the world, the hazard is even higher at an estimated lifetime risk of 1 in 25 persons.[7] The incidence of melanoma is not evenly dispersed among all populations. Race, gender, and age confer different incidence rates.[7] Caucasians have higher risks than Asians, Hispanics, and African Americans.[7] The rate of MM is 10 times higher in whites than in African Americans.[1] From 1985 to 1994, data from the United States National Cancer database show that African Americans comprise 5.4% and Hispanics 3.4% of total melanoma cases.[8] MM generally occurs in the young, and it is diagnosed primarily in the third or fourth decades of life.[8] Sixty-two percent of cases are diagnosed before patients reach 65 years of age, and the median age of death is 67 years.[9] Overall, in the United States, males have higher incidence rates than females.[8] The incidence rises with age, and older men have the highest melanoma risk in the United States.[8]

Risk Factors (Table 94–1)

The maintenance of cellular homeostasis involves a balance of cell division, differentiation, senescence, and apoptosis.

TABLE 94–1. Risk Factors for the Development of Skin Cancer[10]

Exogenous/Environmental Factors	Endogenous/Host Factors	
UV Radiation exposure	**Age (Older)**	
History of blistering sunburn	**Surrogate Measures of Sun Sensitivity**	
Ionizing radiation	Red or blonde hair	RRM = 2.4
Chemical carcinogens	Blue eyes	RRM = 1.6
Arsenic (BCC)	Fitzpatrick Skin (Type I)	RRM = 1.7
Hydrocarbons, soot, tobacco (SCC)	Tendency to develop freckles	RRM = 2.5
Human papilloma virus	Fair skin	
(HPV 6,11, 16, 18) (SCC)	**Family History**	
	Three or more first-degree relatives affected	RRM = 35–70
	Three or more first-degree relatives affected	RRM = 3
	Presence of Nevi	
	Benign melanocytic nevi (greater than 100)	RRM = 11
	Familial dysplastic nevus syndrome	RRM = 11
	Congenital melanocytic nevi	
	Previous Skin Cancer	
	Previous melanoma	RRM = 8.5
	Previous nonmelanoma skin cancer	RRM = 2.9
	Immunosuppression	
	Transplant recipients	RRM = 3
	AIDS patients	RRM = 1.5
	Inherited Medical Disorders	
	Gorlin's syndrome (BCC)	
	Xeroderma pigmentosum (BCC)	
	Genetic Mutations	
	CDKN2A, CDK4, B-RAF (MM)	
	P53 (NMSC)	
	PTCH gene, *Bcl-2* (BCC)	

RRM, relative risk for melanoma; BCC, basal cell carcinoma; NMSC, nonmelanoma skin cancer; MM, malignant melanoma.

Cancer occurs when the growth and function of cells are "out of control" in relation to normal tissue. The combination of genetic alterations and environmental toxins is the most frequent contributor to the process of carcinogenesis. In the development of skin cancer, the risk factors are categorized as environmental (solar UV radiation), genetic (family history), immunosuppression, and previous history of melanoma.[10]

Environmental

Ultraviolet Radiation Exposure

❶ *Exposure to ultraviolet radiation from the sun is recognized as one of the primary triggers for skin carcinogenesis.* Based on their wavelengths, UV radiation is divided into three components: UVA (320–400 nm), UVB (280–320 nm), and UVC (200–280 nm).[15] UVB accounts for only 5% of the solar radiation that reaches the earth, but it is the primary carcinogenic component in the UV spectrum.[15] The following sequence of events describes the process in which UV radiation causes skin cancer: (1) UV radiation reaches the earth, and on the skin, it reaches the cells in the epidermal layer (i.e., squamous cells, basal cells, and melanocytes),[16] (2) the UV radiation (specifically UVB) is absorbed by DNA in the cells and may induce DNA lesions by forming dimers between neighboring pyrimidine bases, resulting in the development of cyclobutane pyrimidine dimers (CPDs) and pyrimidine-pyrimidone(6-4) photoproducts,[17] and (3) if this critical step of damage to the DNA is not repaired, gene mutations may transpire, leading to carcinogenesis.[17] Another mechanism of UV radiation–induced DNA damage is via generating reactive oxygen species (ROS), e.g., 8-hydroxydeoxyguanosine (8-OHdG), which can cause oxidative stress to DNA base pairs. The DNA damage from ROS increases with increasing wavelength over the UV band; therefore, exposure to UVA radiation may be more critical in this pathway.[17] Other modes of DNA damage caused by UV radiation include protein-DNA cross-links and single-strand breaks.[17]

Greater exposure to solar UV radiation by the general population, owing to increased outdoor activities, changes in clothing style, longer lifespan, and ozone depletion, is thought to be a major reason for the rising number of skin cancer diagnoses.[4] It is estimated that 90% of NMSCs and 60% to 70% of MMs are linked to UV exposure.[18] Data from epidemiologic studies indicate that greater cumulative lifetime exposure is associated with a higher risk of developing SCC, whereas severe

sunburns and intense intermittent (recreational or vacation) exposure correlates more with BCC and MM.[9] Geography, as it relates to proximity to the equator, is also linked to melanoma. Among the Caucasian population, the risk of melanoma is inversely related to the distance from the equator.[9] The association between sun exposure and melanoma is not clearly defined, though, because cutaneous melanoma can arise frequently in areas of the body not exposed to the sun.[10]

Tanning Devices: Artificial Sunlamps

Tanning devices provide a source of artificial UV radiation, mainly UVA and UVB, and have been popular since the 1970s.[10] In a large cross-sectional study involving more than 10,000 United States children and adolescents and a telephone survey of more than 1000 people aged 11 to 18 years, it was revealed that at least 10% of the subjects have used a sun bed in the last year.[19,20] There are limited data on the effect of sunlamps or sunbeds on skin cancer risk. In order to assess if there is a correlation between MM and exposure to UV radiation through the use of sun beds, Young[21] conducted a review of 14 epidemiologic case-control studies in melanoma patients. The author concluded that although recent data demonstrate that there is a relationship between MM development and the use of tanning devices, the results are not overwhelmingly conclusive.[21] The same is true for analysis of studies assessing the risk of NMSC and tanning beds.[21] Nevertheless, since there is no clinical benefit to tanning and there is a possibility of an increased risk of skin cancer, some states and France have made the use of tanning beds illegal for anyone under the age of 18.[13]

Genetics and Family History

There is a strong correlation between a family history of MM and the development of MM, yet only 10% of melanoma cases report having a first- or second-degree relative with the diagnosis.[22] Patients with two or more family members with melanoma are significantly more likely to develop melanoma at a younger age and to develop multiple melanomas.[98] The inherited mutation of two highly penetrant melanoma genes has been identified in families with melanoma susceptibility: the *CDKN2A* gene (also known as *INK4/ARF, MTS1,* and *CDK1*) and the *CDK4* gene. The *CDKN2A* gene is located on chromosome 9 (9p21) and encodes for the p16 protein. The *CDK4* gene is located on chromosome 12 (12q13).[2] The *CDKN2A* mutation is present in 30% to 40% of families with three or more members affected by melanoma, and the risk of melanoma is between 50% and 90% by 80 years of age for those who have the mutation.[2] Worldwide, only three families have been reported to be carriers of *CDK4* mutation.[22]

Polymorphism of the *MC1R* gene on chromosome 16 (16q24), which is associated with red hair, also increases susceptibility to melanoma.[23] Mutations affecting the serine–threonine kinase *B-RAF* gene have been reported with high rates in individuals with MM.[24] The *RAF* serine–threonine kinases affect the mitogen-activated protein kinase (MAPK) pathway, mediating cell proliferation, angiogenesis, metastasis, and survival,[25] and confer growth advantage to melanoma cells.[16]

Most cases of BCC are sporadic; however; it occurs frequently in the rare individuals with hereditary disorders such as basal cell nevus syndrome (also known as *Gorlin's syndrome*) and xeroderma pigmentosum (XP). Gorlin's syndrome is an autosomal dominant condition manifesting as pitting of the palms and soles of the feet, jaw cysts, spine and rib abnormalities, calcification of the falx cerebri, and cataracts. XP is a DNA-repair-deficient syndrome.[16] The *patched* gene (*PTCH*), a tumor-suppressor gene, has been shown to be mutated in XP and 50% to 60% of sporadic BCCs.[17] The oncogene *bcl-2,* which suppresses programmed cell death (apoptosis), also has been found to be expressed in high levels in patients with BCC.[26]

Skin Cancer Phenotype

Generally, the phenotype that predisposes an individual to an increased risk of skin cancer is red or blond hair, blue eyes, and fair skin. These characteristics are surrogate measure of the sensitivity of the skin to sun exposure and the tendency to develop nevi, freckles, and sunburns based on the skin type. Freckles, which may appear abruptly after the first high dose of UV radiation sun exposure, represent clones of mutated melanocytes, and their presence is associated with an increased risk of melanoma.[12] The Fitzpatrick classification of skin type is used to determine the response pattern of the skin to UV radiation and assess the risk for melanoma. There are six Fitzpatrick skin types: Type I skin always burns and never tans, type II skin burns easily and tans rarely, type III skin burns sometimes and tans usually, type IV skin burns rarely and always tans, type V skin always tans and is moderately pigmented (brown), and type VI skin always tans and is darkly pigmented (black). Fitzpatrick I and II skin types are commonly affected by NMSC and MM. The susceptibility to skin cancer, both NMSC and MM, is related to the melanin content of the skin and the skin's response to UV radiation.

In individuals without a family history of melanoma (sporadic melanoma), the presence of benign melanocytic nevi (benign moles) is consistently identified as the strongest risk factor for the future development of melanoma.[9] The greater the number of benign nevi (greater than 20), the greater the susceptibility to melanoma growth.[15] There is an inverse relationship between melanin content, which correlates with the ability to tan, and incidence of skin cancers.[15] Melanin functions as a photoprotectant, and this is evidenced by the observation that people with skin types that tan poorly are more susceptible to sunburn, photoaging, and photocarcinogenesis.[12] For example, epidemiologic studies show that Scandinavians, who have fair complexions, have a low incidence of BCC because they have good tanning capacity. On the other hand, Irish people, who are also fair, have a higher incidence of BCC because they tan poorly.[15]

Another risk factor for the development of melanoma is having the dysplastic nevus syndrome (also known as *B-K syndrome, familial atypical mole,* or *Clark's nevus*). This is an autosomal dominant disorder with incomplete penetrance,[19] and the dysplastic nevus is a mole that shares clinical features common to melanoma. Microscopic examination of the nevi shows disordered proliferation of melanocytes with varying degree of atypia without evidence of invasion.[27] The nevi ranges from 6 to 15 mm in diameter, and an individual typically may have 25 to 75 abnormal nevi present on his or her body.[27] The cumulative lifetime risk for melanoma development in individuals with dysplastic syndrome is almost 100%.[27] Congenital melanocytic nevi are nevi that are present at birth, and the risk of developing melanoma is linked with the size of the nevus. Congenital melanocytic nevi that are less than 20 cm have a reported 0% to 4.9% lifetime risk for developing melanoma, and congenital melanocytic nevi that are larger than 20 cm have a lifetime risk of 4.5% to 10%.[20]

Age

Aging is a risk factor for skin carcinogenesis because the passage of time allows more instances for the initiation and promotion of tumor formation through exposure to UV radiation. Furthermore, the capacity to repair DNA decreases with age, and the capability to remove DNA photoproducts such as CPDs and pyrimidine-pyrimodone(6-4) from UV irradiated skin also diminishes with age, leading to an increased rate of genetic mutations.[18] These characteristics may account for the exponential increase in the incidence of NMSC and MM in the elderly population.[18]

The age of exposure to intense UV radiation and experience of severe sunburn has an important significance in the development of skin cancer. The process of skin carcinogenesis is initiated with sunburn episodes, especially when it occurs before the age of 15 years, and the manifestation of the skin cancer may be as late as 40 to 60 years later.[26] The incidence of BCC is more frequent after freckling and severe sunburn in childhood. Sunburns occurring in adulthood do not seem to be associated with BCC development.[17] The same is also true for melanoma, as demonstrated by studies that show that people who migrate to more sunny climates in the first decade of their lives have a higher risk for developing melanoma as compared with people who move as teenagers or young adults.[23]

Immunosuppression

There is clear evidence linking defects of the immune system to the development of NMSC. For example, it is observed that patients receiving chronic immunosuppressant therapy for organ transplantation have a 50% risk of developing SCC within 20 years of transplantation, and 30% of these cancers are highly aggressive.[21] Additionally, patients with human immunodeficiency virus (HIV) infection are predisposed to melanoma.[18] Data also support the idea that UV radiation exposure induces immunosuppression and that this is associated with carcinogenesis.[30] Langerhans' cells are responsible for antigen processing and initiation of the immune cascade in the skin, and it has been demonstrated that UVB alters their function.[30] UV radiation also induces suppressor T cells and activates biologic response modifiers by initiating cytokine cascades, ultimately leading to a state of immune tolerance and unsuppressed tumor growth.[22]

Other Risk Factors

Other factors associated with the risk of NMSC include exposure to ionizing radiation and arsenic, which is connected with BCC. Chemical carcinogens that give rise to NMSC include industrial hydrocarbons that are found in coal tars, soot, asphalt, paraffin waxes, and tobacco.[21] Exposure to the human papilloma virus (HPV-6, -11, -16, and -18) has been linked to SCC.[31] Lastly, a personal history of previous melanoma is a risk factor for developing another primary melanoma.

PATHOPHYSIOLOGY

Skin Anatomy

The skin contains three layers: the epidermis (top layer), the dermis (middle layer), and the subcutis (innermost layer).[23] The epidermis serves as a barrier to the environment to protect internal organs, and within its layers are squamous cells that produce keratin to provide its protective effect.[23] Melanocytes, cells that synthesize melanin, also reside in the epidermis.[23] Melanin is a brown-black pigment that is distributed to surrounding keratinocytes within the dermis and epidermis via dendritic projections.[18] The dermis gives the skin its strength, resiliency, and resistance to tearing.[23] It is made up of a dense network of collagen and elastic fibers that anchors hair follicles, sweat glands, blood vessels, and nerves. Basal cells separate the epidermis from the dermis, and these cells divide continually to replace the older cells that slough off the skin. The subcutis is composed of collagen and loose adipose connective tissue. It serves to conserve heat and act as a shock absorber to protect the inner organs[23] (Fig. 94–1).

NMSCs arise from epidermal keratinocytes and involve primarily squamous cells and basal cells of the epidermis and dermis skin layers. BCCs arise from basal cells or keratinocytes in hair follicles or sebaceous glands. MM involves the abnormal growth and proliferation of melanocytes and begins with the proliferation of a single melanocyte from within the epidermis. After a series of intraepithelial events, the melanocyte migrates to the dermis, possibly deeper into the cutis, and proliferates therein.[25] From within the dermis and subcutis, melanoma may metastasize and spread to distant sites via lymphatic and vascular channels.[25] The overwhelming majority of MMs originate from the skin, although they also may arise less commonly from the retina, meninges, or gastrointestinal tract.

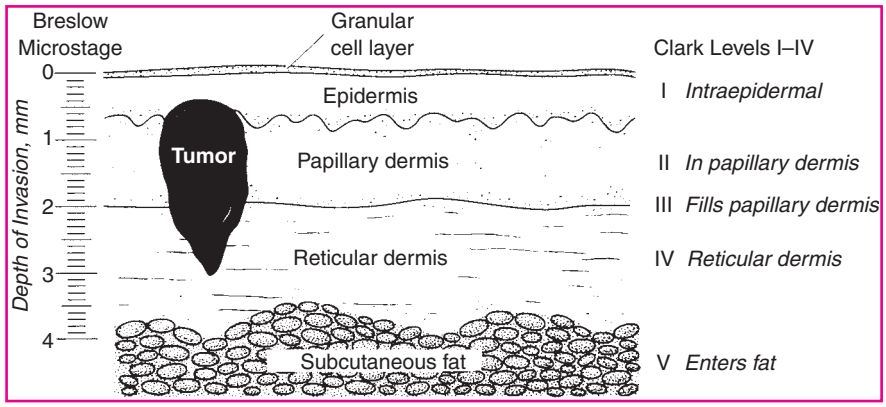


FIGURE 94–1. Skin anatomy: Breslow microstaging and Clark levels. (Reprinted from Langley RGB, Barnhill RL, Mihm Jr MC, et al. Neoplasms: Cutaneous melanoma. In: Freedberg IM, Eisen AZ, Wolff K, et al, (eds.) Fitzpatrick's Dermatology in General Medicine. 6th ed. New York: McGraw-Hill; 2003: 938.)

CLINICAL PRESENTATION AND DIAGNOSIS

Malignant Melanoma

There are four major subtypes of MM: *superficial spreading, nodular, lentigo maligna melanoma,* and *acral lentiginous* (Table 94–2). They each vary in clinical and growth characteristics. Superficial spreading melanoma is the most common histologic sub-type, and it occurs frequently in individuals in their 40s and 50s. When superficial spreading melanoma is confined to the epidermis, it is known as *melanoma in situ.* It has a long horizontal growth phase and may take months to years before it invades deeper into the skin vertically.[32] The most common sites of manifestation for this sub-type of MM are the trunk for men and the lower extremities for women.[9] These sites reflect the differences in skin exposure to sunlight by the clothing men and women wear.[9] Nodular melanoma is the second most common sub-type of MM, and it may occur at any age, although it usually arises in the fifth to sixth decade of life. It grows very rapidly without an identifiable horizontal growth phase and may be deeply invasive at the time of diagnosis. Nodular melanoma is associated with a poor prognosis. Clinically, it presents as an enlarging papule or nodule and often has a history of bleeding.[32] Lentigo maligna is an in situ form of MM before it thickens, becomes invasive, and transforms into lentigo maligna melanoma. The lifetime risk of transformation ranges from 5% to 50%, and it may take months to years for this to occur. The peak incidence for this sub-type of MM is in the seventh decade of life, and it usually arises on the surface of sun-damaged skin of an elderly person.[32] Acral lentiginous melanoma accounts for 50% of all MMs in blacks, Asians, and Hispanics; it comprises only 10% of MMs in Caucasians. The site of manifestation of this sub-type is unique because most lesions occur underneath the nails (subungual melanoma) and on the plantar aspect of the feet.[32]

Basal Cell Carcinoma

BCC has indolent growth characteristics, with a very low metastatic rate, ranging from 0.0028% to 0.55%.[5] Paradoxically, BCCs can cause extensive local destruction and significant disfigurement. Like MM, BCC is also divided into four main histologic subtypes: *nodular, superficial, morpheaform,* and *pigmented* (or *metatypical*) (see Table 94–2). Each sub-type has its own unique characteristic. The most common sub-type is nodular BCC, accounting for 50% to 55% of BCCs. Nodular BCC is mostly red or flesh-colored, but it also may be mistaken for MM because it shows variable amounts of pigmentation.[15] Superficical BCC accounts for 10% of all cases and is the least aggressive of all subtypes because it is very slow growing. Its appearance is similar to plaque, psoriasis, or eczema, and these benign disorders should be included as part of the differential diagnosis. Morpheaform BCC accounts for 2% to 5% of BCCs. It is the most aggressive sub-type because these tumors can be large and difficult to remove surgically.[5] Pigmented BCC may have melanin deposits and may be confused with aggressive melanoma.[5]

Squamous Cell Carcinoma

SCCs are more aggressive than BCCs (see Table 94–2). The rate of metastasis for SCC is 2% to 6% and may be as high as 10% to 14% in high-risk sites such as the ear and lip and 30% in the genital area.[5] SCCs are preceded by leukoplakia, actinic keratosis, radiation damage, or sun damage to the skin.[33] Actinic keratosis, a small papule that appears on areas of sun damage on the skin, has a 1 in 400 risk of transforming to SCC.[5] Common locations for SCCs are on the backs of the hands and the bare scalp. They also may appear on other less common sites such as the lips, ears, genitals, and soles of the feet.

Skin Examination

The *ABCD* acronym is a helpful mnemonic for recognizing the signs and symptoms of early MM (Fig. 94–2). It was devised in 1985 by clinicians working in the Melanoma Clinical Cooperative Group at New York University School of Medicine and is used to educate health care professionals who are not dermatologists in differentiating common moles from cancer.[34] It is

TABLE 94–2. Characteristics of Different Types of Skin Cancer[5, 8, 9, 20, 23]

	Malignant Melanoma				Nonmelanoma Skin Cancer	
	Superficial Spreading	**Nodular**	**Lentigo Maligna Melanoma**	**Acral Lentiginous**	**Basal Cell Carcinoma**	**Squamous Cell Carcinoma**
Frequency	70%	15–30%	4–10%	Less than 10%	60–80%	20%
Location	Trunk in men Legs in women Upper back	Trunk, head, neck	Sun-exposed areas, face	Palms of the hands, soles of feet, nailbeds	Head/neck trunk/lower limbs	Backs of the hand, bare scalp, lips, ears
Age/gender at presentation	Middle 40s Women more than men	Any age (fifth to sixth decades) Men more than women	70s Rare before 50	60s	Incidence increases after age 40	Incidence increases after age 40
Ethnicity	Caucasian	Caucasian	Caucasian	African-American, Asians, Hispanics	Most common in Caucasians, rare in dark-skinned people	Most common in African descendants
Initial growth	Radial	Pure vertical	Radial	Radial	Radial	Radial
Clinical features	Long horizontal growth phase, months to years before invading vertically. *Melanoma in situ*—confined to the epidermis.	Very aggressive without identifiable horizontal growth phase, deeply invasive at the time of diagnosis, associated with poor prognosis.	Lentigo maligna—in situ form of lentigo maligna melanoma; 5–50% transform to malignant melanoma.	50% of all melanomas in blacks, Asians, and Hispanics; 10% of melanomas in Caucasians.	Four subtypes: 1. Nodular BCC (50–55%), most common sub-type 2. Superficial BCC (10%), least aggressive 3. Morpheaform (2–5%), most aggressive 4. Pigmented or metatypical BCC	Usually presents as a painless, erythematous, poorly defined lesion with elevated borders.

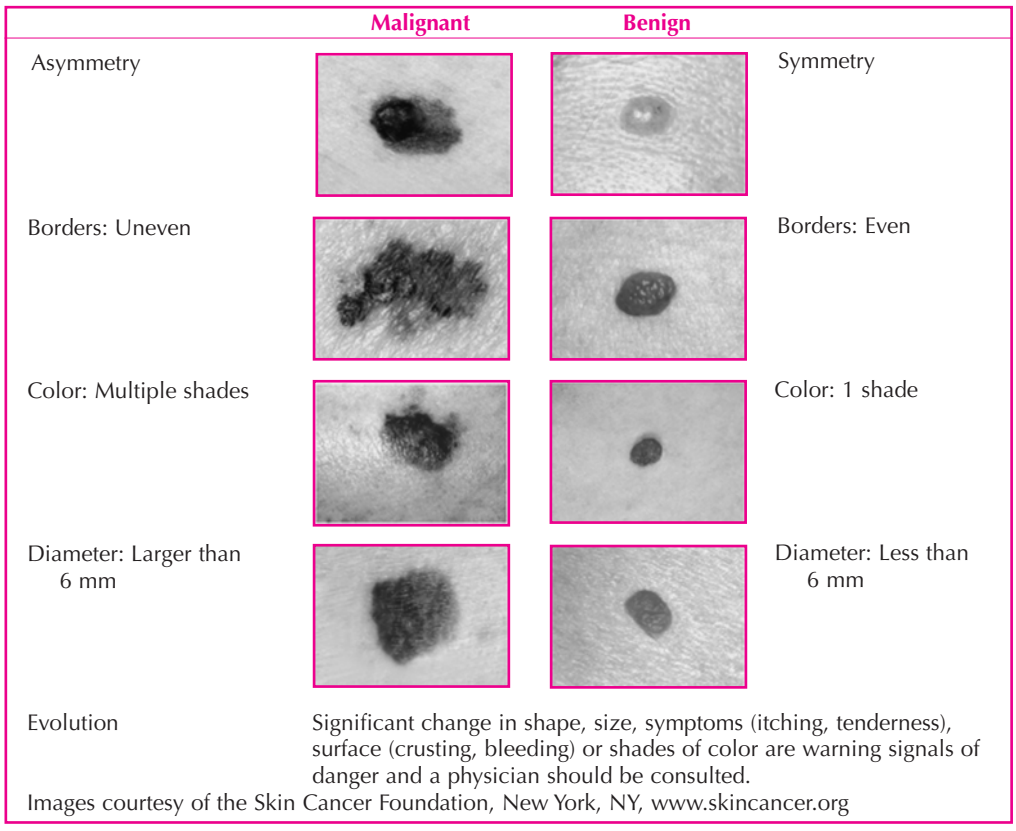


FIGURE 94–2. ABCDE features of early melanoma[25] images courtesy of the Skin Cancer Foundation, New York, NY, www.skincancer.org.

also a useful tool to educate the lay public to assess pigmented lesions and screen for suspicious moles to help identify the MM in its early stage when it is curable. It should be noted that this is only a guide. Not all MMs, including nodular melanoma, have all four ABCD characteristics, and it is not meant to provide a comprehensive list of all MM features. It should be noted that the nodular type may not fit ABCD characteristics.[34] The characteristics for each of the letters are described in the "Clinical Presentation" box. The newest letter that is being proposed to be added to the ABCD acronym is *E,* which stands for "evolving." Evolving lesions are those that have changed significantly in size, shape, symptoms (e.g., itching or tenderness), surface (e.g., crusting or bleeding), or shades of color.[34] Evolution of a lesion is one of the most important warning signs of danger in the assessment of moles for MM.

Early diagnosis of skin cancer is the key to improved prognosis. Diagnostic accuracy and clinical skills are two essential factors in the appropriate management of skin cancer. On presentation to a clinician's office, patients may offer a history of a new growth or an area of irritation. Conversely, the skin cancer may have been present for years undetected by the patient. The definitive diagnosis of any suspected cutaneous malignancy should be confirmed by a biopsy prior to treatment.

STAGING AND PROGNOSIS OF MELANOMA

Data from the Surveillance, Epidemiology, and End Results (SEER) study show that 82% of patients diagnosed with MM present with localized disease, 9% with regional disease, and 4% with distant disease.[7] ❷ *Once skin cancer is diagnosed, it is important to determine the stage of the cancer to find out if the cancer is confined to the original tumor site or has spread to other sites, such as the lymph nodes, liver, brain, lungs, or bone. The purpose of staging cancer is to determine prognosis, categorize patients with regard to metastatic potential and survival probability, and aid in clinical decision making.* As with most solid tumors, the tumor-node-metastasis (TNM) classification is used to stage MM, and the latest guidelines for staging MM proposed by the American Joint Committee on Cancer were implemented in 2002 (see Table 94–3).[36]

Sentinel Lymph Node in Melanoma

For patients with melanomas that are at risk of spreading to the lymph nodes, a **sentinel lymph node** (SLN) biopsy is performed. The SLN, the first lymph node to receive lymph draining from the tumor, is identified by injecting a radioactive material, technetium-99m-labeled radiocolloids, and vital

TABLE 94–3. 2002 AJCC Revised Melanoma Staging System[31]

Stage	Histologic Features	Overall Survival 5 Years	Overall Survival 10 Years
0	Melanoma in situ (involves only the epidermis layer)	**100%**	**100%**
IA	1mm thickness, no ulceration and Clark level[a] II or III		
IB	1mm with ulceration Or 1mm with ulceration or Clark level IV or V Or between 1.01 and 2 mm with no ulceration	**89–95%**	**79–88%**
IIA	Between 1.01 and 2 mm with ulceration Or between 2.01 and 4 mm with no ulceration	**45–79%**	**32–64%**
IIB	Between 2.01 and 4 mm with ulceration Or greater than 4 mm with no ulceration		
IIC	Greater than 4 mm with ulceration		
IIIA	Any tumor thickness with no ulceration with one lymph node involved and micrometastases Or any tumor thickness with no ulceration with two to three lymph nodes involved and micrometastases	**63–70%**	**57–63%**
IIIB	Any tumor thickness with ulceration and one to three lymph nodes involved and micrometastases Or any tumor thickness without ulceration and one to three lymph nodes involved and macrometastases Or any tumor thickness ulceration with in transit metastases/satellite lesions without metastatic lymph nodes	**46–59%**	**36–48%**
IIIC	Any tumor thickness with ulceration with one lymph node involved and macrometastases Any tumor thickness with ulceration with two to three lymph nodes involved and macrometastases Any tumor thickness with four or more metastatic lymph nodes or in transit metastases/satellite lesions with metastatic lymph nodes	**24–29%**	**15–24%**
IV	M_{1a}: Skin, subcutaneous tissue, or distant lymph nodes with normal lactate dehydrogenase M_{1b}: Lung with normal lactate dehydrogenase M_{1c}: To all other visceral sites (liver) or distant metastasis at any site with elevated serum LDH	**7–19%**	**3–16%**

[a]**Clark's level** refers to the level of penetration into the dermis (see Fig. 94–1). **Breslow classification** measures tumor thickness, in millimeters, from the epidermis to the deepest depth of penetration into the dermis (see Fig. 94–1.)

blue dye into the skin next to the tumor and tracing the flow of lymph from the tumor site to the nearest lymph node chain. Once the SLN is located, it is removed and analyzed for the presence of MM cells. If it is positive for the presence of MM, then the whole lymph node basin in that area is dissected; this is also known as a **lymphadenectomy.** A SLN biopsy is the initial procedure to assess the status of lymph node involvement to prevent the morbidity associated with a total lymphadenectomy.

❸ *The status of the SLN is one of the most powerful independent prognostic factors predicting survival. It also provides the oncologist with guidance for therapy decisions.* Furthermore, a SLN biopsy provides accurate staging of the MM.[31] An SLN biopsy should be considered in patients with clinically localized MM that is 1 mm or greater in size (Table 94–4). It also may be considered for patients whose MM is less than 1 mm but has any of the following characteristics: ulceration, extensive vertical regression to at least 1 mm, young age, or high mitotic rate.[31]

TABLE 94–4. Surgical Margins of Excision for Malignant Melanoma[39]

Melanoma Thickness	Margin of Excision	Sentinel Lymph Node Biopsy
Melanoma in situ	0.5 cm	No
Less than 1mm	1 cm	Yes if associated with ulceration, regression on histologic evaluation, positive deep margin on initial biopsy, Clark's level IV or V, and previous history of melanoma
1–2 mm	1–2 cm	Yes
2–4 mm	2 cm	Yes
Greater than 4 mm	Greater than 2 cm	Controversial



Clinical Presentation of MM[26,27]

Patients with skin cancer generally present with a lesion that may be located anywhere on the body. The most common sites are the head, neck, trunk, and extremities. Changes in any characteristics of a lesion are important danger warning signals. Abnormal presentations of a mole/lesion indicate the need for further assessment.

- *A*symmetry*:* Half the lesion does not mirror the other half.
- *B*order*:* Sharp, ragged, uneven, and irregular borders.
- Color*:* Multiple colors of various hues of light brown, dark brown, black, red, blue, or gray.
- *D*iameter*:* Larger than 6 mm or the size of a pencil head eraser.
- *E*volving*:* Significant change in shape, size, symptoms, surface, or shades of color.

Other signs and symptoms to monitor for in a lesion, in addition to ABCDE, include:

- Sudden or continuous enlargement of a lesion or elevation of a lesion
- Changes in the skin surrounding the nevus
- Redness, swelling, itching, tenderness, or pain
- Ulceration: friability of the lesion with bleeding or oozing. This is a danger signal.

Less Common Sites and Manifestations of MM

It is important to examine these sites for "hidden" MM:

- Nailbed
- Mucosal tissue
- Scalp
- Eye

In the nailbed, a black streak or wide variegated brown streak, elevation of nailbed, skin next to nail becomes darker, nail looks deformed or is being destroyed; size of nail streak increases over time.

Diagnosis of MM

- Dermoscopy[29]
- Biopsy[30]



Clinical Presentation of NMSC[27]

Five Warning Signs of BCC

The appearance of some BCCs is similar to plaque, psoriasis, or eczema, and these benign disorders are included in the differential diagnosis.

- An open sore that bleeds, oozes, or crusts and remains open for 3 or more weeks
- A reddish patch or irritated area that may crust, itch, hurt, or persist with no noticeable discomfort
- A shiny bump or nodule that is pearly or translucent and may be pink, red, or white. In dark-haired people, it may be tan, black, or brown and can be confused with a mole.
- A pink growth with slightly elevated, rolled border and a crusted indentation in the center
- A scarlike area that is white, yellow, or waxy with poorly defined borders

Warning Signs and Symptoms of SCC[5,26]

- A wartlike growth, a persistent scaly red patch with irregular borders, or an open sore that crusts or bleeds
- An elevated growth with a central depression that bleeds occasionally. This growth type increases in size rapidly.
- In situ SCC: red scaling macule or plaque
- Invasive SCC: firm or friable red papule or nodule covered with scale or crust
- Precursor of invasive SCC (actinic keratosis): scaly erythematous macule or papule on areas of chronic sun exposure

Lymph Node Consideration in NMSC

In patients with SCC, metastatic spread to the lymph nodes occurs in less than 5%.[32] The lymph nodes of the head and neck are the most common sites of metastasis. Patients are still curable with this stage of the disease, but they are at high risk of experiencing regional relapse and distant metastasis to the bones and lungs. As may be expected, survival is decreased compared with patients who do not present with nodal involvement. Factors that may be useful in predicting lymph node involvement include depth of tumor invasion and tumor thickness. A tumor thickness of greater than 4 mm has been suggested as the threshold at which nodal metastasis should be suspected and an SLN biopsy should be considered.[32]

Other Prognostic Factors

In addition to the stage of the disease and the status of disease involvement in the lymph nodes, other prognostic factors for outcome in MM include patient age and gender, tumor location, and histology of the MM. Table 94–5 provides complete information on factors that confer good prognosis for a patient diagnosed with malignant melanoma.[33]

Additional Diagnostic Work-up Tests

A baseline chest x-ray, lactate dehydrogenase (LDH) level, and computed tomographic (CT) scan of the chest, abdomen, and pelvis may be ordered by the oncologist as indicated clinically, depending on the patient's symptoms, the presence of lymph

TABLE 94–5. Prognostic Factors in Melanoma[31]

Factor (Better Prognosis)	
Age (less than 65 years)	5-year survival (%)
Less than 30 years	87
60 years	78
70 years	71
80 years	60
Gender (female)	10-year survival (%)
Female	86
Male	68
Tumor location (extremities)	10-year survival (%)
Extremities	90
Trunk, head, or neck	70

Histologic Factors (Better Prognosis)	
Tumor thickness (less than 1 mm)	Clark's level (level I)
Ulceration (none)	Tumor vascularity (absent)
Nodal status (none)	Regression (absent)
Vascular invasion (none)	Mitotic rate (low)
Microsatellites (none)	Tumor infiltrating lymphocytes (present)

node involvement, or the stage of the cancer. Positron-emission tomography (PET) and magnetic resonance imaging (MRI) are additional imaging techniques that may be used.

TREATMENT

The modality of treatment for skin cancer depends on the size, location, and stage of the tumor; the age of the patient; and the type of skin cancer. Treatment options for skin cancer include surgery, radiation, chemotherapy, and immunotherapy.

Desired Outcome

The primary goals of therapy for skin cancer are to completely eradicate the tumor and minimize the risk of tumor recurrence and metastasis. Secondary goals of therapy include preserving normal tissue, maintaining function, and providing optimal cosmetic outcomes.[5]

Patients with local disease (stage I and IIA) are curable with surgical resection of the tumor. Thus the aim is to diagnose patients at the earliest stage in order to increase the probability of cure. Patients with regional disease (stage IIB, IIC, and III) have a high recurrence risk, and the goal of therapy is to prevent relapse of the disease. Disseminated, metastatic MM is not curable, and the goal of therapy is local control of the disease and palliation of symptoms.

In patients diagnosed with BCC, metastases and death are rare. SCC is more aggressive than BCC, with metastases occurring in 2% to 6% of patients.[5] The primary goal of therapy for both these types of NMSC is to cure the patient and to prevent recurrence for SCC. Although NMSC has a low mortality rate, morbidity owing to tissue destruction, functional impairment, and disfigurement is a significant issue. Therefore, secondary goals of therapy for NMSC are preservation of function and restoration of cosmesis.[5]

Nonpharmacologic Therapy

Lifestyle Modifications

Primary Prevention of Skin Cancer

Ultraviolet (UV) radiation exposure from the sun is the major cause of NMSC and MM. **Primary prevention** strategies for skin cancer aim at educating people against excessive exposure to the sun and are spearheaded by the American Academy of Dermatology, the American Cancer Society, the Environmental Protection Agency, and the Centers for Disease Control and Prevention. Comprehensive cancer prevention programs sponsored by these organizations include the National Skin Cancer Prevention Educational Program, National Skin Cancer Prevention and Detection Month, The Skin Cancer Foundation's Self Examination Program, and the California and United States Food and Drug Administration sunscreen legislation.[34] The aims of these programs are to increase public awareness about the harmful effects of sun exposure and the risk of skin cancer, change attitudes about the social norms related to sun protection and tanned skin, and decrease the incidence of skin cancer and deaths related to this malignancy.[34] Recommendations for prevention of skin cancer are universal and include a variety of simple strategies to minimize exposure to UV rays:[34]

- Avoid direct exposure to the sun between the hours of 10 AM to 4 PM, when UV rays are most intense.
- Wear hats with a broad enough brim to shade the face, ears, and neck.
- Wear protective clothing (especially tightly woven apparel) that covers as much as possible the arms, legs, and torso.
- Cover skin with a sunscreen lotion with a skin protection factor (SPF) of at least 15, protecting against UV radiation (both UVA and UVB).
- Reapply sunscreens every 2 hours (especially if sweating or swimming).
- Avoid sun lamps and tanning beds, which provide an additional source of UV radiation.
- Seek shade when outdoors.

The use of chemical sunscreen is only one of many strategies, and it should not be the sole agent used for cancer prevention. The lay public should be warned not to use sunscreen with a higher SPF with the intent to extend the duration of exposure because it is observed that DNA damage can occur long before sunburn appears, and the long term-effects of increased sun exposure are not known.[35] Sunscreen protective agents have been proven only to reduce the risk of actinic keratosis and SCC. There is no convincing evidence that sunscreen application has protective effect against BCC or MM.[35]

Routine self-examination of the skin is a method in which individuals can take responsibility for identifying MM early when it is curable. Pamphlets and online information describing the method of skin self-examination are available from agencies such as the American Cancer Society (www.cancer.org), the American Academy of Dermatology (www.AAD.org), and the Skin Cancer Foundation (www.skincancer.org). Patients should be given the following instructions for doing total skin self-examination:[36]

- Make sure that you have good lighting, a full-length mirror, and a hand-held mirror.
- Your fingers, spaces between your fingers, fingernails, palms, backs of your hands, forearms, upper arms, and nails should be examined.
- Examine the entire front of your body in a full-length mirror. Look at your eyes, lips, hairline, chest, abdomen, pubic area, thighs, and lower legs. Lift your arms over your head and examine the right and left sides of your body.
- Turn around and look at the backs of your legs, buttocks, and back. Use a hand-held mirror angled to see in the full-length mirror to examine your ears, neck, scalp, back, and buttocks.
- Sitting on a chair, look on the insides of your legs, feet, toes, toenails, spaces between the toes, and soles of your feet.

Secondary Prevention of Skin Cancer

Secondary prevention of skin cancer involves early detection of premalignant cancers for early intervention with the hope that it will reduce mortality and increase cure. Skin cancer screening consistently identifies MMs that are, on average, thinner than those found during usual care. Unfortunately, at this time, there is no evidence that skin cancer screening reduces morbidity or mortality.[37] Given this lack of evidence for a beneficial effect of skin cancer screening, recommendations vary with different agencies. The American Cancer Society recommends skin examination as part of cancer-related check-ups every 3 years for people between 20 and 40 years of age and on a yearly basis for those over 40 years of age. The American College of Preventive Medicine recommends total-body skin examination only in high-risk individuals. High-risk individuals are defined as those with a family or personal history of skin cancer, predisposing phenotypic characteristics, increased occupational or recreational exposure to sunlight, or clinical evidence of precursor lesions. The National Institutes of Health Consensus Panel recommends screening for MM as part of routine primary care.[37]

Surgery

❹ *Surgery is the primary treatment modality for NMSC and MM.* Surgical approaches for skin cancer are divided into two different categories: (1) superficial ablative techniques that include *electrodesiccation and curettage (ED&C)* and *cryotherapy* and (2) full-thickness ablative techniques that include *primary surgical excision* and *Mohs' micrographic surgery*.[38]

Superficial Ablative Procedures

Electrodesiccation and curettage (ED&C) is a simple, cost-effective technique that requires minimal equipment for ablating NMSC. The curette is either an oval, semisharp, spoon-shaped instrument or an open ring connected to a handle that is available in many sizes to allow the physician to deal with different tumor dimensions. Malignant tissue usually is softer and more friable than normal skin, and the curette is designed to cut through the abnormally soft or friable tissue with minimum force so that the diseased tissue can be selectively removed. Electrodesiccation involves the application of high voltage, low current to the skin, causing drying or desiccation of the tissue. Electrodesiccation usually is performed first, followed by curettage. ED&C is most appropriate for well-defined superficial lesions that are not located in areas with increased risk for metastasis. It is generally well tolerated, but it does produce a large scar and should not be performed on sites where cosmetically unattractive scars are unacceptable.[5] This procedure is contraindicated in tumors that are recurrent, larger than or equal to 2 cm, extending into subcutaneous fat, in high-risk sites, or aggressive subtypes of BCC such as metatypical or morpheaform BCC.[38]

Cryotherapy is a procedure used primarily for smaller, low-risk NMSCs with clearly defined margins. It involves delivering liquid nitrogen at subzero temperatures as a spray or with a supercooled metal probe to destroy the malignant tissue.[5] It is contraindicated in metatypical or morpheaform BCC, in tumors that are invasive or recurrent, in hair-bearing skin that is susceptible to cryotherapy-induced alopecia, or in tumors with poorly defined borders. Cryotherapy is a cost-effective treatment that is easy for clinicians to deliver, but the recurrence rate is high with this procedure.[5]

Full-Thickness Ablative Procedures

Primary excision of the tumor is the most common treatment option for most MMs and a large percentage of NMSCs. Surgical excision involves surgical removal of the cancer along with a margin of normal tissue surrounding the tumor. Obtaining negative surgical margins is critical for cure and decreasing the risk of tumor recurrence. The appropriate margin of resection is not clear and depends on the tumor size, degree of differentiation, and invasion of surrounding structures. For lesions that are less than 2 cm in diameter, a minimum margin of 4 mm probably is adequate.[39] See Table 94–4 for margin recommendations depending on the tumor size.

Mohs' micrographic surgery (MMS) is a surgical technique performed by surgeons trained in this procedure for the removal of both NMSC and MM.[5] The goal of this therapy is complete removal of the cancer with preservation of as much surrounding normal tissue as possible. This procedure is preferred for high-risk or cosmetically sensitive areas such as the

face, ears, or hands. MMS involves careful dissection, staining, and anatomic mapping of the tumor specimen. Sections of the tumors are frozen and assessed immediately under the microscope in the operating theater. If residual tumors are detected microscopically in the frozen section, additional tissue is excised where the residual tumor is found. This process is repeated until a tumor-free margin is attained.[5] MMS conserves normal tissue for preservation of function and cosmesis. It is, however, a tedious procedure and requires exceptional skill on the part of the surgeon.[5]

Radiation

Radiation is not standard therapy for the treatment of skin cancer; however, there are circumstances in which radiation may be preferred. It is used as adjunctive therapy after surgical resection for patients with head and neck MM with metastasis to regional lymph nodes.[40] Radiation is also indicated for patients with unresectable metastases or brain metastases or for palliation of symptoms from metastases.[40] Older patients or patients who are poor candidates for surgery may be offered radiation as an option.[40] Radiation offers good cosmetic results,



Patient Encounter, Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH
- Hypertension, currently controlled
- Gastroesophageal reflux disease

FH
No known family history of cancer; specifically, no NMSC, MM, or hereditary dysplastic nevus syndrome.

SH
Patient is a retired. His sun-exposure history is as described in Patient Encounter, Part 1.

Meds
- Hydrochlorothiazide 25 mg PO once daily
- Famotidine 20 mg PO twice daily

ROS
No changes in vision, headaches, SOB, cough, fever, nausea, vomiting, diarrhea

PE
- **VS:** BP 126/84, P 80, RR 16, T 37°C (98.6°F), ht 68 in (173 cm), wt 72 kg (158 lb)
- **Skin:** Fair complexion, multiple scattered nevi, apparent shoulder wound
- **HEENT:** PERRLA, EOMI, sclera nonicteric, nose and throat clear without exudates or lesions
- **Neck and lymph nodes:** Supple, no lymphadenopathy
- **Lungs:** CTA bilaterally
- **CV:** RRR without murmurs
- **Abdomen:** Soft, nontender, nondistended, no hepatosplenomegaly
- **Exts:** No cyanosis, clubbing, edema
- **Neuro:** Alert and oriented × 3. Cranial nerves II–XII are intact, nonfocal.
- **Labs:** Within normal limits
- **CT scan of chest, abdomen and pelvis:** Negative
- **Chest x-ray:** Negative

Treatment
KM underwent surgical resection of the primary tumor, and an SLN biopsy was positive for lymph node involvement. A lymphadenectomy was performed. After extensive discussion with his oncologist, the decision was made to start KM on interferon-α2b.

- Given this additional information, what is KM's stage of malignant melanoma?
- What is the goal of therapy for KM?
- What are the treatment options for KM after surgery?
- What data support the use of high-dose interferon-α2b in KM?

but it requires multiple visits over the course of several months, making it inconvenient for patients.[38] In the treatment of NMSC, radiation results in poorer cosmetic outcomes than surgery or electrodesiccation and curettage.[17] Disadvantages of radiation include radiation-induced dermatitis, high cost, and the increased risk of secondary malignancy, including SCC and BCC.[17]

Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) is a local treatment option for brain metastases that delivers high doses of focused ionizing external-beam radiation to a well-defined target area in one session of radiation therapy.[41] This technique maximizes the dose of radiation to the tumor with a rapid dose falloff outside the target area, resulting in sparing of the surrounding nontarget normal tissue. SRS is limited to tumor volumes of less than 3 cm and for the treatment of no more than three lesions. Brain metastasis is an ideal target for SRS because of its small size, spherical shape, and minimal invasion of surrounding tissue. SRS is more convenient than surgery because it is performed as an outpatient procedure, and multiple lesions may be treated simultaneously.[41]

Treatment Options for MM (Fig. 94–3)

Stage I and IIA MM

The primary treatment modality for *carcinoma in situ* (stage I and IIA cutaneous MM) is surgical excision of the tumor.[38] The 5-year survival rates for patients with stage I and II tumors are 78% to 95%.[31] Achieving adequate surgical margins for the primary tumor is important in preventing local recurrence and improving overall survival. The thickness of the MM dictates the extent of the surgical margin[39] (see Table 94–4). For tumors that are greater than 1 mm, or if the tumor is less than 1 mm but has ulceration, it is recommended that an SLN biopsy be performed to rule out occult nodal metastasis.[31] There is no recommendation for systemic therapy in patients with stage I or IIA MM.

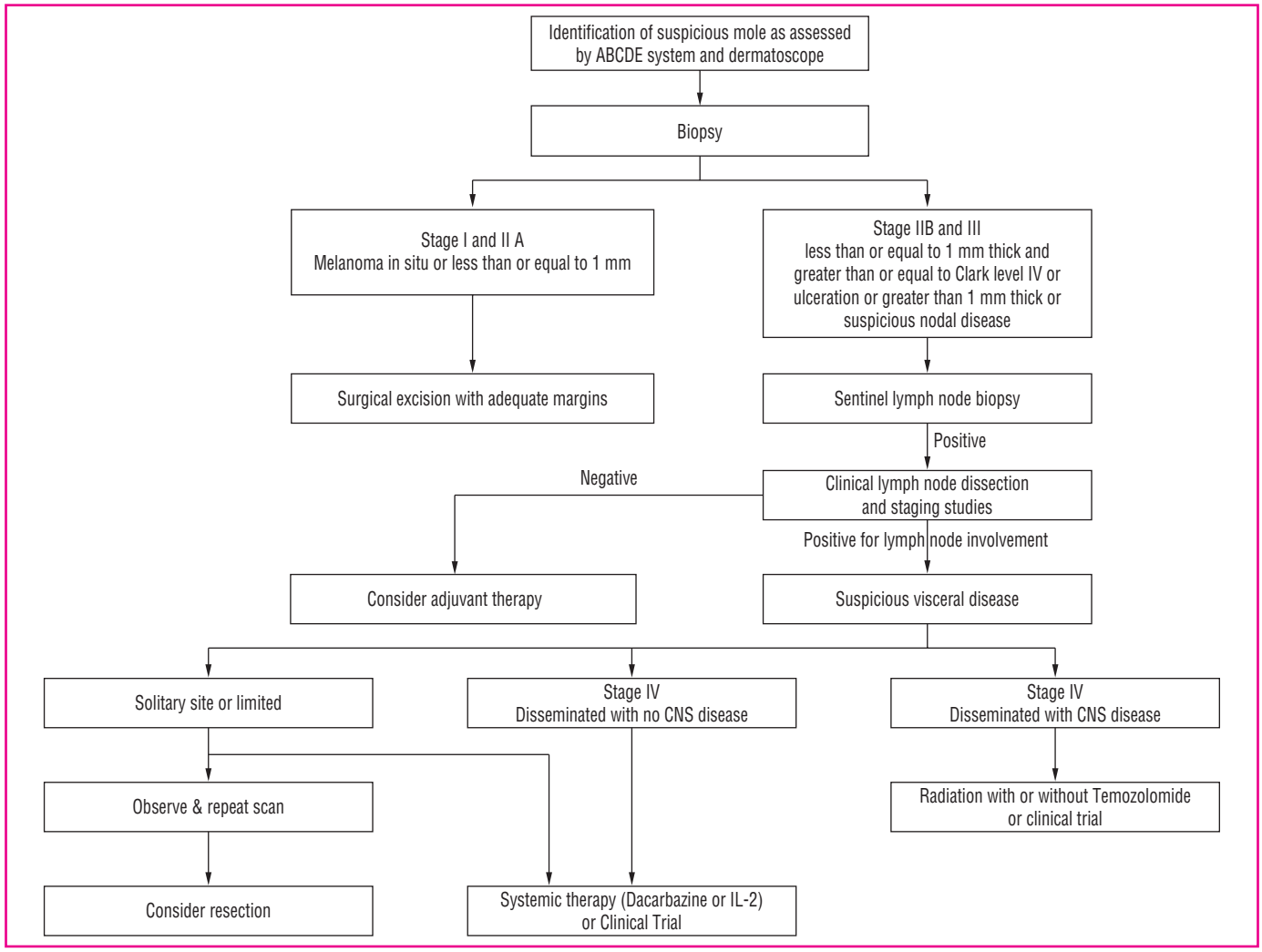


FIGURE 94–3. Algorithm for management of cutaneous melanoma.[58]

Stage IIB, IIC, and III MM (High-Risk MM)

❺ *Excision of the tumor with clear margins is the primary treatment modality for stage IIB and IIC. In addition to surgical excision of the primary tumor site, removal of the involved lymph node chain, a lymphadenectomy, is the standard treatment for stage III MM.*[38] *Patients at these stages are considered to be high risk because of their potential for recurrence and distant metastases.* The role of adjunctive immunotherapy after surgery to decrease the incidence of recurrence for high-risk melanoma is controversial.

Interferon-α2b for High-Risk MM

Interferon-α2b has diverse mechanisms of action, including antiviral activity, impact on cellular metabolism and differentiation, and antitumor activity.[42] The antitumor activity is due to a combination of direct antiproliferative effect on tumor cells and indirect immune-mediated effects.[42] Interferon-α2b is currently approved by the Food and Drug Administration (FDA) as **adjuvant therapy** for patients who are free of disease after curative surgical resection but are at high risk of MM recurrence. This includes patients with bulky disease or regional lymph node involvement such as stage IIB, IIC, or III disease.[43] ❻ *It is controversial if interferon-α2b (IFN) should be offered as adjuvant therapy for every high-risk MM patient. The reason is because clinical trials with different doses of IFN have not proved definitively that IFN improves overall patient survival.*

The doses of IFN used in clinical trials can be classified into three groups: high-dose (HDI), intermediate-dose (IDI), and low-dose (LDI) interferon (Table 94–6). Data from many clinical trials assessing LDI in patients with high or intermediate risk of recurrence did not demonstrate an impact on overall survival, and it is unclear if disease-free survival is improved.[44–46] Therefore, at this time, LDI cannot be considered efficacious as adjuvant therapy for high-risk MM. There are several ongoing trials with IDI and a trial evaluating the use of a slow-release pegylated form of interferon (polyethylene glycol–Intron or PEG-Intron). Until results for these studies are mature, IDI and PEG-Intron cannot be recommended as adjuvant therapy for patients with high-risk MM.[47]

In the evaluation of HDI for high-risk MM, data from a pooled analysis of four major clinical trials that randomized patients to either HDI or observation recently became available. The results showed improved relapse-free survival, with an approximate 10% reduction in the risk of recurrence, but no effect on overall survival in patients receiving HDI.[48] A pooled analysis of several high-dose IFN trials and a trial comparing HDI with vaccine (E1694) also confirmed a reduction in the risk of recurrence with HDI without significant improvement in overall survival.[49,50]

HDI has substantial side effects (Table 94–7) and is an expensive therapy. The constellation of side effects associated with the administration of IFN can be divided into acute and chronic manifestations and categorized into four major side-effect groups: constitutional, neuropsychiatric, hematologic, and hepatic.[42] In the acute setting, the constitutional symptoms of fevers, chills, rigors, and myalgia, along with headache, nausea, and vomiting, usually occurs after initial dosing of IFN and last up to 8 hours.[51] Tolerance may develop with these symptoms. Treatment breaks, however, even for as short as a few days, result in redevelopment of these acute side effects.[42] Neutropenia and elevated liver enzymes may occur acutely and at anytime during chronic administration. Frequent monitoring of hematologic parameters and liver function tests is recommended. The chronic symptoms of IFN include fatigue (70%–100% of patients), anorexia (40%–70%), and neuropsychiatric symptoms (up to 30%).[42] The chronic symptoms do not exhibit tolerance, worsen with continued therapy, and are dose-related. However, most IFN-related toxicities are manageable with appropriate supportive care. The most common side effects and recommendations for monitoring and treatment of these side effects are listed in Table 94–7. It is very important to educate patients on the side effects to expect and the interventions that are available to minimize the toxicities in order to reassure the patient.

The clinical dilemma in the use of HDI as adjuvant therapy for high-risk MM patients becomes: Is the benefit of preventing recurrence in only a small portion of patients without much improvement in overall survival worth the risk of considerable disabling toxicity? Given the modest efficacy, significant toxicity, and considerable expense with HDI therapy, which MM patient at risk for recurrence should receive HDI as adjuvant therapy? The answer possibly may be addressed by using the following decision rules proposed by Kilbridge and colleagues.[47] The intent of these rules is to assist clinicians and

TABLE 94–6. Immunotherapy Dosing [a,38]

Interferon Regimes Used in Clinical Trials	
High dose (HDI)	20 million units (MU)/m^2 intravenously (IV) daily × 5 days/week for 4 weeks, followed by 10 MU/m^2 subcutaneously (SQ) 3 times/week for 48 weeks
Intermediate dose (IDI)	10 MU SQ × 5 days/week for 4 weeks, followed by 10 MU SQ 3 times/week for varying durations
Low dose (LDI)	3 MU SQ 3 times/week for varying durations 1 MU SQ every other day for 1 year
Interleukin 2 Dosing Regimens[a 53, 54]	
IL-2 600,000 or 720,000 units/kg by 15-minute infusion every 8 hours for 14 consecutive doses over 5 days as tolerated.	
Chemotherapy[a, 56]	
Dacarbazine 250 mg/m^2 per day intravenous, days 1 to 5, every 21 days	
Temozolomide 150 to 200 mg/m^2 per day by mouth × 5 days, every 28 days	

[a]The doses presented here are general. Clinicians should refer to clinical trials to determine the specific dose based on the regimen the patient is receiving.

TABLE 94–7. Interferon-α2b Toxicities

Common Acute Toxicity	Management
Fever, rigors, chills, malaise headaches, myalgia	Acetaminophen (APAP). NSAID if APAP is not effective. Meperidine for severe chills and rigors. Bedtime administration.
Nausea, emesis	5-HT_3 antagonist, prochlorperazine, metoclopramide, fluids
Neutropenia	Weekly complete blood count; reduce dose by 30–50%
Hepatic enzyme elevation	Liver function tests (LFTs) weekly; withhold treatment until LFTs normalize; restart at 30–50% dose reduction; reversible on dose reduction or cessation.
Cutaneous—alopecia, transient, mild rashlike reaction	Interferon is contraindicated in patients with psoriasis because exacerbation of psoriasis has been noted during IFN therapy.

Common Chronic Toxicity	Management
Fatigue, weight loss, anorexia	Light exercise, good nutritional intake—small frequent meals; oral supplementation; noncaffeinated fluid intake; stress management technique; **pharmacologic intervention**—megesterol acetate, methylphenidate, to help with either fatigue or anorexia.
Depression, cognitive dysfunction. Rare—mania, mood instability	Psychiatric history prior to therapy and reassess every 4 to 6 weeks; antidepressants—SSRIs, mood stabilizer, gabapentin.
Thyroid dysfunction	Initial thyroid function test (TSH), then monthly; if three sequential values are stable or normal, bimonthly or quarterly TSH.

patients in making decisions regarding HDI. The patient may be treated with HDI if he or she agrees with the statements "If I had a serious disease, I would gladly accept feeling lousy for a year if it improved my chances of having a longer period without the disease" and "I would put up with the side effects of HDI treatment only if it decreased the chance of MM returning in 5 years time by at least *x*%," and the answer for *x* should be 10% or less.[47] Other factors that should be considered in the decision include the patient's comorbidities and/or contraindications to receiving HDI.[47] Information covered during the discussion should include the fact that HDI is the only agent showing activity against MM in the adjuvant setting and that it prolongs 5-year relapse-free survival by approximately 10% at the expense of significant but reversible toxicity.[47] If the patient is eligible, encouragement to participate in clinical trials designed to address the issues of survival, quality of life, and treatment costs is also reasonable.[47]

Stage IV MM

The prognosis for patients diagnosed with stage IV MM varies with the location of the metastases and the number of metastatic sites. Treatment options for stage IV metastatic MM include surgical excision of the lesion and radiation therapy for palliation of symptoms. ❼ *Surgical excision of the tumor is not curative for metastatic MM, and the primary goal of therapy is local control of the disease and relief of identifiable symptoms.* In highly selected patients, such as those with good performance status, less aggressive tumor biology, prolonged period of disease-free interval from the time of primary tumor treatment, and limited disease that is contained within



Patient Encounter, Part 3: Create a Care Plan

Create a care plan while KM is receiving interferon-α2b therapy. Your plan should include (1) the goal of therapy with interferon-α2b and (2) a plan related to dealing with the side effects to expect from this therapy.

What supportive measures should be used to minimize side effects?
What laboratory parameters need to be monitored?
What are the indications to discontinue or hold therapy?
When may the therapy be restarted after the doses were held?
What are the pharmacologic and nonpharmacologic recommendations for managing side effects?
How frequently should KM be monitored while on therapy?
Be able to discuss with the patient the following for interferon-α2b:

- The differences between acute and chronic side effects
- The side effects that the patient will develop tolerance to
- The best time of the day to administer the drug
- The importance of keeping regular follow-up appointments to monitor for long-term side effects of the therapy and draw blood for routine lab tests
- Reassure the patient that therapy may be stopped at any time if side effects are intolerable

- What is the follow-up plan for KM after he has completed therapy with interferon-α2b?

a single location, complete surgical resection results in a median survival of 2 years and a 5-year survival rate of 10% to 25%.[52] For most other patients with stage IV MM, unfortunately, the survival rate is measured in months rather than years, with overall median survival of 5 to 8 months and a 5-year survival rate of less than 5%.[52]

Interleukin 2 for Stage IV MM

❽ *Interleukin 2 (IL-2) therapy is approved by the FDA for the treatment of metastatic MM, and it is a reasonable option for patients with this stage of the disease.* IL-2 does not have a direct toxic effect on MM cells. It indirectly causes tumor cell lysis by proliferating and activating cytotoxic T lymphocytes.[53] The overall objective response rate for patients with metastatic MM receiving high-dose IL-2 is 16%, with a complete response in 6% of patients and a partial response in 10% of patients.[54] The median duration of response is 8.9 months for all responding patients and 5.9 months for patients with a partial response.[54] The median duration of complete response has not been reached but is at least 59 months. Disease progression is not observed in any patient responding for longer than 30 months.[54] Good performance status and no prior systemic therapy are the only prognostic factors that are associated with response, with objective response rate being twice that of patients with poor performance status and who received prior chemotherapy.[55] The site of metastasis did not influence response, and patients had responses in all organ sites, including lung, liver, adrenal, bone, liver, kidney, and spleen.[55] The data are encouraging because for the small number of patients who responded to therapy, the effect is of a long duration, and some patients may be considered to be cured of the disease (Refer to Table 94–6 for an example dosing regimen).

High-dose IL-2 therapy is associated with severe toxicities.[55,56] All patients will experience a flulike syndrome that consists of fever [reaching as high as 39–40°C (102.2–104°F)], chills, myalgia, and malaise and occurs 3 to 6 hours after the first injection of IL-2.[56] The most common cardiovascular toxicities are hypotension and capillary leak syndrome (CLS). The cause for this is the release of nitric oxide from endothelial cells, resulting in vasodilation and increased permeability of the blood vessels.[56] The early signs and symptoms of CLS include hypotension and tachycardia, which are observed 2 hours after the first dose of IL-2. Within the first 8 hours of IL-2, there is decreased urine output owing to hypotension, as well as decreased intravascular volume.[56] Pulmonary congestion, manifested as progressive shortness of breath, is also attributed to the increased vascular permeability from CLS. Total-body edema and consequent weight gain, between 5 and 10 kg, are also due to CLS.[56] The other common side effects of IL-2 are gastrointestinal, neuropsychiatric, hematologic, and dermatologic.[56] Table 94–8 lists the most common side effects experienced by patients receiving IL-2 therapy and recommendations for management. Patients receiving IL-2 may be managed on the oncology unit as long as telemetry is available; however, it is important that all medical staff involved with the care of patients receiving IL-2 be well educated on the side effects to monitor for and are well trained in management of critical-care issues such as hypotension.[55]

Chemotherapy for Stage IV MM

Dacarbazine, an alkylating agent, is the most active single-agent chemotherapy against MM, achieving response rates of 15% to 25%.[57] It is the only chemotherapy agent approved by the FDA for the treatment of metastatic MM. A recent phase III clinical trial in patients with advanced metastatic MM demonstrated a response rate of 12% and stable disease in 16% of patients treated with dacarbazine alone.[57] The response duration was not long-standing, with a median survival time of 6.4 months.[57] Nausea and vomiting are the most common side effects of dacarbazine. Combining dacarbazine with other chemotherapy agents with activity against MM in single-institution phase 2 trials resulted in response rates of between 30% and 50%.[58] Two phase III clinical trials assessing the CVD (cisplatin, vinblastine, and dacarbazine) regimen and the Dartmouth regimen (carmustine, cisplatin, dacarbazine, and tamoxifen) versus single-agent dacarbazine showed that there was a trend toward improved response rate, but the results were not statistically significant.[51] Furthermore, there was no significant survival advantage over single-agent dacarbazine alone, but toxicity was greater with the combination chemotherapy.[53] Therefore, combination chemotherapy is not a standard of care for stage IV MM.

Biochemotherapy for Stage IV MM

Clinical trials combining chemotherapy and immunotherapy are based on the observations of independent clinical activity of each of these treatment modalities in treating metastatic MM. This combination is known as *biochemotherapy.* Only one phase III clinical trial showed significant improvement in response rate, time to progression, and median survival favoring the biochemotherapy arm versus the combination-chemotherapy arm.[59] Currently, the use of biochemotherapy is not justified outside a clinical trial in patients with stage IV MM.[53,58,60]

In summary, systemic therapy for stage IV MM is controversial. ❾ *Combination chemotherapy and biochemotherapy increase toxicity significantly without offering overall survival benefit; thus they are not the standard of care for stage IV MM.* Both high-dose IL-2 and dacarbazine are approved for the treatment of stage IV MM. High-dose IL-2 may be preferred in patients with a good performance status. Enrollment in a clinical trial and best supportive care are also reasonable alternatives.[61]

MM with Brain Metastases

Radiation for Brain Metastases

One of the most common sites of metastasis for MM is the brain, and MM is reported to be the third most common cause

TABLE 94–8. Interleukin 2 Toxicities[53,54]

Toxicity (% of Patients)	Management
Cardiovascular Toxicity	
Hypotension (64%), supraventricular tachycardia (17%)	Discontinue antihypertensive medications IV fluids to maintain systolic blood pressure greater than 80–90 mm Hg or vasopressor support with an α-agonist such as phenylephrine as indicated.
Gastrointestinal	
Vomiting and diarrhea (55%), nausea (24%), stomatitis (14%)	5-HT_3 antagonist, prochlorperazine for emesis (avoid corticosteroids), H_2 blocker for gastritis, antidiarrheal as needed (loperamide, diphenoxylate/atropine, codeine).
Neurologic	
Confusion (30%), somnolence	Haldol for agitation, lorazepam for anxiety, temazepam or zolpidem for insomnia.
Pulmonary	
Dyspnea (31%), pulmonary edema, and adult respiratory distress syndrome	Advise smokers to quit 2 weeks before therapy; be judicious in use of IV fluids for hypotension; discontinue therapy if requiring greater than 4 L O_2 or 40% O_2 mask for saturation greater than 95%.
Hepatic	
Elevated bilirubin (51%), transaminase (39%), alkaline phosphatase	Consider discontinuing therapy if severe.
Renal	
Oliguria (49%), elevated serum creatinine (35%), anuria (8%)	Normal saline or dopamine at renal perfusion dose of 2 mcg/kg per minute for oliguria; monitor for electrolyte abnormalities and replace as indicated.
Hematologic	
Thrombocytopenia (43%), anemia (29%), leukopenia (21%)	Transfuse with packed red blood cells and platelets as needed
Skin	
Rash (27%), exfoliative dermatitis (15%), pruritus	Hydroxyzine, diphenhydramine, oatmeal powder baths, lubriderm lotion
General	
Fever and or chills (47%), malaise (34%), infection (15%)	Acetaminophen and NSAID around the clock for fever and chills; add meperidine if chills are severe; clindamycin or cefazolin to prevent infection.
Hypothyrodism	May occur in one third of patients; thyroid function tests.

of brain metastasis.[62] The incidence of brain metastasis is reported to range from 10% to 40% in clinical studies.[62] ⑩ *Treatment options for brain metastases include surgery, radiation [which includes whole-brain radiotherapy and stereotactic surgery (SRS)], or chemotherapy. The choice of therapy depends on the number of metastatic lesions, accessibility of the lesion for surgery, the presence of neurologic symptoms, and the status of extracranial disease.*

Surgery followed by whole-brain radiotherapy (WBRT) is best indicated for patients with an accessible single brain lesion and controlled or limited systemic MM.[62] Two randomized studies reported improved survival in patients treated with combination surgery and WBRT compared with WBRT alone.[62,63] For those patients with multiple metastatic brain lesions and systemic disease, surgery generally is not considered to be appropriate.[61] In some cases, however; it may be necessary to resect the one "dominant" lesion that is causing symptoms such as intracranial hypertension, seizures, hemorrhage, or other severe neurologic side effects.[62,63] SRS may be considered over surgery for patients with fewer than three metastatic central nervous system (CNS) lesions that are deep, nonsymptomatic, and less than 3 cm in size.[41] WBRT is indicated for patients with multiple (more than three) CNS metastases, surgically inaccessible lesions, and extensive systemic disease.[41] WBRT for metastatic CNS MM does not improve survival or provide a cure; however, it is effective in relieving neurologic symptoms.[41]

The median survival for patients with CNS metastasis is 3.5 months with best supportive care and corticosteroids.[40] Patients

treated with WBRT and SRS or SRS alone have a median survival of 28 to 40 weeks, and the cause of death for most of these patients is progressive extracranial disease.[62] Median survival of 5 to 12 months has been reported for surgical patients, with 1-year disease-free survival rates of 28% to 36%.[64]

Systemic Therapy for Brain Metastases

Temozolomide (TMZ) is an oral chemotherapy agent that is structurally and functionally similar to dacarbazine, and it belongs to a new class of alkylating agents known as *imidazotetrazines.* Temozolomide possesses activity against MM cells and the ability to cross the blood-brain barrier because of its lipophilicity, thus making it an ideal chemotherapy agent to be investigated for the treatment of MM with CNS metastases.[65] It is stable in the acidic pH of the stomach and is absorbed readily in the digestive tract with 100% bioavailability. Once it is in the CNS, temozolomide is hydrolyzed to the active metabolite MTIC [5-(3-dimethyl-1-triazenyl) imidazole-4-carboxamide].[65] MTIC breaks down rapidly to form the reactive methyldiazonium ion, which methylates guanine residues in the DNA molecule causing cytotoxicity. TMZ does not cause cross-linking of DNA strands, making it less toxic to hematopoetic progenitor cells in the bone marrow than the nitrosoureas, platinum compounds, procarbazine, and dacarbazine.[65]

A recent phase III clinical trial comparing single-agent TMZ with dacarbazine demonstrated that TMZ is at least as effective as dacarbazine against advanced metastatic MM without CNS involvement.[57] The role of TMZ, either alone or as combination therapy, in the prevention and treatment of MM CNS metastasis is an area of active research.[66–68] In a phase II trial involving patients who have not received prior systemic chemotherapy for the treatment of MM brain metastases, single-agent TMZ showed a response rate of 7%, stable disease in 29% of patients, and a median overall survival of 3.5 months.[69] When TMZ was administered in combination with WBRT in patients with CNS metastasis, the response rate was only 10%, with the duration of response ranging from 2 to 7 months.[66] The combination of TMZ and a biochemotherapy regimen that included cisplatin, IL-2, and interferon-α2b was evaluated in a phase II outpatient clinical trial for metastatic MM.[67] The results suggest that the rate of CNS metastasis may be decreased in patients who have either a complete or partial response owing to the addition of a CNS-active agent (TMZ).[67] Thalidomide is an agent that possesses antiangiogenic and immunomodulatory properties, and since MM metastases tend to be very vascular, they may respond to antiangiogenic therapy. In a phase II trial that combined TMZ and thalidomide for the treatment of chemotherapy-naive patients with brain metastases, a response rate of 12% was observed, with a median duration of response of 4 months.[68] In light of these promising data with TMZ, further trials are being conducted to confirm the benefit of TMZ in preventing progression or treating CNS metastases.

Treatment Options for NMSC

Surgery

Surgery is the primary treatment modality for all patients diagnosed with either BCC or SCC. Full-thickness ablative procedure is the preferred method for high-risk tumors. Low-risk tumors can be treated with superficial ablative techniques.[38] NMSC is considered to be high risk if it has any of the following features: it is recurrent, the location is at a high-risk site (e.g., mask areas of the face, lips, ears, hands, and feet), it is larger than 2 cm in diameter or greater than or equal to 4 mm in depth, it is moderately or poorly differentiated, it is fast growing, it has ill-defined borders, there is positive perineural or vascular invasion, the patient is immunosuppressed, or it is the morpheaform or metatypical sub-type of BCC.[38] If the tumor is located on the trunk or extremities, less than 2 cm in diameter and less than 4 mm in depth, well differentiated, slow growing, has well-defined borders, and is the nodular or superficial sub-type of BCC, then it is considered to be low risk.[38] The 5-year survival rate for surgical excision, electrodesiccation and curettage, and Mohs' micrographic surgery is 90% or better for NMSC.[38]

Photodynamic Therapy

Photodynamic therapy is a noninvasive treatment option for superficial BCC and SCC. This method uses a combination of a photosensitizing drug and light to cause selective damage to target tissues.[70] The sensitizer absorbs energy directly from a light source. The energy then is transferred to molecular oxygen to create an activated form of oxygen called *singlet oxygen* that reacts with cellular component to cause cell damage and death.[70] The photosensitizing agent is administered intravenously or topically. In the treatment of skin cancer, the topical agent 5-aminolevulinic acid is approved by the FDA for the treatment of actinic keratosis, and studies are evaluating its role in the treatment of BCC and SCC. 5-Aminolevulinic acid is available in the United States as a solution that is applied for 14 to 18 hours to the lesion.[71] Then the lesion is irradiated with a blue light for 5 to 20 minutes.[71] The most common side effects are a burning, stinging, or prickling sensation restricted to the area of treatment. Erythema, hypo- or hyperpigmentation, and edema at the lesion also may occur. The thickness of the tumor is a determinant of response to therapy.[71] Superficial BCC has a complete response rate of 90% to 100% compared with a response rate of 10% to 70% for nodular BCC.[17] There is no evidence of its effectiveness with SCC at present.

Imiquimod

Imiquimod is an immune response modifier that has the ability to activate acquired and innate immune response. It is a topical agent that has been shown to be effective for SCC in case reports. It has been studied more extensively in superficial and nodular BCC, with response rates of 70% to 88%.[72] The most common side effects are erythema, itching, pain, and crusting

that are mild to moderate. At this time, the optimal frequency of application, duration of treatment, and recurrence rates after long-term follow-up still need to be determined before it can be recommended as standard of care for NMSC.[72]

OUTCOME EVALUATION

The outcome of patients diagnosed with MM depends on the stage of the disease at diagnosis. The overall 5-year survival rate for patients with localized disease (stage I and IB) is the best at 89% to 95%.[31] For patients with stage IIA to IIIA disease, the 5-year survival rate is greater than 50%, ranging from 63% to 77%.[31] In patients with more advanced regional metastatic disease (stage IIIB to IIIC), the 5-year survival rate ranges from 27% to 53%.[31] Patients with stage IV distant metastatic disease have the worst 5-year survival rate at only 10% to 19%.[31] BCC and SCC have excellent outcomes, with cure rates approaching 98%.[5]

After diagnosis and treatment of skin cancer, the next crucial step in the management of this diagnosis is monitoring for recurrence. The risk of recurrence depends on the stage of the disease, and recurrences may develop even decades after the initial diagnosis. However, most recurrences materialize in the first 5 years, and the majority appear within the first 2 to 3 years following treatment.[38] The site of recurrence can be at the original site of the disease or in a different, distant anatomic location. Early detection of tumor recurrence is crucial because response rate is decreased significantly with tumor relapse.[5] Recurrences are found equally by physicians and patients, and one study demonstrated that 94% of recurrences were detected by the patient.[73] Thus it is imperative to educate patients on how to perform a total skin self-examination appropriately. Additionally, patients need to understand the importance of scheduling regular follow-up visits with the oncologist or dermatologist after the diagnosis and treatment of skin cancer. The purpose of these visits is for the clinician to monitor for new tumor appearance or recurrence of the original cancer. During the follow-up visit, the clinician will perform a total skin examination with special attention to previous biopsy and lesion sites. A palpation of the lymph nodes and careful review of system also are performed.[38]

There is no universal guideline for follow-up care for MM. The National Comprehensive Cancer Network recommends annual skin examination for all patients.[61] Educate patients with stage IA disease to have a history and physical examination every 3 to 12 months as clinically indicated and an annual skin examination for life. For stage IB to III disease, schedule a history and physical examination every 3 to 6 months for 3 years, every 4 to 12 months for 2 years, and then annually as indicated. It is optional to obtain a chest x-ray, LDH, complete blood count (CBC), and liver function tests (LFTs) every 3 to 12 months. CT scan can be obtained as indicated clinically.[61] For NMSC, educate patients to schedule follow-up visits with the oncologist after treatment every 3 months for the first year and then every 6 months thereafter for at least 5 years.[5]

Patients who received immunotherapy after stage III or IV MM may experience fatigue and other chronic side effects. Develop a plan to order laboratory tests such as LFTs, thyroid-stimulating hormone, and white blood cell count at baseline and on a weekly or monthly basis as indicated. Monitor and evaluate patients for side effects of IL-2 or interferon-α2b, and educate patients on what to expect and how the side effects will be managed. Assess the patients' psychological, physical, and social functioning. Counsel patients to contact the hospital's social service department or the American Cancer Society for assistance in dealing with the disease emotionally, and recommend that patients consider attending support group meetings or talking to a counselor if or before they become overwhelmed with the diagnosis.



Patient Care and Monitoring

1. Obtain a thorough patient medication history, both prescription and nonprescription, to prevent drug interactions with the current therapy the patient is receiving.
2. Obtain the appropriate baseline laboratory tests, and determine a time interval for reevaluation of specific laboratory tests to determine toxicity.
3. Provide education on the side effects of therapy.
   - What to administer/take to prevent side effects
   - When to administer/take the medication to decrease side effects
   - Nonpharmacologic recommendations to minimize side effects
   - Drugs that may interact with therapy
   - Lab tests that need to be monitored on a regular basis
   - What are the parameters for discontinuing or holding therapy?
   - If therapy is to be reinitiated, what should the new dose of therapy be?
4. Assess the patient for adverse drug reactions and drug-drug interactions.
5. Educate the patient on the signs and symptoms of infection.
6. Assess for changes in the patient's quality of life owing to side effects of drug therapy.
7. Educate the patient on measures that should be undertaken to limit sun exposure and prevent skin cancer.
8. Educate the patient on how to do skin self-examination for suspicious moles.
9. Educate the patient on follow-up recommendations after treatment for skin cancer is completed.

ABBREVIATIONS

BCC: basal cell carcinoma
CLS: capillary leak syndrome
CNS: central nervous system
CTL: cytotoxic T lymphocyte
FDA: Food and Drug Administration
HDI: high-dose interferon-α2b
IDI: intermediate dose interferon-α2b
IFN: interferon-α2b
IL-2: interleukin 2
LDI: low-dose interferon-α2b
MM: malignant melanoma
MMS: Mohs' micrographic surgery
NMSC: nonmelanoma skin cancer
SCC: squamous cell carcinoma
SLN: sentinel lymph node
SRS: stereotactic radiosurgery
SSRI: selective serotonin reuptake inhibitor
TMZ: temozolamide
UV: ultraviolet
WBRT: whole-brain radiation therapy

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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95 Hematopoietic Cell Transplantation

Jeannine S. McCune



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Explain the rationale for using hematopoietic cell transplant (HCT) to treat cancer.
2. Compare the different types of HCTs, specifically (a) the types of donors (i.e., autologous and allogeneic), (b) the source of hematopoietic cells (i.e., umbilical cord, peripheral blood progenitor cells, and bone marrow), and (c) the type of preparative regimen (i.e., myeloablative and nonmyeloablative).
3. List the nonhematologic toxicity to high-dose chemotherapy used in myeloablative preparative regimens, specifically busulfan-induced seizures, hemorrhagic cystitis, gastrointestinal toxicities, and sinusoidal obstruction syndrome.
4. Develop a plan for monitoring and managing engraftment of hematopoiesis.
5. Explain graft-versus-host disease (GVHD).
6. Recommend a prophylactic and treatment regimen for graft-versus-host disease (GVHD).
7. Choose an appropriate regimen to minimize the risk of infectious complications in HCT patients.
8. Evaluate the long-term health care of hematopoietic cell transplant (HCT) survivors.

Key Concepts

❶ Hematopoietic cell transplantation (HCT) is a procedure used mainly to treat hematologic malignancies via high-dose chemotherapy and/or a graft-versus-tumor effect.

❷ An autologous HCT involves the infusion of a patient's own hematopoietic cells and allows for the administration of higher doses of chemotherapy, radiation, or both to treat the malignancy. Infusion of another's hematopoietic cells is an allogeneic HCT; these cells can be from donors related or unrelated to the recipient.

❸ Umbilical cord blood, peripheral blood progenitor cells (PBPC) and bone marrow can serve as the source of hematopoietic cells. The optimal cell source differs based on the donor and recipient characteristics but has not been clearly identified for all patients.

❹ A myeloablative preparative regimen involves the administration of sublethal doses of chemotherapy to the recipient. The recipient will not regain his or her own hematopoiesis (i.e., graft failure or graft rejection) and will be at risk for substantial life-threatening nonhematologic toxicity.

❺ A nonmyeloablative preparative regimen is less toxic than a myeloablative regimen in hopes of being able to offer the benefits of an allogeneic HCT to more patients. A nonmyeloablative HCT is based on the concept of donor immune response having a graft-versus-tumor effect.

❻ Nonhematologic toxicity differs based on the preparative regimen administered.

❼ Engraftment is the reestablishment of functional hematopoiesis. It is commonly defined as the point at which a patient can maintain a sustained absolute neutrophil count (ANC) of greater than 500 cells/mm^3 (0.5×10^9/L) and a sustained platelet count of greater 20,000/mm^3 (20×10^9/L) lasting for 3 or more consecutive days without transfusions.

❽ Graft-versus-host disease (GVHD) is caused by the activation of donor lymphocytes leading to immune damage to the skin, gut, and liver in the recipient. An immunosuppressive regimen is administered to prevent GVHD in recipients

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of an allogeneic graft; this regimen is based on the type of preparative regimen and the source of the graft.

❾ Recipients of HCT are at higher risk of bacterial, viral, and fungal infections and usually receive a prophylactic or preemptive regimen to minimize the morbidity and mortality owing to infectious complications.

❿ Long-term survivors of HCT should be monitored closely, particularly for infections and secondary malignant neoplasms.

❶ *Hematopoietic cell transplantation (HCT) is a procedure used mainly to treat hematologic malignancies via high-dose chemotherapy and/or a graft-versus-tumor effect.* An essential component of this procedure is the infusion of hematopoietic cells into the recipient to treat disease and/or restore normal hematopoiesis and lymphopoiesis. HCT developed from allogeneic bone marrow transplant (BMT), which involved administration of a high-dose myeloablative preparative regimen followed by true "transplantation" of bone marrow from one individual to another. Bone marrow contains pluripotent stem cells and postthymic lymphocytes, which are responsible for, respectively, long-term hematopoietic reconstitution, immune recovery, and its associated graft-versus-host disease (GVHD).[1] Subsequently, the dose-intensity concept for cancer treatment was expanded to using myeloablative preparative regimens followed by autologous HCT.

The type of HCT performed depends on a number of factors, including type and status of disease, availability of a compatible donor, patient age, performance status, and organ function. In addition to bone marrow, hematopoietic cells may be obtained from the peripheral blood progenitor cells (PBPCs) and umbilical cord blood. The essential properties of the hematopoietic cells are their ability to engraft, the speed of **engraftment,** and the durability of engraftment.[1]

Examples of diseases treated with HCT are listed in Table 95–1. **Autologous HCT,** or infusion of a patient's own hematopoietic cells, allows for the administration of higher doses of chemotherapy, radiation, or both to treat the malignancy or autoimmune disorder. In this setting, the hematopoietic cells "rescue" the recipient from otherwise dose-limiting hematopoietic toxicity. Autologous HCT is used to treat intermediate- and high-grade non-Hodgkin's lymphoma (NHL), acute myeloid leukemia (AML), multiple myeloma (MM), neuroblastoma, and relapsed or refractory Hodgkin's disease.[2] ❷ *Allogeneic HCT involves the transplantation of hematopoietic cells obtained from a different person's (termed the donor) bone marrow, peripheral blood, or umbilical cord blood to the recipient.* Unless the donor and the recipient are identical twins (referred to as a *syngeneic HCT*), they are dissimilar genetically. **Allogeneic HCT** is used to treat both nonmalignant (e.g., aplastic anemia, thalassemia major, severe combined immunodeficiency disease, Wiskott-Aldrich syndrome, Fanconi's anemia, and infantile osteopetrosis) and malignancies [e.g., AML and chronic myeloid leukemia (CML)].[2]

The infusion of hematopoietic cells follows the administration of a combination of chemotherapy and/or radiation—termed the *conditioning* or ***preparative regimen.*** ❹ *A* ***myeloablative preparative regimen*** *involves the administration of sublethal doses of chemotherapy to the recipient. The recipient will not regain his or her own hematopoiesis (i.e., graft rejection) and will be at risk for substantial life-threatening nonhematologic toxicity.* For those undergoing an autologous HCT, their hematopoietic cells must be obtained (i.e., harvested) before the myeloablative preparative regimen is administered and stored subsequently. After administration of the preparative regimen is completed, these hematopoietic cells serve as a rescue intervention to reestablish bone marrow function and avoid long-lasting life-threatening marrow aplasia that results from the myeloablative preparative regimen.[3] In the setting of an allogeneic HCT, the preparative

TABLE 95–1. Diseases Commonly Treated with HCT

	Autologous Graft	Allogeneic Graft
Cancers	Multiple myeloma Non-Hodgkin's lymphoma Hodgkin's disease Acute myeloid leukemia Neuroblastoma Germ cell tumors	Acute myeloid leukemia Acute lymphoblastic leukemia Chronic myeloid leukemia Myelodysplastic syndrome Myeloproliferative disorders Non-Hodgkin's lymphoma Hodgkin's disease Chronic lymphocytic leukemia Multiple myeloma
Other diseases	Autoimmune diseases Amyloidosis	Aplastic anemia Paroxysmal nocturnal hemoglobinuria Fanconi's anemia Thalassemia major Sickle cell anemia Severe combined immunodeficiency Inborn errors of metabolism

regimen is designed to suppress the recipient's immunity, eradicate residual malignancy, or create space in the marrow compartment. At most HCT centers, normal renal, hepatic, pulmonary, and cardiac function and age younger than 65 years are necessary for eligibility for myeloablative allogeneic HCT. A myeloablative or nonmyeloablative preparative regimen may be used with allogeneic HCT; only myeloablative preparative regimens are used for autologous HCT. Allogeneic HCT offers the potential for a graft-versus-tumor (GVT) effect in which immune effector cells from the donor recognize and eliminate residual tumor in the recipient.[4]

The recognition of GVT effect, which likely is caused by cytotoxic T lymphocytes in the donor stem cells, led to investigations with nonmyeloablative transplants (NMTs), in which less toxic preparative regimens are used in the hope of expanding the availability of HCT to recipients whose medical condition or age prohibits use of myeloablative regimens.[4]

EPIDEMIOLOGY AND ETIOLOGY

Each year, the number of allogeneic HCTs is less than the number of autologous HCTs. Worldwide, approximately 25,000 autologous HCTs and 15,000 allogeneic HCTs were performed in 2000.[5] Since 1998, the number of allogeneic HCTs reached a plateau, most likely owing to the limited availability of suitable donors, limited success to date with HLA-disparate donors, and the increasing availability of targeted therapies for diseases that traditionally were treated with HCT (e.g., imatinib for newly diagnosed chronic-phase chronic myelogenous leukemia).[5] In the year 2000, NMT represented approximately 25% of allogeneic HCTs.[5]

Autologous peripheral blood progenitor cell (PBPC) use has increased and essentially has replaced bone marrow in many transplant centers. In 2000, over 95% of autologous HCTs in adults and 80% in children used PBPCs as the source of hematopoietic cells.[5] Autologous HCT is used to treat a variety of malignancies; non-Hodgkin's lymphoma (NHL) and multiple myeloma are the most common indications for this procedure and represent over one-third of all autologous HCTs.[5] Autologous HCT circumvents the need for histocompatible donors, is associated with lower mortality, and is not restricted by age to patients younger than 50 years.[6] The use of allogeneic PBPCs is increasing; in the year 2000, 40% of allogeneic HCTs performed worldwide used PBPCs as the source of hematopoietic cells rather than bone marrow.[5]

PATHOPHYSIOLOGY

For an allogeneic HCT, the recipient and the donor are dissimilar genetically unless they are identical twins (referred to as a *syngeneic HCT*). The tissue transplanted is immunologically active, and thus there is potential for bidirectional graft rejection.[7] In the first scenario, cytotoxic T cells and natural killer (NK) cells belonging to the host (recipient) recognize minor histocompatibility (MHC) antigens of the graft (donor hematopoietic cells) and lead to a rejection response. In the second scenario, immunologically active cells in the graft recognize host MHC antigens and elicit an immune response. The former is referred to as *host-versus-graft disease* and the latter as **graft-versus-host disease (GVHD).** Host-versus-graft effects are more common in solid-organ transplantation. When host-versus-graft effects occur in allogeneic HCT, they are referred to as *graft failure* or *rejection,* which results in ineffective hematopoiesis (i.e., adequate ANC and/or platelet counts were not obtained). ❼ *Engraftment is defined as the point at which a patient can maintain a sustained absolute neutrophil count (ANC) of greater than 500 cells/mm^3 (0.5 × 10^9/L) and a sustained platelet count of greater than or equal to 20,000/mm^3 (20 × 10^9/L) lasting greater than or equal to 3 consecutive days without transfusions.*[8] Therefore, an essential first step for patients eligible for HCT is finding a human leukocyte antigen (HLA)–compatible graft with an acceptable risk of graft failure and GVHD. GVHD is caused by the activation of donor lymphocytes, leading to immune damage in the recipient.

Histocompatibility

Histocompatibility differences between the donor and the recipient necessitate immunosuppression after an allogeneic HCT because considerable morbidity and mortality are associated with graft failure and GVHD.[9] Rejection is least likely to occur with a syngeneic donor, meaning that the recipient and host are identical (monozygotic) twins. In patients without a syngeneic donor, initial HLA typing is conducted on family members because the likelihood of complete histocompatibility between unrelated individuals is remote. Siblings are the most likely individuals to be histocompatible within a family. The chance for complete histocompatibility occurring in an individual with only one sibling is 25%. Approximately 40% of patients with more than one sibling will have an HLA-identical match. Having a matched sibling donor is no longer a requirement for allogeneic HCT because improved immunosuppressive regimens and the National Marrow Donor Program have allowed an increase in the use of unrelated or related matched or mismatched HCTs.[10] The use of alternative sources of allogeneic hematopoietic cells, such as related donors mismatched at one or more HLA loci or phenotypically (i.e., serologically) matched unrelated donors, has been evaluated.[10] Establishment of the National Marrow Donor Program has helped to increase the pool of potential donors for allogeneic HCT.[10] Through this program, an HLA-matched unrelated volunteer donor might be identified. Recipients of an unrelated graft are more likely to experience graft failure and acute GVHD relative to recipients of a matched-sibling donor.[11] Thus work is ongoing to identify factors that predict for graft failure or GVHD to improve the availability and safety of unrelated-donor transplants.[12]

Determination of histocompatibility between potential donors and the patient is completed before allogeneic HCT. Initially, HLA typing performed using blood samples and compatibility for class I MHC antigens (i.e., HLA-A, HLA-B, and HLA-C) is determined through serologic and DNA-based testing methods.[13] In vitro reactivity between donor and recipient also can be assessed in mixed-lymphocyte culture, a test used to measure compatibility of the MHC class II antigens (i.e., HLA-DR, HLA-DP, HLA-DQ).[13] Currently, most clinical and research laboratories are also performing molecular DNA typing using polymerase chain reaction methodology to determine the HLA allele sequence.[13,14]

The preparative regimen or GVHD prophylaxis may be altered based on the mismatch between the donor and the recipient. The risk of graft failure decreases with better matches such that those with a class I (i.e., HLA-A, -B, or -C) antigen mismatch have the highest risk of rejection, whereas those with just one class I allele mismatch have a minimal risk. Graft failure does not appear to be associated with mismatch at a single class II antigen or allele.[14] GVHD, both acute and chronic, and survival also have been associated with disparity for class I and II antigens and alleles.[15,16]

Autologous hematopoietic stem cells are obtained (or "harvested") from bone marrow or peripheral blood. The technique for harvesting autologous hematopoietic cells depends on the anatomic source (i.e., bone marrow or peripheral blood). A surgical procedure is necessary for obtaining bone marrow. Multiple aspirations of marrow are obtained from the anterior and posterior iliac crests until a volume with a sufficient number of hematopoietic cells is collected (i.e., 600–1200 mL of bone marrow). The bone marrow then is processed to remove fat or marrow emboli and usually is infused intravenously into the patient like a blood transfusion.

The shift to the use of PBPCs over bone marrow for autologous HCT is primarily because of the more rapid engraftment and decreased health care resource use. Because the harvest occurs before administering the preparative regimen, autologous hematopoietic cells must be cryopreserved and stored for future use.

Transplantation with PBPCs essentially has replaced bone marrow transplantation (BMT) as autologous rescue after myeloablative preparative regimens.[17] Autologous PBPCs are obtained by administering a mobilizing agent(s) followed by apheresis, which is an outpatient procedure similar to dialysis. Hematopoietic growth factors (HGFs) alone or in combination with myelosuppressive chemotherapy are used for mobilization of autologous PBPCs with similar results.[18] The HGFs granulocyte-macrophage colony-stimulating factor (sargramostim, Leukine®) and granulocyte colony-stimulating factor (filgrastim, Neupogen®) are used as mobilizing agents.[17] In this setting, the most frequently used filgrastim doses are in the range of 5 to 16 mcg/kg per day, administered subcutaneously, with higher doses (greater than 10 mcg/kg per day) of filgrastim yielding more PBPCs.[18,19] The highest values of mobilized progenitor cells are observed 5 to 6 days after mobilization with filgrastim alone.[18]

The combination of chemotherapy with an HGF enhances PBPC mobilization relative to HGF alone.[18,20] In addition to treating the underlying malignancy, this approach lowers the risk of tumor cell contamination and the number of apheresis collections required, but there is a greater risk of neutropenia and thrombocytopenia.[18] The HGF is initiated after completion of chemotherapy and continued until apheresis is complete. Many centers monitor the number of cells that express the CD34 antigen (i.e., CD34+ cells) to determine when to start apheresis.[17] Apheresis is continued daily until the target number of PBPCs per kilogram of the recipient's weight is obtained. For adult recipients, the number of CD34+ cells correlates with time to engraftment.[21] The CD34 antigen is expressed on almost all unipotent and multipotent colony-forming cells and on precursors of colony-forming cells but not on mature peripheral blood cells. In adults, the target number of 1.5 to 5 $\times$ 10^6 CD34+ cells per kilogram of recipient weight is needed for autologous PBPC transplant.[22] Lower yield of CD34+ cells is associated with administration of stem cell toxic drugs (e.g., carmustine and melphalan) and intensive prior chemotherapy or radiotherapy.[18] There is a paucity of information regarding the parameters associated with engraftment in children undergoing an autologous PBPC transplant.[23]

TREATMENT

Desired Outcome

The desired outcome with HCT is to cure the patient of his or her underlying disease, typically cancer, while minimizing the short- and long-term morbidity associated with HCT. Nonpharmacologic therapies include choosing the optimal source of hematopoietic cells, whether autologous or allogeneic, and if an allogeneic donor is used, finding a donor with the closest HLA match to lower the risk of graft failure and GVHD. The pharmacologic therapies include the preparative regimen with the necessary supportive care measures for its hematologic and nonhematologic toxicity and the regimens to prevent and treat GVHD.

Nonpharmacologic Therapy

Harvesting, Preparing, and Transplanting Allogeneic Hematopoietic Cells

❸ *Bone marrow, peripheral blood progenitor cells (PBPCs) and umbilical cord blood can serve as the source of hematopoietic cells. The optimal cell source differs based on the donor and recipient characteristics but has not been clearly identified for all patients.*

Bone Marrow

Harvesting the bone marrow from an allogeneic donor is conducted via the same process as for an autologous HCT. The harvest occurs on day 0 of the HCT such that it is infused into the recipient immediately after processing. The marrow may

need additional processing if the donor and recipient are ABO-incompatible, which occurs in up to 30% of HCTs. Red blood cells (RBCs) may need to be removed before infusion into the recipient to prevent immune-mediated hemolytic anemia and thrombotic microangiopathic syndromes.[24]

Peripheral Blood Progenitor Cells (PBPCs)

The allogeneic (healthy) donor first undergoes mobilization therapy with an HGF to increase the number of hematopoietic cells circulating in the peripheral blood.[25] The most commonly used regimen to mobilize allogeneic donors is a 4- to 5-day course of filgrastim, 10 to 16 mcg/kg per day, administered subcutaneously, followed by leukopheresis on the fourth or fifth days when peripheral blood levels of CD34+ cells peak. An adequate number of hematopoietic cells usually is obtained with one to two apheresis collections, with the optimal number of CD34+ collected being a minimum of 5 to 8×10^6 cells/kg of recipient body weight.[26] Higher cell doses have been associated not only with more rapid engraftment but also with fewer fungal infections and improved overall survival.[27] Hematopoietic cells obtained from the peripheral blood are processed like bone marrow–derived stem cells and may be infused immediately into the recipient or frozen for future use. In comparison with bone marrow donation, allogeneic PBPC donation leads to quicker recovery.[26] The donor may experience musculoskeletal pain, headache, mild increases in hepatic enzyme or lactate dehydrogenase levels owing to filgrastim administration, and hypocalcemia owing to citrate accumulation, which decreases ionized calcium concentrations during apheresis.[25,28]

Allogeneic PBPC grafts contain approximately 10 times more T and B cells than bone marrow grafts. Because these cells survive long term, lymphocytes subsets are higher, and the rate of severe infections after engraftment is lower with a PBPC graft.[29] Historically, there also has been significant concern that the greater T- and B-cell content of PBPCs could increase the risk of acute and/or chronic GVHD. In patients with a hematologic malignancy who have an HLA-matched sibling donor, a PBPC graft is optimal relative to bone marrow graft because the PBPC graft is associated with quicker neutrophil and platelet engraftment, lower relapse rates, and improved disease-free survival rates.[30] Grafts from PBPCs are associated with a similar incidence of acute GVHD but an approximately 20% increase in the incidence of extensive-stage and overall chronic GVHD.[30] Similar trends for engraftment and GVHD have been found with unrelated donors.[31]

Umbilical Cord Blood

Transplant with umbilical cord blood (UCB) offers an alternative stem cell source to patients who do not have an acceptable matched related or unrelated donor. When allogeneic hematopoietic cells are obtained from UCB, the cord blood is obtained from a consenting donor in the delivery room after birth and delivery of the placenta.[32] The cord blood then is processed, a sample is sent for HLA typing, and the cord blood is frozen and stored for future use. Numerous UCB registries exist, with the goal of providing alternative sources of allogeneic stem cells.[33] Functional hematopoietic progenitor and stem cells can be found in UCB cryopreserved for up to 15 years; however, their ability to engraft successfully in a patient is unknown.[34] UCB transplantation, from a related or unrelated donor, is effective in children with cancer and nonmalignant conditions.[34] Engraftment is slower in UCB transplants, with a lower risk of GVHD and similar survival rates relative to BMT.[35–37] In children receiving a UCB graft from an unrelated donor, cell dose (e.g., nucleated cells) is related to engraftment, transplant-related morbidy, and survival.[38] Although there were initial concerns regarding whether a UCB transplant could provide enough nucleated cells to engraft adequately within an adult, there is growing experience to indicate that a UCB transplant is feasible when at least 1×10^7 nucleated cells per kilogram of recipient body weight are administered.[38,39]

T-Cell Depletion

Immunocompetent T lymphocytes may be depleted from the donor bone marrow ex vivo before infusion (referred to as *T-cell-depleted hematopoietic cells*) into the recipient as a means of preventing GVHD. Depletion of T lymphocytes in donor hematopoietic cells is completed ex vivo using physical (e.g., density-gradient fractionation) and/or immunologic [e.g., antithymocyte globulin (ATG) and CAMPATH-1 antibodies] methods.[40] Functional recovery of T cells in the recipient is delayed, and the risk of Epstein-Barr virus–associated lymphoproliferative disorders is higher with the use of T-cell-depleted bone marrow.[40] The use of T-cell-depleted grafts reduces the incidence of GVHD,[40] but graft failure and relapse are more common. The use of donor lymphocyte infusion (DLI) in patients who relapse after receiving a T-cell-depleted BMT also is under study.[41]

Engrafment

After chemotherapy and radiation, pancytopenia lasts until the infused stem cells reestablish functional hematopoiesis (i.e., engraftment is attained). The median time to engraftment is a function of several factors, including the source of stem cells with peripheral blood progenitor cells (PBPCs), which can result in earlier engraftment than bone marrow.[42,43] Myeloablative preparative regimens have significant regimen-related toxicity and morbidity and thus usually are limited to healthy, younger (i.e., usually younger than 50 years) patients. Alternatively, nonmyeloablative transplants (NMT), also referred to as *nonablative stem cell transplants* or *minitransplants,* are being performed with the hope of curing more patients with cancer by increasing the availability of HCT with less regimen-related toxicity and by using the GVT effect.[6]

A delicate balance between host and donor effector cells is necessary, and residual host-versus-graft effects may lead to graft failure, which is also known as *graft rejection. Graft failure* is defined as the lack of functional hematopoiesis after HCT and can occur early (i.e., lack of initial hematopoietic

recovery) or late (i.e., in association with recurrence of the disease or reappearance of host cells after initial donor cell engraftment).[44] The incidence of graft rejection is higher in patients with aplastic anemia and in patients undergoing allogeneic HCT with histoincompatible marrow or T-cell-depleted marrow. Engraftment usually is evident within the first 30 days in patients undergoing an NMT with this preparative regimen; however, rejection can occur after initial engraftment.[4] Therapeutic options for the treatment of graft rejection are limited, and a second HCT is the most definitive therapy, although the toxicities are formidable.[45]

Graft-versus-Tumor (GVT) Effect

A GVT effect occurs owing to the donor lymphocytes, as supported by three observations after myeloablative allogeneic HCT. Namely, (1) lower relapse rates in patients with GVHD relative to those who did not have GVHD, (2) a higher rate of leukemia relapse after T-cell-depleted BMT, and (3) the effectiveness of donor lymphocyte infusions (DLIs) in reinducing a remission (i.e., no evidence of cancer) in patients who relapsed after allogeneic HCT. In DLI, lymphocytes are collected from the peripheral blood of the donor and administered to the recipient. Eradication of the recurrent malignancy is due to either specific targeting of the tumor antigens or to GVHD, which may affect cancer cells preferentially. Patients with hematologic malignancies and certain solid tumors (e.g., renal cell carcinoma) appear to benefit from a GVT effect. These data gave rise to the use of nonmyeloablative preparative regimens.



Patient Encounter 1

LL, a 47-year-old man, was diagnosed with high-risk diffuse large cell B-cell non-Hodgkin's lymphoma (NHL) 12 months ago. LL had a complete response to his initial treatment of six cycles of RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). LL is participating in a clinical trial and is randomized to receive a myeloablative autologous HCT: TBI days 8 to 5, etoposide day 4, rest day 3, cyclophosphamide day 2, rest day 1, with infusion of autologous PBPC on day 0.

What additional data do you need to know before creating a monitoring plan for LL?
What nonhematologic toxicity should be monitored?
What pharmacologic management is necessary during administration of the preparative regimen?

It is day +1, and LL has a white blood cell (WBC) count with differential of 0/mm^3, ANCs 0/mm^3 (0 × 10^9/L), platelets 30,000/mm^3 (30 × 10^3/μL), and hemoglobin 9 g/dL (5.6 mmol/L). Renal clearance and liver function are within normal limits. Vital signs are bp 130/80, RR 18, and T 39°C (102.2°F). Medications include ceftazidime 2 g IV tid and filgrastim 480 mcg subcutaneously daily.

- Develop a monitoring plan for LL's hematologic function.
- Identify your treatment goals for LL's hematologic function.

Pharmacologic Therapy

Preparative Regimens for HCT

Examples of commonly used preparative regimens are included in Table 95–2. ❻ *The nonhematologic toxicity differs based on the preparative regimen administered.*

Myeloablative Preparative Regimens

In both autologous and allogeneic HCT, infusion of stem cells circumvents dose-limiting myelosuppression, maximizing the potential value of the steep dose-response curve to alkylating agents and radiation, suppressing the host immune system, and creating space in the marrow compartment to facilitate engraftment. The preparative regimen is designed to eradicate immunologically active host tissues (lymphoid tissue and macrophages) and to prevent or minimize the development of host-versus-graft reactions. A myeloablative preparative regimen may not be necessary if a histocompatible

TABLE 95–2. Commonly Used Preparative Regimens for HCT[a]

Type of HCT	Preparative Regimen	Dose/Schedule for Adults
Allogeneic[108]	Myeloablative CY-TBI	CY 60 mg/kg per day IV on 2 consecutive days before TBI 1000–1575 rads fractionated over 1–7 days
Allogeneic, autologous[109]	Myeloablative BU-CY	BU: 1 mg/kg per dose PO or 0.8 mg/kg per dose IV q6hours × 16 doses; CY 60 mg/kg per day IV QD × 2 days following BU
Autologous[110]	Myeloablative BEAM (carmustine/etoposide/-cytarabine/melphalan)	Carmustine 150 mg/m^2 per day IV × 2, days –6 to –5 Etoposide 200 mg/m^2 per day IV bid × 4, days –5 to –2 Cytarabine 200 mg/m^2 per day IV bid × 4, days –5 to –2 Melphalan 140 mg/m^2 per day IV × 1, day –2
Allogeneic[64]	Nonmyeloablative FLU-TBI	Fludarabine 30 mg/m^2 per day IV on 3 consecutive days (–4, –3, –2), TBI2 Gy as a single fraction on day 0
Allogeneic	Nonmyeloablative	CY 60 mg/kg per day IV on 2 consecutive days (–7, –6), fludarabine 25 mg/m^2 per day IV (days –5 to –1)

[a]BU, busulfan; CY, cyclophosphamide; FLU, fludarabine; TBI, total body irradiation.

allogeneic HCT is performed on a patient with a poorly functioning immune system [e.g., severe combined immunodeficiency disease (SCID)]. In the absence of a functioning immune system, the likelihood of a host-versus-graft reaction to histocompatible donor hematopoietic cells is small. Similarly, patients undergoing syngeneic transplantation do not require immunosuppressive preparative regimens before HCT because the donor and the patient are genetically identical. Thus the preparative regimen is tailored to the primary disease and to HLA compatibility between the recipient-donor pair.

Most allogeneic preparative regimens for the treatment of hematologic malignancies contain either cyclophosphamide or radiation or both. The combination of cyclophosphamide and total-body irradiation (TBI) was one of the first preparative regimens developed and is still used widely today. This regimen is immunosuppressive and has inherent activity against hematologic malignancies (e.g., leukemias and lymphomas). TBI has the added advantage of being devoid of active metabolites that might interfere with the activity of donor hematopoietic cells. In addition, TBI eradicates residual malignant cells at sanctuary sites such as the central nervous system (CNS). Modifications of the cyclophosphamide-TBI preparative regimen include replacing TBI with other agents (e.g., busulfan) or adding other chemotherapeutic or monoclonal agents to the existing regimen in hopes of minimizing long-term toxicities. In the case of a mismatched allogeneic HCT with a substantially increased chance of graft rejection, ATG also may be added to the preparative regimen to further immunosuppress the recipient.

The optimal myeloablative preparative regimen is challenging to study because several indications for HCT (e.g., SCID and thalassemia) are rare enough that it is not feasible or is cost-prohibitive to conduct clinical trials that are powered adequately to detect clinically relevant differences. The long-term outcomes of busulfan-cyclophosphamide (BU-CY) and cyclophosphamide-TBI (CY-TBI) in patients with AML and CML, the more common indications for allogeneic HCT, have been compared in a meta-analysis of four clinical trials.[46] Equivalent rates of long-term complications were present between the two preparative regimens, except that there was a greater risk of cataracts with CY-TBI and alopecia with BU-CY. Overall and disease-free survivals were similar in patients with CML, whereas there was a trend for improved disease-free survival with CY-TBI in AML patients. Thus the preparative regimen can be tailored to the primary disease and to the HLA compatibility.

Nonmyeloablative Preparative Regimens

❺ *A nonmyeloablative preparative regimen is less toxic than a myeloablative regimen in hopes of being able to offer the benefits of an allogeneic HCT to more patients. A nonmyeloablative HCT is based on the concept of donor immune response having a graft-versus-tumor effect.*

Because of the severe regimen-related toxicity of a myeloablative preparative regimen, the use of HCT traditionally was limited to younger patients with minimal comorbidities. Most patients diagnosed with cancer are elderly, and thus myeloablative HCT could not be offered to a substantial portion of cancer patients.[47] The concept of donor immune response having a GVT effect gave rise to the theory that a strongly immunosuppressive but not myeloablative preparative regimen [i.e., a nonmyeloablative transplant (NMT)] may result in a state of chimerism in which the recipient and donor are coexisting.[48] The toxicity and efficacy of NMT are being evaluated in patients with nonmalignant conditions, such as congenital immunodeficiency, who are not eligible for a myeloablative HCT.[49]

A nonmyeloablative preparative regimen allows for development of mixed chimerism (defined as 5% to 95% peripheral donor T cells) between the host and recipient to allow for a GVT effect as the primary form of therapy (Fig. 95–1) Chimerism is

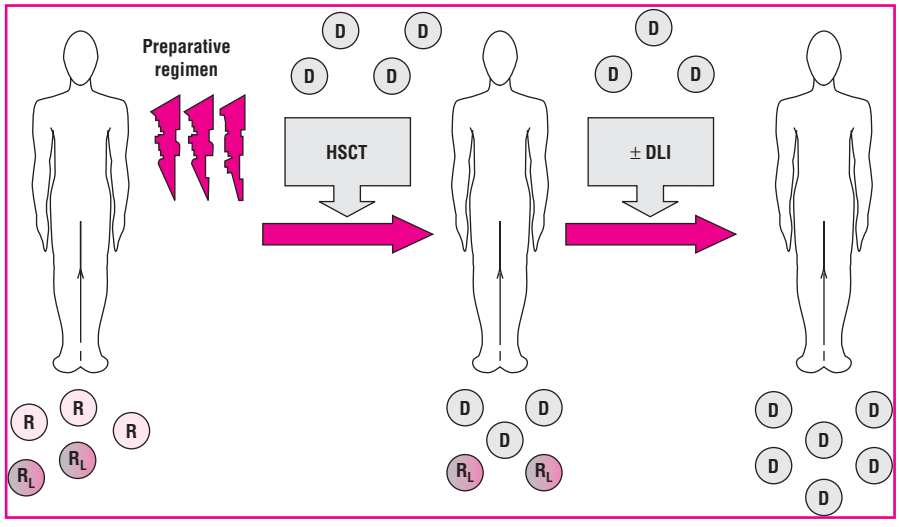


FIGURE 95–1. Schema for nonmyeloablative transplantation. Recipients (R) receive a nonmyeloablative preparative regimen and an allogeneic HCT. Intially, mixed chimerism is present with the coexistence of donor (D) cells and recipient-derived normal and leukemia/lymphoa (R_L) cells. Donor-derived T cells mediate a graft-verus-host hematopoietic effect that eradicates residual recipient-derived normal and malignant hematopoietic cells. Donor lymophycyte infusions (DLI) may be administered to enhance graft-versus-tumor effects. (Adapted from Champlin R, Khouri I, Anderlini P, et al. Nonmyeloablative preparative regimens for allogeneic hematopoietic transplantation: Biology and current indications. Oncology 2003; 17: 94–100.)

assessed within peripheral blood T cells and granulocytes and bone marrow using conventional (e.g., using sex chromosomes for opposite-sex donors) and molecular (e.g., variable number of tandem repeats) methods for same-sex donors.[50]

The nonmyeloablative preparative regimen does not completely eliminate host normal and malignant cells. Donor cells eradicate residual host hematopoiesis, and the GVT effects generally occur after the development of full donor T-cell chimerism.[51] After engraftment, mixed chimerism should be present and is shown by the presence of both donor- and recipient-derived cells. Autologous recovery should occur promptly if the graft is rejected. The intensity of immunosuppression required for engraftment depends on the immunocompetence of the recipient and the histocompatibility and composition of the HCT.[52] More intensive regimens that are required for engraftment in the setting of unrelated-donor- or HLA-mismatched-related HCT recently have been termed *reduced-intensity myeloablative transplants.*[52] After chimerism develops, donor-lymphocyte infusion can be administered safely in patients without GVHD to eradicate malignant cells.

Nonmyeloablative preparative regimens typically consist of a purine analog (e.g., fludarabine) in combination with an alkylating agent or low-dose TBI.[49,53] Adverse effects are decreased because of the lower-intensity preparative regimen, thus making HCT available to patients who in the past were not healthy or young enough to receive a myeloablative preparative regimen. The risk of GVHD remains with NMT; the GVHD prophylaxis regimens are reviewed in the GVHD section below. Presently, NMT is not indicated as first-line therapy for any malignant or nonmalignant conditions. NMT is being evaluated for cancers sensitive to a GVT effect (e.g., CML and AML), in older patients, or for those with comorbidities who would not be able to tolerate a myeloablative HCT.[52,54]

Toxicities and Management of Preparative Regimens

Myelosuppression is a frequent dose-limiting toxicity for antineoplastics when administered in the conventional doses used to treat cancer. However, because myelosuppression is circumvented with hematopoietic rescue in the case of patients receiving HCT, the dose-limiting toxicities of these myeloablative preparative regimens are nonhematologic and vary with the preparative regimen used. Most patients undergoing HCT experience toxicities commonly associated with chemotherapy (e.g., alopecia, mucositis, nausea and vomiting, and infertility), albeit these toxicities are magnified in the HCT population.

Busulfan Seizures

Seizures have been reported in both adult and pediatric patients receiving high-dose busulfan for HCT preparative regimens. Anticonvulsants are used to minimize the risk of seizures. Anticonvulsants are begun shortly before busulfan, with the loading dose completed at least 6 hours prior to the first busulfan dose. Oral loading and maintenance regimens generally are sufficient because target phenytoin concentrations of 10 to 20 mcg/mL (40–79 μmol/L) can be achieved by the peak time of seizure risk. If patients are experiencing significant vomiting or have difficulty maintaining therapeutic phenytoin concentrations, intravenous (IV) phenytoin should be substituted. Benzodiazepines such as lorazepam or clonazepam also have been used for seizure prophylaxis during high-dose busulfan therapy before HCT.[55] Antiseizure medications usually are discontinued 24 to 48 hours after administration of the last dose of busulfan. Seizures still can occur despite the use of prophylactic anticonvulsants and usually do not result in permanent neurologic deficits.

Adaptive Dosing of Busulfan

The considerable interpatient variability in the clearance of both oral and IV busulfan, along with the identified concentration-effect relationships, has led to the adaptive dosing of busulfan. Adjusting the oral busulfan dose to achieve a target concentration minimizes the toxicities of the BU-CY regimen, particularly hepatic sinusoidal obstruction syndrome (SOS, formerly referred to as *veno-occlusive disease*),[56] while improving engraftment and relapse rates. Complete reviews of these relationships after oral busulfan administration are available elsewhere.[57,58] An intravenous busulfan product, Busulfex®, was approved by the FDA in February 1999 in combination with cyclophosphamide as a preparative regimen prior to allogeneic HCT for CML. Recent data with Busulfex® in combination with either cyclophosphamide or fludarabine suggest that therapeutic drug monitoring may be needed.[59] Pharmacokinetic data are also represented as area under the plasma concentration time curve (*AUC*) or C_{SS}; data are easily converted to C_{SS} ($C_{SS} = AUC \div$ dosing interval). One also must pay close attention to the units used in these studies. Results are expressed as micromolar-minutes or nanograms per milliliter; an *AUC* of 1500 mcM · minute is roughly equivalent to a C_{SS} of 1025 ng/mL in those receiving busulfan every 6 hours.

Hemorrhagic Cystitis

High-dose cyclophosphamide causes moderate to severe hemorrhagic cystitis; acrolein, a metabolite of cyclophosphamide, is the putative bladder toxin. Preventive measures to lower the risk of hemorrhagic cystitis include vigorous hydration, continuous bladder irrigation, and/or concomitant use of the uroprotectant mesna. The American Society of Clinical Oncology (ASCO) Guidelines for the Use of Chemotherapy and Radiotherapy Protectants recommends the use of mesna plus saline diuresis or forced saline diuresis to lower the incidence of urothelial toxicity with high-dose cyclophosphamide

in the setting of HCT.[60] The optimal mesna dose with high-dose cyclophosphamide in preparation for myeloablative HCT is unknown. A number of different regimens have been used, including intermittent bolus dosing (mesna dose 20% to 40% of cyclophosphamide dose administered for three or four doses) or continuous-infusion regimens (mesna 80% to 160% of cyclophosphamide dose). Mesna should be continued for 24 to 48 hours after the last cyclophosphamide dose such that mesna is present within the bladder to donate free thiol groups at the same time as the urotoxic metabolite acrolein.

Chemotherapy-Induced Gastrointestinal Effects

Preparative regimens for myeloablative HCT result in other end-organ toxicities, such as renal failure, and idiopathic pneumonia syndrome. In addition, recipients of myeloablative preparative regimens are at risk for severe gastrointestinal (GI) toxicity, specifically chemotherapy-induced nausea and vomiting (CINV) and mucositis. CINV can be due to administration of highly emetogenic chemotherapy over several days, TBI, and also poor control of CINV prior to HCT. Thus patients who are undergoing a myeloablative HCT should be treated with a corticosteroid plus a serotonin antagonist, with higher doses of serotonin antagonists potentially being needed in this patient population.[61]

Virtually all patients receiving a myeloablative preparative regimen experience severe mucositis owing to its effects on rapidly dividing cells of the oral epithelium. Recently, the FDA approved palifermin—a recombinant human form of keratinocyte growth factor that specifically acts on epithelial cells. In recipients of an autologous HCT, palifermin lowered the incidence and average duration of severe oral mucositis.[62] Patients still may require parenteral opioid analgesics for pain relief[63] owing to mucositis and total parenteral nutrition to prevent the development of nutritional deficiencies.

Sinusoidal Obstruction Syndrome (SOS)

Hepatic SOS is a life-threatening complication that may occur secondary to preparative regimens or radiation.[44,64] The pathogenesis of SOS is not understood completely, although several mechanisms have been proposed. The key event appears to be endothelial damage caused by the preparative regimen. The primary site of the toxic injury is the sinusoidal endothelial cells; the endothelial damage initiates the coagulation cascade, induces thrombosis of the hepatic venules, and eventually leads to fibrous obliteration of the affected venules.[44]

The clinical manifestations of SOS are hyperbilirubinemia, jaundice, fluid retention, weight gain, and right upper quadrant abdominal pain.[44] To make a clinical diagnosis of SOS, these features must occur in the absence of other causes of posttransplant liver failure, including GVHD, viral hepatitis, fungal abscesses, or drug reactions. A clinical diagnosis can be confirmed histologically via liver biopsy.

Patients with mild SOS have an excellent prognosis, whereas those with more severe disease [i.e., bilirubin greater than 20 mg/dL (342 μmol/L) or weight gain greater than 15%] have a high mortality rate.[44] Risk factors for SOS include a mismatched or unrelated graft, cyclophosphamide administration, increased transaminases prior to HCT, and a history of hepatitis.[65] Interpatient variability in the metabolism and clearance of the chemotherapy (i.e., busulfan and cyclophosphamide) used within the preparative regimen also may be associated with a poor outcome, although the relationships vary within the various preparative regimens.[57,66] The association of SOS with busulfan concentrations is discussed in the section on adaptive dosing of busulfan. Preliminary data suggest that IV busulfan may be associated with a lower risk of SOS, although more data are needed.[67] Because its use has been associated with a lower incidence of SOS, single-agent ursodiol (600 mg PO daily) is recommended for SOS prophylaxis.[44]

The mainstay of treatment for established SOS is supportive care aimed at sodium restriction, increasing intravascular volume, decreasing extracellular fluid accumulation, and minimizing factors that contribute to or exacerbate hepatotoxicity and encephalopathy. Defibrotide has shown promising results in the treatment of SOS.[44]

Myelosuppression and Hematopoietic Growth Factor (HGF) Use

HGFs may be used prior to an HCT to mobilize PBPCs during the period of aplasia after an autologous HCT to hasten recovery and in cases where the patient fails to engraft.[19]

Autologous HCT is associated with profound aplasia owing to the myeloablative preparative regimen. Aplasia typically lasts 7 to 14 days after an autologous PBPC transplant. During this period of aplasia, patients are at high risk for complications such as bleeding and infection. Filgrastim and sargramostim exert their effects by stimulating the proliferation of committed progenitor cells, and once engraftment occurs, hematopoietic recovery may be accelerated. The anatomic source of hematopoietic cells predicts the degree of benefit, with the greatest benefit when bone marrow is the graft source. With autologous PBPC transplant, the effect of HGF on neutrophil recovery is variable.

The use of HGF after allogeneic HCT—whether from bone marrow or PBPC grafts—is controversial.[68] The limited amount of data with GM-CSF in this setting suggest increased adverse effects,[69] whereas data with G-CSF have shown more rapid neutrophil but slower platelet engraftment in those receiving grafts from bone marrow or PBPCs.[70] The effects of post-HCT use of G-CSF on acute and chronic GVHD have been conflicting, with either no effect or increases in both the incidence of acute and chronic GVHD and treatment-related mortality.[70] Thus there is little reason to treat allogeneic bone marrow transplant with G-CSF as prophylaxis after HCT.

Graft Failure

A delicate balance between host and donor effector cells is necessary, and residual host-versus-graft effects may lead to graft rejection. The incidence of graft rejection is higher in patients with aplastic anemia and those undergoing HCT with histoincompatible marrow or T-cell-depleted marrow.[2] Graft rejection is uncommon in leukemia patients receiving myeloablative preparative regimens with a histocompatible allogeneic donor.

Therapeutic options for the treatment of graft rejection or graft failure are limited. A second HCT is the most definitive therapy, although the toxicities are formidable.[45] Graft rejection is best managed with immunosuppressants such as antithymocyte globulin. Primary graft failure occasionally can be treated successfully using hematopoietic growth factors, although patients who received purged autografts are less likely to respond.

Graft-Versus-Host Disease (GVHD)

❸ *GVHD is caused by the activation of donor lymphocytes, leading to immune damage to the skin, gut, and liver in the recipient.* Immune-mediated destruction of tissues, a hallmark of GVHD, disrupts the integrity of protective mucosal barriers and thus provides an environment that favors the establishment of opportunistic infections. ❸ *An immunosuppressive regimen is administered to prevent GVHD in recipients of an allogeneic graft; this regimen is based on the type of preparative regimen and the source of the graft.* The combination of GVHD and infectious complications is a leading cause of mortality for allogeneic HCT patients. GVHD is divided into two forms (i.e., acute and chronic) based on clinical manifestations. Traditionally, the boundary between acute and chronic GVHD was set at 100 days after HCT; however, more recent definitions hinge on different clinical symptoms rather than the time of onset.[71]

Acute Graft-versus-Host Disease

The degree of histocompatibility between donor and recipient is the most important factor associated with the development of acute GVHD. The pathophysiology for acute GVHD is a multistep phenomenon, including (1) the development of an inflammatory milieu that results from host tissue damage induced by the preparative regimen, (2) both recipient and donor antigen-presenting cells and inflammatory cytokines triggering activation of donor-derived T cells, and (3) the activated donor T cells mediate cytotoxicity through a variety of mechanisms, which leads to tissue damage characteristic of acute GVHD.[72]

Clinically relevant grade II to IV acute GVHD occurs in 20% to 50% of HLA-matched sibling grafts and 50% to 80% of HLA-mismatched sibling or HLA-identical unrelated donors[44] (Fig. 95–2.) Other factors that increase the risk of acute GVHD include increasing recipient or donor age (older than 20 years), female donor to a male recipient, and previous recipient infections with herpesvirus.[44] T-cell depletion and receipt of an UCB graft lower the risk of acute GVHD.[2]

Clinical Presentation of Acute GVHD

Acute GVHD usually is not evident until the time of engraftment, when donor lymphoid elements begin to proliferate. The primary targets of immune-mediated destruction of host tissue by donor lymphocytes in acute GVHD are the skin, liver, and GI tract.[44] A diffuse maculopapular rash on the face, truck, face, extremities, palms, soles, and ears is the usual sign of acute GVHD of the skin. In more severe cases, it can

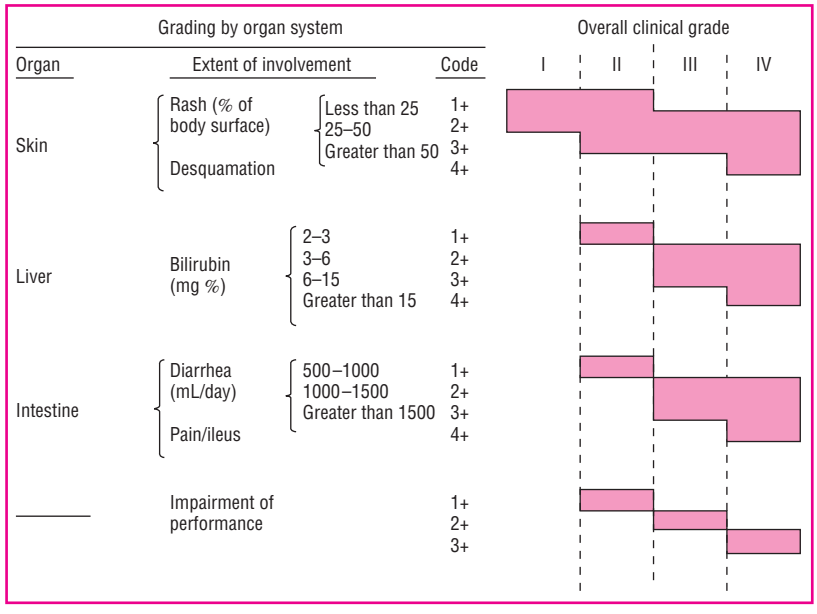


FIGURE 95–2. Clinical grading of acute GVHD. The left panel summarizes the grading of one organ system; the right panel shows the overall clinical grade. With grade I, only the skin can be involved. With more extensive involvement of the skin or involvement of liver and intestinal tract and impairment of the clinical performance status, either alone or in any combination, the severity grade advances from II to IV. (From Perkins JB, Yee GC. Hematopoietic stem cell transplantation. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 2552.)

progress to a generalized total-body erythroderma, bullous formation, and skin desquamation.[44] Acute GVHD of the GI track may present as persistent nausea and anorexia; watery or bloody diarrhea also occurs, which can result in electrolyte abnormalities, dehydration, or ileus in severe cases. [44] Clinical manifestations of liver GVHD include elevated bilirubin, alkaline phosphatase, and hepatic transaminases, which can progress to fulminant hepatic failure.[44] Acute GVHD must be distinguished accurately from other causes of skin, liver, or GI toxicity in the HCT patient (e.g., a maculopapular rash may be due to an allergic reaction to antibiotics). A staging system based on clinical criteria is used to grade acute GVHD. The severity of organ involvement is scored on an ordinal scale from 0 (no symptoms) to IV (severe symptoms), and then an overall grade is established based on the number and extent of involved organs.

Immunosuppressive Prophylaxis of Acute GVHD

GVHD is a leading cause of morbidity and mortality after allogeneic HCT, and thus efforts have focused on preventing acute GVHD. The donor graft and preparative regimen influence the prophylactic regimen for acute GVHD, with two approaches having been taken. One approach involves T-cell depletion, which was discussed more fully in the section on T-cell depletion earlier. The more common method is to use two-drug immunosuppressive therapy that typically consists of a calcineurin inhibitor (i.e., cyclosporine or tacrolimus) with methotrexate after myeloablative HCT and a calcineurin inhibitor with mycophenolate mofetil after nonmyeloablative HCT.

After myeloablative conditioning, acute GVHD rates have been similar or lower with triple-drug regimens, but infectious complications are higher, and overall survival is similar to that with two-drug regimens.[73,74] With the two-drug regimen, a short-course methotrexate (e.g., to day +11) is used and thus can delay engraftment, increase the incidence and severity of mucositis, and cause LFT elevations. The methotrexate dose is reduced in the setting of renal or liver impairment. The calcineurin inhibitors (i.e., cyclosporine and tacrolimus) should be initiated before donor cell infusion (e.g., day –1) when used for GVHD prophylaxis. This schedule is recommended because of the known mechanism of action of cyclosporine, which entails blocking the proliferation of cytotoxic T cells by inhibiting production of T-helper-cell-derived interleukin 2 (IL-2). Administering cyclosporine before the donor cell infusion allows inhibition of IL-2 secretion to occur before a rejection response has been initiated. Studies comparing cyclosporine and tacrolimus in combination with methotrexate have shown that tacrolimus administration is associated with a lower incidence of grade II to IV acute GVHD and a similar incidence of chronic GVHD but variable effects on overall survival.[75–77] Because of the mucosal toxicity to myeloablative preparative regimens, the calcineurin inhibitors are administered intravenously until the GI toxicity from a myeloablative preparative regimen has resolved (e.g., for 7–21 days).[78] Most centers use a 1:2 to 1:3 ratio for conversion of IV to oral cyclosporine with the Neoral formulation; the ratio for tacrolimus conversion from IV to oral is often 1:4. Different conversion ratios for IV to oral regimens may be used when patients are receiving concomitant medications that affect cytochrome P-450 3A or p-glycoprotein, which are involved in the metabolism and transport of the calcineurin inhibitors (e.g., itraconazole).

Prophylaxis of acute GVHD for nonmyeloablative preparative regimens is varied, but a calcineurin inhibitor with either methotrexate or mycophenolate mofetil is used.[6] To date, trials evaluating the optimal acute GVHD prophylaxis regimen have not been conducted.

Adaptive Dosing of the Calcineurin Inhibitors

Most HCT centers have their own standardized approach to dose adjust the calcineurin inhibitors cyclosporine and tacrolimus to target concentration ranges. Cyclosporine trough concentrations are associated with the acute GVHD and nephrotoxicity. Cyclosporine trough concentrations usually are maintained between 150 to 400 ng/mL (125–333 nmol/L) in patients undergoing allogeneic HCT. Tacrolimus trough concentrations are targeted to a range of 10 to 20 ng/mL (10–20 mcg/L).[79] Dosage adjustments to either calcineurin inhibitor also should be made for elevated serum creatinine (SrCr) regardless of their serum concentrations. Nephrotoxicity can occur despite low or normal concentrations of the calcineurin inhibitor cyclosporine and may be a consequence of other drug- or disease-related factors known to influence the development of nephrotoxicity (e.g., genetic risk factors, concurrent use of other nephrotoxic agents, and sepsis). Careful monitoring for drug interactions via cytochrome P-450 3A4 and p-glycoprotein is also warranted.[79] The calcineurin inhibitor doses are adjusted based on serum drug levels and the SrCr concentration. Their dose is escalated when serum concentrations are below the lower limits of normal because this is associated with GVHD.[80] Common adverse effects to these agents include neurotoxicity, hypertension, and/or nephrotoxicity (which may lead to an impaired clearance of methotrexate).

Tapering schedules for the calcineurin inhibitors after myeloablative HCT varies widely. In patients without GVHD, the calcineurin inhibitor doses usually are stable to day +50 and then are tapered slowly with the intent of discontinuing all immunosuppressive agents by 6 months after HCT. By this time, immunologic tolerance has developed, and patients no longer require immunosuppressive therapy. There is a paucity of information regarding the optimal duration of GVHD prophylaxis after nonmyeloablative HCT, with recent data suggesting that a 2-month duration of cyclosporine with a 4-month taper lowers the rate of severe acute GVHD.[81]

Treatment of Acute Graft-Versus-Host Disease

The most effective way to treat GVHD is to prevent its development. Corticosteroids, usually in combination with a calcineurin inhibitor, are the first-line therapy for treatment of established acute GVHD.[72] Corticosteroids indirectly halt the progression of immune-mediated destruction of host tissues by blocking macrophage-derived IL-1 secretion. IL-1 is a primary stimulus for T-helper-cell-induced secretion of IL-2, which, in turn, is responsible for stimulating proliferation of cytotoxic T lymphocytes. The recommended dosage of methylprednisolone in this setting is 2 mg/kg per day; there is no advantage to higher corticosteroid doses (i.e., 10 mg/kg per day).[82] A partial or complete response is seen in approximately 50% of patients treated with corticosteroids. Once a clinical improvement occurs, there is no consensus on the optimal method for tapering the corticosteroids.[72] Patients with steroid-refractory acute GVHD have a poor prognosis, and a number of medications are being studied for "salvage" therapy.[72]

Chronic Graft-Versus-Host Disease

Occurring in 20% to 70% of HCT recipients surviving over 100 days, chronic GVHD is the most frequent and serious late complication of allogeneic HCT.[83] Chronic GVHD is the major cause of nonrelapse mortality and morbidity.[7,83] The clinical course of chronic GVHD is multifaceted, involving almost any organ in the body, and its symptoms resemble autoimmune and immunologic disorders (e.g., scleroderma) (Table 95–3). Chronic GVHD symptoms usually present within 3 years of allogeneic HCT and often are preceded by acute GVHD.[71] Traditionally, the boundary between acute and chronic GVHD was set at 100 days after HCT; however, more recent definitions hinge on different clinical symptoms rather than the time of onset.[83] A consensus document regarding the diagnosis and scoring of chronic GVHD has been published recently.[71] The diagnosis of chronic GVHD requires (1) distinction from acute GVHD, (2) presence of at least one diagnostic clinical sign of chronic GVHD or presence

TABLE 95–3. Abbreviated Table of Signs and Symptoms of Chronic GVHD[71,a]

Affected Organ	Diagnostic	Distinctive	Other Features[b]	Common (Seen with Both Acute and Chronic GVHD)
Skin	Poikiloderma Lichen planus-like features Sclerotic features Morphea-like features Lichen sclerosus-like features	Depigmentation	Seat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hypergimentation	Erythema Maculopapular rash Pruritus
Eyes		New onset drug, gritty or painful eyes[c] Cicatrical conjunctivitis Keratoconjunctivitis sicca[c] Confluent areas of punctuate keratopathy decreased tear formation, dry eyes, burning, photophobia	Photophobia Periorbital hyperpigmentation Erythema of the eyeslids with edema	
GI Tract	Esophageal web stricture or stenosis in the upper to middle third of the esophagus[d]		Exocrine Pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss Failure to thrive (infants and children)
Liver				Total bilirubin, alkaline phosphatase greater than 2 times upper limit of normal[d]
Lung	Bronchiolitis obliterans diagnosed with lung biopsy	Bronchiolitis obliterans diagnosed with pulmonary function tests and radiology[c]		Bronchiolitis obliterans organizing pneumonia

[a]Signs and symptoms for nails, scalp and body hair, mouth, genitalia, muscles, fascia, joints, hematopoietic and immune, and other organs are also described by Filipovich et al.
[b]Can be acknowledged as part of chronic GVHD symptomatology if the diagnosis is confirmed.
[c]Diagnosis of chronic GVHD requires biopsy or radiology confirmation (or Chirmer test for eyes).
[d]Infection, drug effects, malignancy, or other causes must be excluded.

of at least one distinctive manifestation confirmed by pertinent biopsy or other relevant tests, and (3) exclusion of other possible diagnoses. The clinical scoring system is categorized by numerical values of 0 to 3, with more severe symptoms receiving a higher number. Subsequently, a global score is calculated by including the number of organs involved and the severity within each affected organ. The global score reflects the clinical effect of chronic GVHD on the patient's functional status and can be used to evaluate whether treatment (i.e., systemic immunosuppression) of chronic GVHD is needed.

Prevention and Treatment of Chronic GVHD

Chronic GVHD is not a continuation of acute GVHD, and separate approaches are needed for its prevention and management.[83] Prevention of chronic GVHD through prolonged use of immunosuppressive medications has been unsuccessful.[83] Thus its prevention is focused on minimization of factors associated with higher rates of chronic GVHD. Several recipient, donor, and transplant factors are relevant. Recipient risk factors that are not modifiable include older age, certain diagnoses (e.g., chronic myeloid leukemia), and lack of an HLA-matched donor. Modifiable factors that may lower the risk of chronic GVHD include selection of a younger donor, avoidance of a multiparous female donor, use of UCB or bone marrow grafts rather than PBPCs, and limitation of CD34+ and T-cell dose infused.[83,84] Development of acute GVHD is a major predictor for chronic GVHD, and 70% to 80% of those with grade II to IV acute GVHD develop chronic GVHD.[83]

Relative to no treatment, survival in those with chronic GVHD is improved by extended corticosteroid therapy; however, multiple long-term adverse effects are associated with the corticosteroids.[83] The prednisone dosage is 1 mg/kg per day administered orally in divided doses for 30 days and then slowly converted to an alternate-day therapy by increasing the "on day" and decreasing the "off day" dose until a total of 2 mg/kg per day on alternate days is administered. Once therapy is initiated, 1 to 2 months may pass before an improvement in clinical symptoms is noted, and therapy usually is continued for 9 to 12 months. Therapy can be tapered slowly after resolution of signs and symptoms of chronic GVHD. If a flare of chronic GVHD occurs during the tapering schedule or after therapy is discontinued, immunosuppressive therapy is restarted. Other potential approaches for patients who are refractory to initial therapy include etanercept, infliximab, mycophenolate mofetil and tacrolimus, tacrolimus alone, extracorporeal photochemotherapy, acitretin, clofazimine, or hydroxychloroquine.[85,86]

When immunosuppressive therapy is administered for long periods, the patient must be monitored closely for chronic toxicity. Blood counts should be monitored routinely in patients on azathioprine because hematologic toxicity resulting in infection and bleeding may occur. Cushingoid effects, aseptic necrosis of the joints, and diabetes can develop with long-term corticosteroid use. Other severe complications include a high incidence of infection with encapsulated organisms and atypical pathogens such as *Pneumocystis jiroveci*, cytomegalovirus (CMV), and varicella-zoster virus (VZV).

Infectious Complications

❾ *Recipients of HCT are at higher risk of bacterial, viral, and fungal infections and usually receive a prophylactic or preemptive regimen to minimize the morbidity and mortality owing to infectious complications.* After myeloablative and nonmyeloablative HCT, opportunistic infections are a major source of morbidity and mortality. There are three periods of infectious risks, early (days 0–30), middle (engraftment to day plus 100), and late (after day plus 100). From days 0 to 30 after HCT, particularly for patients undergoing myeloablative HCT, the primary pathogens are aerobic bacteria, *Candida,* and herpes simplex virus (HSV). Respiratory viruses such as respiratory syncytial virus (RSV), influenza, adenovirus, and parainfluenza virus are recognized increasingly as pathogens causing pneumonia, particularly during community outbreaks of infection with these organisms. To reduce potential exposure of HCT recipients to such respiratory viruses, visitors and staff members with respiratory signs and symptoms of a viral illness may not be allowed direct contact with patients.

The second period of infectious risk occurs after engraftment to posttransplant day +100. Bacterial infections are still of concern, but pathogens such as CMV, adenovirus, and *Aspergillus* are common. A common manifestation of infection is interstitial pneumonitis (IP), which can be caused by CMV, adenovirus, *Aspergillus,* and *P. jiroveci.* Immune suppression from acute GVHD and corticosteroids contributes to the risk of such infections during this period. Therefore, patients undergoing NMT who are receiving corticosteroids to treat GVHD can be expected to have a similar risk for infection as those undergoing myeloablative HCT.[87] Invasive fungal infections over the first year after HCT occur at a similar rate in NMT when compared with historical controls receiving a myeloablative preparative regimen.[88]

During the late period (after day +100), the predominant organisms are the encapsulated bacteria (e.g., *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Neisseria meningitidis*), fungi, and VZV. The encapsulated organisms commonly cause sinopulmonary infections. The risk of infection during this late period is increased in patients with chronic GVHD as a result of prolonged immunosuppression.

Owing to the morbidity associated with these opportunistic infections in HCT recipients, optimal pharmacotherapy for preventing and treating infections in this patient population is critical. In 2000, the Center for Disease Control and Prevention (CDC) published guidelines for preventing these infections among HCT recipients.[8] These guidelines were constructed from available data by an expert panel from the CDC, the Infectious Disease Society of America, and the American

Society for Blood and Marrow Transplantation. These guidelines provide a comprehensive review of the data regarding prevention of opportunistic infections in HCT recipients. The review below incorporates information from the CDC guidelines and also provides an update on the pharmacotherapy of opportunistic infections for all types of HCTs (i.e., myeloablative autologous, myeloablative allogeneic, and nonmyeloablative allogeneic HCT recipients).

Prevention and Treatment of Bacterial and Fungal Infections

Because of disease-related immunosuppression, intensive preparative regimens, and/or posttransplant immunosuppressive therapy, patients undergoing allogeneic HCT require close monitoring for regimen-related toxicities and intensive supportive care directed toward maintaining an adequate CBC, preventing or treating infection, and providing adequate nutrition. The need to administer chemotherapy, blood products, antibiotics, parenteral nutrition, and adjunctive medications precludes the use of peripheral access sites that require frequent rotation. Placement of a semipermanent double- or triple-lumen central venous catheter (e.g., Hickman, Groshong, Broviac, or Neostar) is necessary. The use of central venous catheters also allows delivery of maximumally concentrated medications into an area of high blood flow, which reduces infusion times and minimizes daily fluid infusion. However, the indwelling IV central catheters put HCT recipients at increased risk for *Staphylococcus* infections.

Between the time of administration of the preparative regimen and successful engraftment, allogeneic myeloablative HCT patients undergo a period of pancytopenia that can last from 2 to 6 weeks. During this time, multiple RBCs and platelet transfusions are needed when the hematocrit is less tham 25% (0.25) and platelets are less than 10,000 or 20,000/mm^3 ($10–20 \times 10^9$/L $10–20 \times 10^3$/μL). Transfusions with multiple blood products place patients at risk for blood product–derived infection (e.g., CMV and hepatitis) and sensitization to foreign leukocyte HLA antigens (i.e., alloimmunization), which can lead to immune-mediated thrombocytopenia. Thus blood product support in the myeloablative allogeneic HCT patient must incorporate strategies that reduce the risk of viral infection and alloimmunization by minimizing the number of pretransplant infusions, use of single-donor (rather than pooled-donor) blood products, irradiating blood products, or filtering blood products with leukocyte-reduction filters. Given the reduced intensity of the preparative regimen, NMT patients may or may not experience neutropenia and generally have reduced requirements for blood products. Many centers perform NMT in the outpatient setting and admit patients to the hospital only if they have complications requiring more intensive management.

The risk of infection in autologous and allogeneic myeloablative HCT patients is minimized through a variety of measures. Private reverse isolation rooms equipped with positive-pressure HEPA filters and adherence to strict handwashing techniques reduce the incidence of bacterial and fungal infections.[8] To reduce exposure to exogenous sources of bacteria, immunosuppressed-patient (low-microbial) diets are used, and plants or flowers are not allowed in the patient's room. Chemotherapy-induced mucosal damage serves as a portal of entry for many organisms (e.g., *Streptococcus viridans*, aerobic gram-negative bacteria, and fungi) into the bloodstream. The mouth should be kept clean by using frequent (four to six times daily) mouth rinses with sterile water, normal saline, or sodium bicarbonate.[8] Brushing or flossing teeth is avoided during periods of thrombocytopenia and neutropenia. In the first 30-days after HCT, those undergoing a nonmyeloablative preparative regimen have a significantly reduced incidence of mucositis, along with reduced bacteremia and fewer episodes of infection attributable to mucositis, relative to those receiving a myeloablative preparative regimen.

The risk of infection is also reduced by aggressive use of antibacterial, antifungal, and antiviral therapy both prophylactically and for the treatment of documented infection. Antibiotics with a broad gram-negative spectrum may be instituted prophylactically on the day of donor cell infusion (i.e., day 0), once the patient becomes neutropenic, or empirically after the patient is neutropenic and experiences a first fever. The antibacterial prophylactic regimens vary substantially among HCT centers. Some HCT centers use prophylactic fluoroquinolone (e.g., ciprofloxacin) on admission for HCT and then switch to a broad-spectrum IV antibiotic (e.g., ceftazidime) when the patient experiences his or her first neutropenic fever. Although fluoroquinolones reduce the incidence of gram-negative bacteremia, they do not affect the number of days with fever or mortality.[8] Concerns with quinolone use in the prophylactic setting during HCT include the emergence of resistant organisms and an increased risk for streptococcal infection.[8] Prophylactic antibiotics with activity against *Streptococcus* (e.g., penicillin and vancomycin) have been studied, but their use is not recommended owing to a lack of efficacy in preventing streptococcal infections and concern over antibiotic-resistant bacteria.[8,89]

Broad-spectrum IV antibiotics should be initiated or added at the time of the first neutropenic fever under the treatment guidelines endorsed by the Infectious Disease Society of America for management of fever of unknown origin in the neutropenic host.[89]

Prevention of Herpes Simplex Virus (HSV) and Varicella-Zoster Virus (VZV)

Patients who are HSV- or VZV-seronegative prior to HCT rarely develop primary HSV or VZV infection; therefore, prophylactic antivirals are not warranted. Patients who are HSV-antibody-seropositive before HCT are at high risk for reactivation of their

HSV infection. Acyclovir is highly effective in preventing HSV reactivation, and thus prophylactic acyclovir is used commonly in HSV-seropositive patients who are undergoing an allogeneic or autologous HCT.[8] In the setting of HSV prophylaxis, dosing regimens for prophylactic acyclovir vary widely, and most centers discontinue acyclovior at the time of hematopoietic recovery.[8] Valacyclovir, a prodrug of acyclovir with improved bioavailability, may allow for adequate serum concentrations to prevent HSV in patients with mucositis or gastrointestinal GVHD.[90] Typically, valacyclovir is administered as 500 mg orally once or twice daily in the prophylactic setting.

In those with a history of VZV infection, VZV disease occurs in 30% of allogeneic HCT recipients.[91] The appropriate duration of VZV prophylaxis is controversial.[8] Although VZV infections are reduced by prophylactic acyclovir (800 mg twice daily), administered from 1 to 2 months until 1 year after HCT, the risk of VZV persists in those on continued immune suppression.[91]

Prevention and Preemptive Therapy of Cytomegalovirus (CMV) Disease

After allogeneic HCT, CMV disease is common and has high morbidity and mortality rates. Allogeneic patients are at greater risk than autologous recipients primarily because the latter more efficiently reconstitute their immune system after transplantation. However, autologous HCT recipients who are CMV-seropositive before HCT are at risk of CMV infection, and prophylaxis should be considered in a select minority of patients.[8] Two CMV syndromes can occur. CMV infection usually is asymptomatic and develops when CMV replication occurs primarily in body fluids such as the blood (viremia), bronchoalveolar fluid, or urine (viruria). CMV disease is symptomatic and occurs when the virus invades an organ or tissue. Pneumonia and gastritis are the most common types of CMV disease after allogeneic HCT. The presence of a CMV infection substantially increases the risk for developing invasive CMV disease. Strategies to prevent CMV infection have resulted in dramatic reductions in the incidence of CMV disease.

Primary CMV can be prevented with CMV seromatching, which includes transplanting PBPCs or bone marrow from CMV-seronegative donors and infusing CMV-negative blood products to CMV-negative recipients. Antivirals are essential in those who are CMV-seropositive or have a CMV-seropositive graft, with two available approaches to minimize the morbidity associated with CMV. The first is universal prophylaxis, in which ganciclovir is begun at the time of engraftment and is continued until approximately day +100. Second is preemptive therapy, also called *risk-adjusted therapy,* for which ganciclovir is selectively administered based on detection of CMV reactivation.

Preemptive therapy is the most commonly used strategy for preventing CMV disease after allogeneic HCT because ganciclovir is used only in patients at highest risk for developing CMV disease. This approach minimizes administration of ganciclovir, thus lowering the risk of ganciclovir-induced neutropenia with its subsequent increased risk of invasive bacterial and fungal infections or interruptions of ganciclovir and/or filgrastim administration to maintain adequate neutrophil counts. Preemptive therapy hinges on the ability to detect early reactivation of CMV using shell vial cultures, assays of blood for CMV antigens (such as pp65), or viral nucleic acids using polymerase chain reaction (PCR).[92] Antigenemia-based preemptive therapy has similar efficacy in preventing CMV disease as universal ganciclovir prophylaxis, and preemptive therapy also has been associated with a significant reduction in CMV mortality. Preemptive strategies typically use an induction course of ganciclovir 5 mg/kg IV every 12 hours for 7 to 14 days, followed by a maintenance course of 5 mg/kg IV daily until 2 or 3 weeks after the last positive antigenemia result or until day +100 after HCT.[8] Oral valganciclovir is an orally bioavailable prodrug of ganciclovir that is converted to ganciclovir in vivo after intestinal absorption.[93] Foscarnet may be given as an alternate to ganciclovir to prevent CMV disease, although its use is complicated by nephrotoxicity and electrolyte wasting.

CMV infection and disease in patients undergoing NMT appears to have a different temporal pattern than in patients receiving myeloablative preparative regimens. The onset of CMV antigenemia was similar between the groups, but patients undergoing NMT are at increased risk for developing late CMV disease (greater than 100 days after transplantation) compared with their myeloablative counterparts. For this reason, it is recommended that NMT patients receive preemptive antiviral therapy and be monitored for the development of CMV antigenemia for 1 year after transplantation.[87]

Fungal Infections

Prevention of Fungal Infections Prophylactic fluconazole (400 mg/day) until day +75 after allogeneic HCT decreases the incidence of systemic fungal infection and death compared with placebo.[94] The widespread use of fluconazole (400 mg/day) prophylaxis since the early 1990s has led to a significant decline in the morbidity and mortality associated with invasive candidiasis in BMT recipients. However, invasive aspergillosis (IA) and fluconazole-resistant *Candida* species, such as *C. krusei* and *C. glabrata,* have increased markedly in incidence.[95] Itraconazole, another azole antifungal agent, has better in vitro activity against fluconazole-resistant fungi (e.g., *Aspergillus* and some *Candida* spp.) and was more effective than fluconazole for long-term prophylaxis of invasive fungal infections after allogeneic HCT.[96] Itraconazole was associated with more frequent GI side effects (e.g., nausea and vomiting), and its concomitant use with cyclophosphamide is associated with increased exposure to toxic cyclophosphamide metabolites and increased hepato- and

nephrotoxicity, presumably via inhibition of cytochrome P-450 by itraconazole.[96,97] Prophylactic itraconazole should be initiated after cyclophosphamide administration, its plasma concentrations are maintained greater than 500 ng/mL for effective prophylaxis, and patient education should be provided regarding the importance of compliance with the unpleasant-tasting itraconazole solution.[94]

Risk Factors for Invasive Mold Infections Invasive mold infections (e.g., *Aspergillus* spp., *Fusarium* spp., Zygomycetes, and *Scedosporium* spp.) are an increasing cause of morbidity and death after allogeneic and autologous HCT. In HCT recipients, risk factors for invasive fungal infections include previous history of invasive aspergillosis; recipient factors, including age greater than 40 years, CMV seropositivity, type of cell transplant (i.e., UCB or donor-recipient HLA mismatch, and T-cell-depleted grafting); treatment factors (e.g., a fludarabine-based preparative regimen); and transplant complications (e.g., prolonged neutropenia, graft failure, and higher-grade GVHD).[98] Infections with *Aspergillus* species are the most common mold infections, with an annual incidence of invasive aspergillosis (IA) of 10.5% among allogeneic and 5.3% among autologous HCT recipients.[99]

Treatment of Invasive Aspergillosis Early diagnosis and initiation of appropriate therapy may reduce the high mortality of IA. Outcomes also depend on recovery of the recipient's immune system and reduction of immune suppression. Diagnosis is difficult with the use of computed tomographic (CT) scans and cultures. Research is ongoing to evaluate the benefit of using non-culture-based methods, such as galactomannan, which is a component of the fungal cell wall that can be detected by ELISA.[100] Invasive procedures to diagnosis IA can be avoided by determining a patient's likelihood of having IA with the use of a galactomannan assay in combination with CT scans and the known risk factors for IA.[100]

Practice guidelines are available for the treatment of fungal infections in HCT patients.[101] Available mold-active agents include itraconazole, voriconazole, caspofungin, and amphotericin B formulations. Conventional amphotericin B (c-AmB) at a minimum dose of 1 mg/kg per day traditionally has been the "gold standard" antifungal therapy for any IA infection. Most patients respond to single-agent c-AmB; however, 65% of responders eventually die of their infection. Significant toxicity occurs with c-AmB administration, with nephrotoxicity being the most troublesome side effect. Altered renal function occurs in up to 80% of patients receiving c-Amb, particularly in those with additional risk factors for nephrotoxicity (e.g., concomitant aminoglycosides and cyclosporine). Infusion-related reactions (e.g., fever, chills, rigors, hypotension, and hypoxia), electrolyte wasting, nausea, and anemia are additional toxicities of c-Amb. Acetaminophen, diphenhydramine, meperidine, and/or hydrocortisone are administered before each c-Amb dose to ameliorate these infusion-related events with variable success. Electrolyte wasting, especially potassium and magnesium, secondary to c-Amb can be significant and persist well beyond discontinuation of the drug. Most patients require daily potassium and magnesium supplementation, particularly if they require prolonged amphotericin therapy.

Lipid analogs of amphotericin B were developed with the specific intent of reducing nephrotoxicity. These include amphotericin B lipid complex (Abelcet®, ABLC), liposomal amphotericin B (Ambisome®, L-Amb), and amphotericin B colloidal dispersion (Amphotec®, ABCD).[100] Overall, studies of single-agent liposomal formulations of amphotericin B for patients with IA who have failed or are intolerant to c-Amb therapy reveal response rates in the range of 23% to 71% regardless of the agent used. However, no randomized studies have evaluated ABLC and L-Amb for IA treatment, whereas ABCD has similar efficacy, less renal toxicity, but greater infusion reactions than c-Amb.[100] Notably, their high cost relative to c-Amb limits widespread use of the liposomal products.

Select azole antifungals (e.g., itraconazole, voriconazole, and posaconazole) and the echinocandins are available for IA treatment. For initial therapy of IA, voriconazole had higher response and survival rates than c-AMB.[102] An advantage of voriconazole is its 96% oral bioavailability, making use of this oral drug an attractive and less expensive alternative. The dose of voriconazole was 6 mg/kg IV every 12 hours for two doses, followed by 4 mg/kg IV every 12 hours for at least 7 days, at which time oral voriconazole 200 mg every 12 hours could be administered. Common toxicities reported with voriconazole include infusion-related, transient visual disturbances (i.e., blurred vision, altered color perception, photophobia, and visual hallucinations), skin reactions (i.e., rash, pruritus, and photosensitivity), elevations in hepatic transaminases and alkaline phosphatase, nausea, and headache.[102] In addition, voriconazole increases the serum concentrations of medications cleared by cytochrome P-450 2C9, 2C19, and 3A4 (e.g., cyclophosphamide and calcineurin inhibitors); concomitant voriconazole-sirolimus should be avoided.[103]

In patients who have failed initial therapy (i.e., salvage), liposomal amphotericin products, itraconazole, or the echinocandin caspofungin can be used. Itraconazole has a response rate of approximately 40%.[100] Oral itraconazole exhibits erratic absorption; the IV formulation is suspended in cyclodextrin, which is eliminated renally, and thus IV itraconazole should be avoided in patients with a creatinine clearance of less than 30 mL/minute (0.29 mL/s · m^2).[103] Itraconazole also has negative inotropic cardiac effects and increases the serum concentrations of medications (e.g., cyclophosphamide, etoposide, calcineurin inhibitors, and sirolimus).

The echinocandins have a unique target for their antifungal activity—specifically, β-1,3-glucan synthase, an enzyme that produces an important component of the fungal wall. Caspofungin is currently the only product of this class that is FDA approved; it is indicated for treatment of IA refractory

to alternate therapy. Caspofungin is absorbed poorly and is available only as an IV formulation.[103] Most common adverse effects include mild to moderate infusion reactions and headache, with a smaller number of patients experiencing dermatologic reactions related to histamine release (e.g., flushing, erythema, and wheals). Caspofungin therapy has been associated with elevations in hepatic transaminases in patients receiving concomitant cyclosporine, and this combination should be used with caution.[103]

There is an increasing amount of data regarding combination therapy with newly available triazoles, echinocandins, and polyenes in patients with fungal infections. Given the overall poor prognosis of IA in HCT recipients, many practitioners are treating patients with combination therapy known to be synergistic in vitro in order to maximize the chance of response.

The optimal duration of appropriate antifungal therapy for treating IA is individualized to the reconstitution of the patient's immune system and his or her response to antifungal treatment. Most clinicians will continue aggressive antifungal therapy until the infection has stabilized radiographically and may continue with less aggressive "maintenance" therapy (e.g., oral voriconazole) until immunosuppression is lessened or completed. In general, it is not uncommon to require several months of antifungal therapy to treat IA.

Pneumocystis jiroveci

After allogeneic HCT, prophylaxis for *P. jiroveci* (formerly *P. carinii*) pneumonia (PCP) is used because *Pneumocystis* is a common infection with a high mortality rate if left untreated. The optimal prophylactic regimen in this setting is unclear, with most centers using cotrimoxazole for 6 to 12 months after HCT.[8] Dapsone and aerosolized pentamidine are alternatives for patients who are allergic to sulfa drugs or who do not tolerate cotrimoxazole. Because PCP most often occurs after engraftment, cotrimoxazole usually is begun after neutrophil recovery because of its myelosuppressive effects. Patients receiving prophylactic cotrimoxazole should be monitored closely for rash and unexplained neutropenia or thrombocytopenia. Cotrimoxazole usually is avoided on days of methotrexate administration because the sulfonamides can displace methotrexate from plasma binding sites and decrease renal methotrexate clearance, resulting in higher methotrexate concentrations. Autologous HCT patients do not receive posttransplant immunosuppression, and thus their risk of developing PCP is lower.[8] Thus PCP prophylaxis is used often after autologous HCT in patients with a hematologic malignancy.

Issues of Survivorship after HCT

The number of long-term HCT survivors is increasing as 5-year disease-free survival rates improve. Since nonmyeloablative preparative regimens were developed over the past decade, the late effects reported in HCT survivors describe those resulting from myeloablative preparative regimens.[44,104] HCT recipients—with either an autologous or an allogeneic graft—have higher mortality than the general population.[105,106] ⑩ *Long-term survivors of HCT should be monitored closely, particularly for infections and secondary malignant neoplasms.*

HCT survivors are at higher risk for secondary malignant neoplasms.[104] Long-term impairment of end-organ function, including kidney, liver, and lungs, may be due to the preparative regimen, infectious diseases (e.g., hepatitis C), infection complications (either autologous or allogeneic grafts), and posttransplant immunosuppression (allogeneic grafts only).[105] Many HCT recipients experience endocrine dysfunction, such as hypothyroidism from total-body irradiation, adrenal insufficiency from long-term corticosteroids to treat GVHD, and infertility from radiation and/or high doses of alkylating agents in myeloablative preparative regimens.[105] Osteopenia has been found in over half of HCT recipients, most likely from gonadal dysfunction and/or corticosteroid administration.[105]

Close monitoring of HCT recipients for infections is necessary because recovery of immune function is slow, sometimes requiring over 2 years, even in the absence of immunosupressants.[104] Fevers should be assessed and treated rapidly to minimize the likelihood of a fatal infection. HCT recipients—both autologous and allogeneic—lose protective antibodies to vaccine-preventable diseases; the CDC and the European Group for Bone Marrow Transplantation have issued recommendations for reimmunization for HCT recipients.[107]

HCT survivors should be monitored routinely for signs of relapse and, if an allogeneic graft was used, chronic GVHD. They should be advised regarding revaccination and obtaining prompt medical care for fevers or signs of infection. Routine evaluations of organ function (i.e., renal, hepatic, thyroid, and ovarian) and osteopenia should occur and the appropriate management strategies started if necessary.



Patient Encounter 2

AS is a 65-year-old woman with relapsed acute myelogenous leukemia. PMH is significant for type II diabetes and renal insufficiency (CrCl 20 mL/minute). She is day +1 from a nonmyeloablative HCT with fludarabine (30 mg/m^2 per day IV for 3 days) and total-body irradiation preparative regimen and a graft from a full HLA-matched sibling.

- What preventative measures are needed for the complications of HCT?
- How would you monitor AS for GVHD?
- What would you recommend for treatment of GVHD?

OUTCOME EVALUATION

To monitor for the effectiveness of the HCT, monitor for symptoms and signs of the disease that is being treated by HCT. For example, the monitoring plan for a patient with CML would be to monitor disease response by PCR of the *BCR-ABL* transcript. The actual clinical outcome monitored, along with the frequency of monitoring, is based on the underlying disease.

Monitor for nonhematologic toxicity of the preparative regimen during its administration. Monitor these symptoms at least daily, with more frequent monitoring if the patient is experiencing these nonhematologic effects. The goal is to prevent or minimize these adverse effects. Specifically,

- *Busulfan:* Seizures, busulfan concentrations if being used with the BU-CY preparative regimen, number of vomiting episodes, nausea by patient self-report
- *Cyclophosphamide:* Electrocardiogram during IV administration, RBCs in urine, frequency of urination, pain on urination, urinary output, number of vomiting episodes, nausea by patient self-report
- *Etoposide:* Blood pressure, respiratory rate, serum pH, serum bicarbonate with arterial blood gases, and evaluation of anion gap if necessary
- *Total-body irradiation:* Number of vomiting episodes, nausea by patient self-report, sudden weight changes (SOS), total bilirubin

Until the patient has achieved engraftment, monitor the patient for the engraftment with at least daily CBCs with differentials; these tests may be needed more often if the patient is critically ill or had a prior low hemoglobin.

Until engraftment has occurred, monitor the patient's temperature every 4 to 8 hours for signs of infection. Also guide monitoring signs of focal point of infection based on clinical symptoms. For example, if the patient develops shortness of breath, then imaging of the lungs should occur to assess pulmonary infection. Monitor for the toxicity of prophylaxis and/or treatment of bacterial, fungal, or viral infections.

Monitor for acute nonhematologic toxicity to the preparative regimen to approximately day +30. Specifically,

- Monitor the inside of the mouth and assess the patient's mouth pain for signs and symptoms of mucositis.
- Monitor weight and skin color daily to observe sudden weight changes suggesting SOS. Obtain a total bilirubin determination at least twice weekly or more frequently if SOS is suspected based on weight change.

Monitor for signs of acute GVHD at least daily until engraftment and more often if GVHD is suspected or diagnosed. The patient and his or her caregivers should be educated regarding the signs and symptoms to self-monitor for GVHD. The signs and symptoms for acute GVHD that occur between day +0 and day +100 are rash, nausea, diarrhea, jaundice, elevated liver function tests, and elevated bilirubin.



Patient Care and Monitoring

1. Assess the patient regarding the indication for HCT, the type of preparative regimen, and the type of donor. Determine the the nonhematologic toxicity of the preparative regimen, the expected timing of engraftment after the graft is infused, along with the need for GVHD prophylaxis.
2. Determine the supportive care needs during administration of the preparative regimen, including use of indwelling central venous catheters, blood product support, and pharmacologic management of chemotherapy-induced nausea and vomiting (CINV), mucositis, and pain.
3. After the graft is infused, monitor CBC with differential at least daily to evaluate engraftment. Allogeneic HCT patients experience an initial period of pancytopenia followed by a more prolonged period of immunosuppression, which substantially increases the risk of bacterial, fungal, viral, and other opportunistic infections.
4. Counsel the patient regarding adherence to prophylactic antibiotic, antifungal, and antiviral regimens. Evaluate the patient for infection and adverse drug reactions to antibiotics, antifungals, and antivirals. Ensure that the patient is appropriately immunized after recovery from HCT.
5. Counsel the patient regarding adherence to GVHD prophylaxis and treatment. Monitor and manage for adverse drug reactions.

ABBREVIATIONS

CMV:	cytomegalovirus
DLI:	donor lymphocyte infusion
GVHD:	graft-versus-host disease
HLA:	human leukocyte antigen
HCT:	hematopoietic cell transplantation
HSV:	herpes simplex virus
IA:	invasive aspergillosis
NMT:	nonmyeloablative transplant
PCP:	*Pneumocystis jiroveci* pneumonia (formerly *Pneumocystis carinii*)
SOS:	sinusoidal obstruction syndrome
VZV:	varicella-zoster virus

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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96 Oncologic Emergencies

Brad L. Stanford



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Describe the impact of various oncologic emergencies on the prognosis of patients with cancer.
2. Discuss the causes of various oncologic emergencies in relation to their underlying cancer types.
3. Identify risk factors for oncologic emergencies in relation to prevention and treatment options.
4. Recognize typical presenting signs and symptoms of oncologic emergencies.
5. Outline an appropriate prevention strategy for various oncologic emergencies.
6. Recommend optimal nonpharmacologic and pharmacologic management strategies for patients with oncologic emergencies.
7. Prepare a monitoring plan to evaluate the efficacy and toxicity of pharmacotherapy for oncologic emergencies.

Key Concepts

❶ A risk assessment should be performed at presentation of febrile neutropenia to identify low-risk patients for potential outpatient treatment. Patients who do not meet low-risk criteria should be hospitalized for immediate parenteral administration of broad-spectrum antibacterials before culture results are obtained.

❷ The success of the treatment of febrile neutropenia hinges on the adequate recovery of the absolute neutrophil count and either optimal antimicrobial coverage of identified organisms or empirical coverage of unidentified organisms.

❸ The primary goal of treatment of superior vena cava (SVC) syndrome is to relieve obstruction of the superior vena cava by treating the underlying malignancy.

❹ Since patients with spinal metastases generally are incurable, the primary goal of treatment of spinal cord compression is palliation. The most important prognostic factor for patients presenting with spinal cord compression is the underlying neurologic status.

❺ The goals of treatment of brain metastases are to manage symptoms by reducing cerebral edema, treat the underlying malignancy both locally and systemically, and improve survival.

❻ The use of effective prevention strategies can decrease the incidence of hemorrhagic cystitis to less than 5% in patients receiving cyclophosphamide or ifosfamide. There are three methods to reduce the risk: administration of mesna, hyperhydration, and bladder irrigation with catheterization.

❼ The primary goal of treatment for hypercalcemia is to control the underlying malignancy. Therapies directed at lowering the calcium level are temporary measures that are useful until anticancer therapy begins to work.

❽ Therapeutic options for the treatment of hypercalcemia should be directed toward the level of corrected serum calcium and the presence of symptoms. Adequate treatment of mild or asymptomatic hypercalcemia may be achieved on an outpatient basis with nonpharmacologic measures. Moderate to severe or symptomatic hypercalcemia almost always requires pharmacologic intervention.

❾ The primary goals of management of tumor lysis syndrome are (1) prevention of renal failure and (2) prevention of electrolyte imbalances. Thus the best treatment for tumor lysis syndrome is prophylaxis to enable delivery of cytotoxic therapy for the underlying malignancy.

❿ Chemotherapy extravasation may be avoided in many cases by the use of successful prevention strategies. The most important preventative measure is proper patient education.

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Patients with cancer are at risk for life-threatening events from the malignancy itself or various treatments for their cancer. These events traditionally have been defined as oncologic emergencies. Although some of these conditions are not imminently life-threatening (e.g., chemotherapy extravasation), they do require rapid assessment and treatment.

Oncologic emergencies may best be subdivided according to the following systems of origin:

- Hematologic
- Cardiovascular
- Neurologic
- Urologic
- Metabolic
- Miscellaneous

The onset of oncologic emergencies affecting these systems may herald the onset of an undiagnosed malignancy or progression/relapse of a preexisting malignancy. Prompt recognition and optimal management of patients with various oncologic emergencies can decrease morbidity significantly and potentially save lives. Pharmacists and other midlevel practitioners may play a key role in this area.

HEMATOLOGIC COMPLICATIONS

Febrile Neutropenia

Febrile neutropenia is a common adverse effect of the administration of cytotoxic chemotherapy. The mortality rate owing to infectious complications currently remains between 5% and 10%; therefore, febrile neutropenia is considered a true oncologic emergency. Patients frequently require hospitalization for prompt administration of broad-spectrum antibiotics that are critical to avoid morbidity and mortality.

Epidemiology and Etiology

The microorganisms responsible for infections in neutropenic patients have changed significantly in the last 50 years. From the 1960s through the mid-1980s, gram-negative organisms were the most common bacteria isolated. This pattern shifted to the gram-positive organisms in the late 1980s, which remain the most common isolates. Recent data indicate that gram-positive organisms account for 62% to 76% of all bloodstream infections.[1] The causes of this change are attributed to the widespread use of central venous catheters and more aggressive chemotherapy regimens, as well as the use of prophylactic antibiotics with relatively poor gram-positive coverage (quinolones). Commonly isolated pathogens are shown in Table 96–1. Although gram-negative infections are less common, they cause the majority of infections in sites other than the blood and are particularly virulent. It should be noted that isolates vary considerably between institutions; thus attention to institutional isolation patterns is prudent.

Fungal infections due to *Candida* spp. (especially *C. albicans*) have emerged as significant pathogens, especially in patients with hematologic malignancies and those undergoing bone marrow transplantation. In addition, *Aspergillus* spp. are important pathogens in patients with prolonged and severe neutropenia.



Patient Encounter 1, Part 1

BR is a 62-year-old woman who was recently diagnosed with stage IV large B-cell lymphoma. Her bone marrow is positive for lymphoma, and she has type II diabetes and hypertension.

- What risk factors for febrile neutropenia does this patient have?
- What signs and symptoms of infection would you counsel this patient to watch for following treatment?

TABLE 96–1. Commonly Isolated Pathogens in Patients with Febrile Neutropenia

Type of Organism	Comments
Bacteria	
Gram-positive organisms	Most common isolates in febrile neutropenia
Coagulase-negative staphylococci (i.e., *St. epidermidis*)	Between 70% and 90% resistance to methicillin; indolent course with low mortality
Staphylococcus aureus	Some centers report greater than 50% resistance to methicillin
Enterococcus spp.	Resistance to vancomycin greater than or equal to 30%
Viridans streptococci	Increasing resistance to penicillin; result of fluoroquinolone prophylaxis; associated with mucositis
Gram-negative organisms	Infections rapidly fatal
Pseudomonas aeruginosa	High mortality; increasing resistance to quinolones
Escherichia coli	Increased incidence of beta-lactamase producing strains
Klebsiella spp.	Increased incidence of beta-lactamase producing strains
Enterobacter spp.	Occur primarily after prolonged neutropenia (greater than 1 week)
Fungi	
Yeasts	
Candida albicans	Increasing incidence (approximately 10%); high mortality
Non-*albicans Candida* (*C. krusei, C. glabrata*)	Resistant to fluconazole; high mortality
Molds	Resistant to fluconazole; high mortality
Aspergillus spp.	Pulmonary infection common
Fusarium spp.	Emerging pathogen
Scedosporium spp.	Emerging pathogen

Data from refs. 2 and 3.

Pathophysiology

The neutrophils are the primary defense mechanism against bacterial and fungal infection. Most infections in neutropenic patients are a result of organisms contained in endogenous flora, both on the skin and within the gastrointestinal (GI) tract. These organisms are provided access to the bloodstream through breakdowns in host defense barriers (i.e., **mucositis** and use of central venous catheters). Mucositis in particular is a significant risk factor for sepsis and is increasingly more common owing to the widespread use of aggressive chemotherapy regimens.[4]

Neutropenia is defined as an absolute neutrophil count (ANC) of less than $0.5 \times 10^3/\mu L$ ($0.5 \times 10^9/L$) cells or an ANC of less than $1.0 \times 10^3/\mu L$ ($1.0 \times 10^9/L$) cells with a predicted decrease to less than $0.5 \times 10^3/\mu L$ ($0.5 \times 10^9/L$) cells. The ANC is calculated by multiplying the total white blood cell (WBC) count by the percentage of neutrophils (segmented neutrophils plus bands). *Fever* is defined as a single oral temperature of 38.3°C (101°F) or greater or a temperature of 38.0°C (100.4°F) or greater for at least 1 hour. The combination of these two factors defines febrile neutropenia.[5] The risk of infection during the period of neutropenia depends primarily on two factors:

- The duration of the neutropenia [time period of ANC less than $0.5\ 10^3/\mu L$ ($0.5 \times 10^9/L$)]
- The severity of the neutropenia [lowest ANC level reached (nadir)]

A multitude of other risk factors for febrile neutropenia have been identified (Table 96–2). Many of these are also risk factors for poor outcome in patients who experience febrile neutropenia.

TABLE 96–2. Risk Factors for Febrile Neutropenia

Patient-Related	Therapy-Related
Age greater than or equal to 60 years	History of prior extensive chemotherapy
Poor **performance status**	Planned full **dose intensity** of chemotherapy
Bone marrow involvement by tumor	High-dose chemotherapy (i.e. bone marrow transplant)
Poor nutritional status	
Hematologic malignancy	
Elevated LDH	
Decreased hemoglobin level	
Baseline or first-cycle low neutrophil counts	
History of previous febrile neutropenia	
Uncontrolled or advanced stage cancer	

LDH, lactate dehydrogenase.
Data from ref. 6.

TABLE 96–3. Multinational Association for Supportive Care in Cancer (MASCC) Risk Index for Identifying Low-Risk Patients with Febrile Neutropenia[7]

Characteristic	Score
Extent of illness[a]	
No symptoms	5
Mild symptoms	5
Moderate symptoms	3
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or no fungal infection	4
No dehydration	3
Outpatient onset of fever	3
Age less than 60 years[b]	2

Note: A risk index score of 21 or greater indicates that the patient is likely to be at low risk for complication and morbidity.
[a]Choose one item only.
[b]Does not apply to patients 16 years of age and younger.

It is clear that patients with febrile neutropenia represent a heterogeneous group. Some patients are at lower risk and potentially could be treated as outpatients, thereby avoiding the risk and cost of hospitalization. The Multinational Association for Supportive Care in Cancer (MASCC) has validated a risk-assessment tool that assigns a risk score to patients presenting with febrile neutropenia[7] (Table 96–3). Patients with a risk-index score of 21 or greater are identified as low risk and are candidates for outpatient therapy (discussed under "Treatment").



Clinical Presentation and Diagnosis

General

- Only 50% of patients with febrile neutropenia have a clinically documented infection.
- Only 25% of patients with febrile neutropenia have a microbiologically documented infection.

Signs and Symptoms

- Fever is typically the only sign of infection, although septic patients may have chills.
- Infected catheter sites may be erythematous and tender to the touch.

Laboratory Tests

- Complete blood count (CBC) with differential
- Blood cultures × 2 from *each* access site (peripheral and central), urinalysis, urine culture, chest x-ray, sputum cultures

Other Diagnostic Tests

Detailed physical examination of oral mucosa, sinuses, skin, catheter access sites, and perineal area (no rectal examination owing to risk of bacteremia)



Patient Encounter 1, Part 2

BR arrives at the clinic to receive her first dose of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) at full doses.

- What preventative measures should be taken to decrease her risk of febrile neutropenia?
- What specific agent(s) would you consider for prophylactic use in this patient?

Prevention

Three primary modalities for preventing infection in patients who are expected to become neutropenic have been used, the first of which is the cheapest and simplest:

- Careful hand washing
- Prophylactic antibiotics
- Colony-stimulating factors

The advantages and disadvantages of these strategies will be discussed individually in the following sections.

Hand Washing

As discussed previously, most infections in neutropenic patients are a result of endogenous flora; however, prevention of further acquisition of environmental pathogens is also important. Patients who are or will become neutropenic should practice careful hand washing, and contact with people who neglect hand washing should be avoided. In addition, ingestion of fresh fruits and vegetables as well as nonprocessed dairy products, should be avoided during the neutropenic period.

Prophylactic Antibiotics

Routine antibacterial prophylaxis is controversial and has been attempted primarily with sulfamethoxazole-trimethoprim (SMZ-TMP) and quinolones. SMZ-TMP offers improved prophylaxis for gram-positive organisms compared with quinolones, whereas quinolones are more effective prophylaxis against gram-negative infections. The 2002 Infectious Diseases Society of America (IDSA) guidelines for the use of antimicrobial agents in cancer do not recommend the use of these agents for routine prophylaxis.[5] Reasons for this recommendation include the lack of a clear benefit on mortality rates and concerns regarding increasing antibiotic resistance. One exception is that SMZ-TMP is recommended for prophylaxis of *Pneumocystis jiroveci* pneumonitis (PCP) in all at-risk patients (i.e., bone marrow transplant recipients and AIDS patients) regardless of the presence of neutropenia.

Two recent meta-analyses add fuel to this controversial area.[8,9] Decreases in infection-related mortality and gram-negative bacteremia were demonstrated with the use of quinolones, but overall adverse events were higher, and most of the studies were conducted in patients with hematologic malignancies (an inherently high-risk group). Therefore, the use of prophylactic quinolones in patients with hematologic malignancies is reasonable, but pay particular attention to changes in local patterns of resistance if widely implemented.

Colony-Stimulating Factors

The colony-stimulating factors (CSFs) stimulate the maturation and differentiation of neutrophil precursors. Three agents are currently approved for use in the United States (Table 96–4). The prophylactic use of these agents decreases days of hospitalization and use of empirical antibiotics by shortening the duration of neutropenia [defined as an ANC of less than $0.5 \times 10^3/\mu L$ ($0.5 \times 10^9/L$)]. There is little to no effect on the depth of neutrophil nadir. A recent meta-analysis found that the use of prophylactic granulocyte colony-stimulating factor (either filgrastim or peg-filgrastim) resulted in a 46% risk reduction of febrile neutropenia and a 48% risk reduction in infectious mortality, although absolute differences were small (3.3% versus 1.7%).[10] It is critical to note that patients who receive these agents still may experience febrile neutropenia despite the risk reduction.

The primary limitation of the use of these agents is cost. Clinical practice guidelines for the use of CSFs have been developed by the National Comprehensive Care Network (NCCN).[11] These guidelines recommend the use of CSFs beginning with the first cycle (primary prophylaxis) of chemotherapy when the risk of febrile neutropenia is approximately 20% or more. This is the point where the use of CSFs is cost-effective when balanced against the cost of hospitalization and antimicrobials. *Secondary prophylaxis* refers to the subsequent prophylactic use of a CSF after a patient has had a prior episode of febrile neutropenia. This strategy should be used especially when the chemotherapy is being given in patients with the intention of cure (e.g., non-Hodgkin's lymphoma and early breast cancer). In this circumstance, administration of full doses of chemotherapy on time without delays has been shown to improve outcome.

Although generally well tolerated, CSFs may cause bone pain in around 25% of patients. This may be managed with acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs), although attention to the platelet count is warranted with the use of NSAIDs. Sargramostim in particular may result



Patient Encounter 1, Part 3

BR presents to the clinic approximately 8 days after her second cycle of R-CHOP with a temperature of 101.2°F (38.4°C). Her CBC reveals a WBC count of $0.84 \times 10^3/\mu L$ ($0.84 \times 10^9/L$) with 10% (0.10) neutrophils and 15% (0.15) bands.

- What is BR's absolute neutrophil count?
- What treatment goals do you have for BR?
- Construct a treatment plan for this patient with specific monitoring criteria for therapy adjustment.

TABLE 96–4. Overview of Colony-Stimulating Factors[11]

Agent	Effector Cell(s)	Dosage	Common Adverse Effects	Comments
Filgrastim Neupogen® GCSF	Neutrophil	5 mcg/kg per day SQ or IV *or* round to 300- or 480-mcg vial size	Bone pain (approximately 25%)	Begin 1–3 days after chemotherapy
Pegfilgrastim Neulasta®	Neutrophil	6 mg SQ one time	Bone pain (approximately 25%)	Once per cycle dosing Administer 1–3 days after chemotherapy
Sargramostim Leukine® GMCSF	Neutrophil, Eosinophil, Macrophage	250 mcg/m^2 per day SQ or IV *or* round to 250- or 500-mcg vial size	First-dose effect (hypotension, flushing) Low-grade fever Bone pain Injection-site skin reaction	Indicated for use following induction chemotherapy in older patients with AML Limited experience and lack of FDA approval for prevention of febrile neutropenia

GCSF, granulocyte colony stimulating factor; GMCSF, granulocyte-macrophage colony stimulating factor; SQ, subcutaneous; IV, intravenous; AML, acute myeloid leukemia.

in low-grade fever and myalgias, perhaps as a result of its wider pattern of effector cell stimulation.

Treatment

Desired Outcomes

Since rapid death may occur with certain infections in neutropenic patients, prompt and emergent treatment is indicated. The primary goal is to prevent morbidity and mortality during the neutropenic period. This is accomplished by effectively treating subclinical infections or established infections.

General Approach to Treatment

❶ *A risk assessment should be performed at presentation of febrile neutropenia to identify low-risk patients for potential outpatient treatment* (see Table 96–3). *Patients who do not meet low-risk criteria should be hospitalized for parenteral administration of broad-spectrum antibacterials.* The IDSA has published evidence-based guidelines for the management of febrile neutropenia[5,12] (Fig. 96–1). The choice of initial antimicrobial agent(s) depends on the following factors:

- Drug allergies
- Concurrent renal dysfunction or use of nephrotoxic agents
- Use of prophylactic antibiotics
- Institutional susceptibility patterns
- Cost

❶ *The administration of empirical therapy should begin immediately after cultures are taken. Therapy should not be withheld until after culture results are obtained.*

As illustrated in Fig. 96–1, specific criteria exist for the addition of vancomycin for coverage of resistant gram-positive organisms or agents for coverage of fungal infections. Additional agents are necessary in the setting of continued fever or declining clinical status in neutropenic patients. In general, all empirical therapy is continued until recovery of the ANC to levels above $0.5 \times 10^3/\mu L$ ($0.5 \times 10^9/L$) in patients with negative cultures. If a specific etiology is identified, appropriate therapy should be continued until 7 days after neutropenia resolves. Specific regimens with recommended dosages are summarized in Table 96–5.

Pharmacologic Therapy

There are two primary choices for the initial management of high-risk febrile neutropenia: monotherapy and dual therapy (see Fig. 96–1). Both regimens have been shown to be equivalent in randomized studies and meta-analyses. Monotherapy avoids the nephrotoxicity of the aminoglycosides and is potentially less expensive but lacks significant gram-positive coverage and may increase selection of resistant organisms. Dual therapy provides synergistic activity, decreased resistance, and permits dual coverage of *Pseudomonas aeruginosa* but requires therapeutic monitoring for aminoglycosides.

Vancomycin adds broad-spectrum gram-positive coverage, but increasing emergence of vancomycin-resistant organisms (e.g., *Enterococcus* spp.) prompts conservative use. Thus vancomycin should be included as part of the initial therapy only in the following cases:

- Severe mucositis
- Quinolone prophylaxis
- Hypotension
- Colonization with resistant gram-positive organisms (e.g., methicillin-resistant *Staphylococcus aureus*)
- Evidence of central venous catheter infection

Vancomycin may be added to the empirical regimen after 3 to 5 days in persistently febrile patients or if cultures reveal gram-positive organisms. Vancomycin should be changed if the gram-positive organism is susceptible to other antibacterials or discontinued in patients with persistent fever after 3 days with negative cultures.

Empirical antifungal agents typically are added in persistently febrile patients after 5 to 7 days, especially if continued

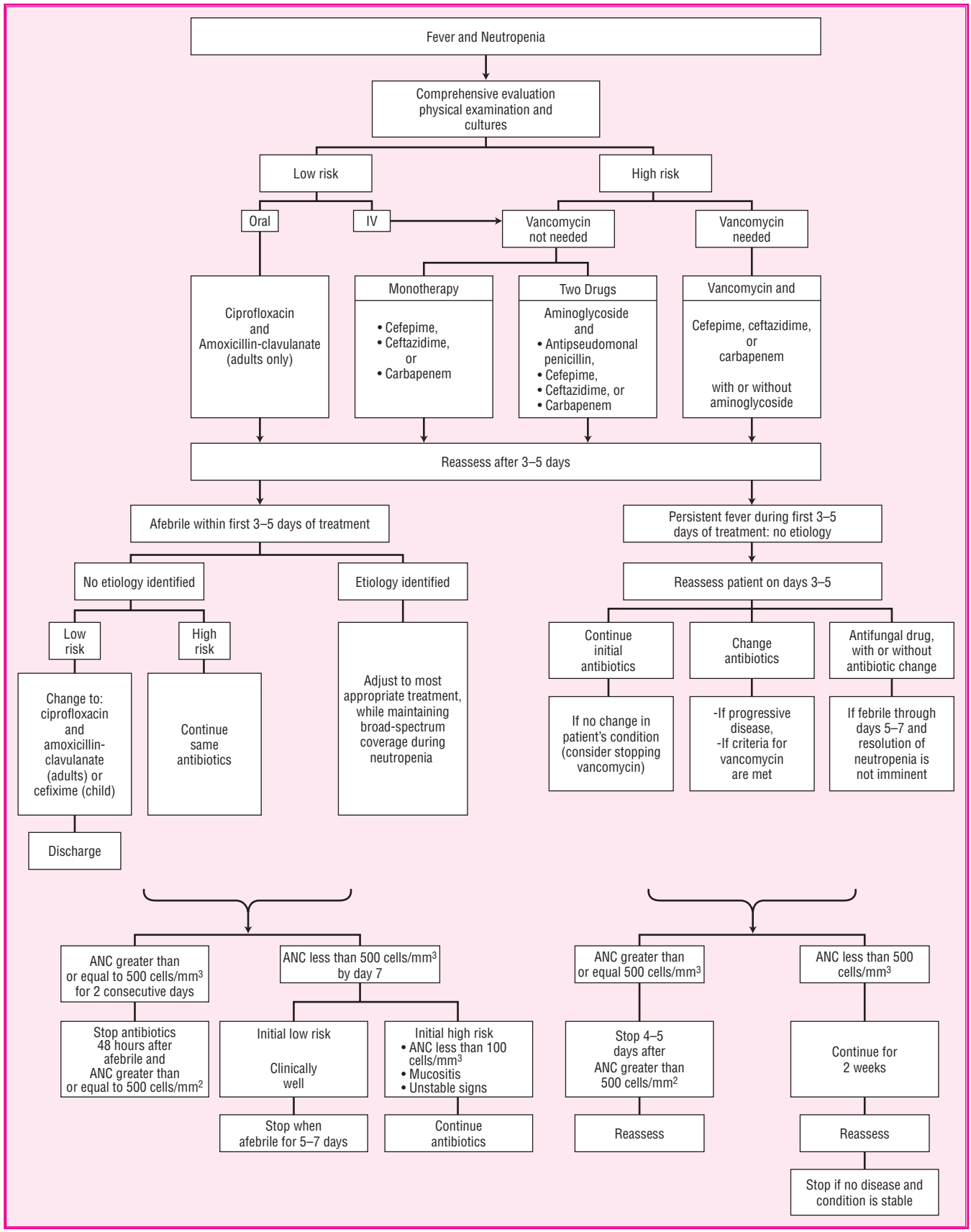


FIGURE 96–1. Management of febrile episodes in neutropenic cancer patients.[5,12]

TABLE 96–5. Dosing Guidelines for Empirical Antimicrobial Agents in Febrile Neutropenia

Regimen Type	Agents and Dosing[a]	Comments
Antibacterial		
β-Lactam monotherapy	Cefepime 2 g IV every 8 hours Ceftazidime 2 g IV every 8 hours Imipenem 500 mg IV every 6 hours Meropenem 1g IV every 8 hours Piperacillin tazobactam 4.5 g IV every 8 hours	Although piperacillin-tazobactam is not recommended in the IDSA guidelines, recent data demonstrate equivalence to other monotherapy and dual-therapy regimens.
Dual therapy with antipseudomonal β-lactam plus aminoglycoside	Cefepime, ceftazidime, imipenem, meropenem, piperacillin-tazobactam (above dosages), ticarcillin–clavulanic acid 3.1 g IV every 6 hours and gentamicin or tobramycin	Gentamicin or tobramycin 2 mg/kg loading dose followed by doses adjusted by serum concentrations; once-daily dosing of aminoglycosides may be used.
Empirical regimens containing vancomycin	Cefepime, ceftazidime, imipenem, meropenem (above dosages) and vancomycin 0.5–1 g every 6–12 hours with or without aminoglycoside	Vancomycin dosages may be adjusted based on serum levels.
Dual therapy containing fluoroquinolone	Ciprofloxacin 400 mg IV every 8 hours and piperacillin-tazobactam, ceftazidime (above dosages)	Cannot be used in patients who receive fluoroquinolone prophylaxis.
Low-risk oral regimen	Ciprofloxacin 750 mg PO every 12 hours and amoxicillin-clavulanate 500–875 mg PO every 12 hours	For patients with MASCC score of 21 or greater not receiving fluoroquinolone prophylaxis.
Antifungal		
Amphotericin B deoxycholate	0.5–1 mg/kg IV daily	Premedication with acetaminophen and diphenhydramine; 500 mL normal saline boluses before and after.
Liposomal amphotericin B	3 mg/kg IV daily	Lower incidence of nephrotoxicity and infusion reactions; more expensive.
Caspofungin	70 mg/kg IV loading dose on day 1 followed by 50 mg/kg IV daily	Dosage adjustment in hepatic dysfunction.
Voriconazole	6 mg/kg IV loading dose every 12 hours on day 1 followed by 4 mg/kg PO/IV every 12 hours	Dosage adjustment in hepatic dysfunction; IV formulation contraindicated if creatinine clearance less than 50 mL/minute; multiple drug interactions.

[a]Dosing for adult patients.
IV, intravenous; PO, by mouth.

neutropenia is expected. Amphotericin B historically has been the drug of choice owing to its broad-spectrum activity against both yeast (*Candida* spp.) and mold (*Aspergillus* spp.) infections. Because frequent toxicity (e.g., nephrotoxicity and infusion reactions) limits the use of amphotericin B, less toxic alternatives have been studied. Lipid formulations of amphotericin provide decreased toxicity, and liposomal amphotericin B (AmBisome®) has been shown to be equivalent to conventional amphotericin B as empirical therapy but is significantly more expensive. The role of voriconazole is unclear at this time; however, caspofungin has been shown to be equivalent with less toxicity than liposomal amphotericin B in a randomized trial and is approved by the Food and Drug Administration (FDA) for this indication.[13] Itraconazole also has been used in some institutions, but its use is complicated by poor bioavailability of oral preparations and numerous drug interactions.

As stated earlier, low-risk patients fulfilling the MASCC criteria (see Table 96–3) may be treated empirically as an outpatient with a regimen combining amoxicillin–clavulanic acid and ciprofloxacin. Clindamycin is a reasonable alternative for penicillin-allergic patients.

The CSFs should not be used routinely for treatment of febrile neutropenia in conjunction with antimicrobial therapy.[5] However, the use of CSFs in certain high-risk patients with hypotension, documented fungal infection, pneumonia, or sepsis is reasonable. A recent meta-analysis demonstrated that hospitalization and neutrophil recovery are shortened and that infection-related mortality is marginally improved.[14] As with prophylactic use of these agents, cost considerations limit their use to high-risk patients.

Outcome Evaluation

❷ *The success of the treatment of febrile neutropenia depends on the adequate recovery of the ANC and either optimal antimicrobial coverage of identified organisms or empirical coverage of unidentified organisms.* Monitor the CBC with differential and T_{max} (maximum temperature during previous 24 hours) daily. Assess renal and hepatic function at least twice weekly,



Patient Care and Monitoring

1. Counsel patients receiving cytotoxic chemotherapy to report fever promptly. Provide patients with a diet to use during the neutropenic period. Counsel patients to avoid close contact with sick friends and relatives, and remind the patient and caregivers of the importance of hand washing.
2. If febrile neutropenia occurs, patient history is important:
   - What chemotherapy did the patient receive and when? Is the ANC on the way down (before nadir) or on the way up (after nadir)? Was the patient receiving prophylactic antibiotics, prophylactic filgrastim, or sargramostim or received prophylactic pegfilgrastim?
   - Did the patient have previous episodes of febrile neutropenia? What were the previous culture results to determine colonization status?
3. Assess the patient daily for any new signs or symptoms of infection. Evaluate the patient for adverse drug reactions, drug allergies, and drug interactions. Have all antibiotics been dose adjusted for renal or hepatic dysfunction?
4. For patients receiving oral antibiotics either prophylactically or as treatment of febrile neutropenia, counsel them that initial or persistent fever should be reported promptly and that compliance with the regimen is critical. Patients also should have easy access to medical care and adequate caregiver support. Provide information on drug interactions and adverse effects.

especially in patients receiving nephrotoxic agents. Vital signs should be taken every 4 hours. Follow up on blood and urine culture results daily because many cultures do not become positive for several days. Assess the patient daily for pain that may indicate an infectious source. Conduct daily physical examination of common sites of infection. Repeat cultures and chest x-ray in persistently febrile patients, and culture developing sources of infection (e.g., stool cultures for diarrhea).

CARDIOVASCULAR COMPLICATIONS

Superior Vena Cava Syndrome (SVCS)

Superior vena cava syndrome (SVCS) is a relatively rare complication of underlying cancer, although nonmalignant causes also may occur in patients with cancer. SVCS is rarely immediately life-threatening, except in patients with airway compromise and/or laryngeal or cerebral edema. However, rapid recognition of typical presenting symptoms facilitates referral for tissue diagnosis (if unknown) and treatment.

Epidemiology and Etiology

SVCS occurs in around 15,000 patients per year, of which approximately 90% are caused by malignancy. Specific cancers associated most commonly with SVCS are listed in Table 96–6. Lung cancer is the most frequent cause, of which small cell lung cancer (SCLC) is the most frequent sub-type associated with SVCS. This is thought to be due its predilection for the central and **perihilar** areas of the lung. Interestingly, right-sided lung cancers are four times more likely than left-sided lesions to cause SVCS. Mediastinal masses from lymphomas are the second most common cause.

The most common nonmalignant etiology of SVCS is catheter-related thrombosis primarily owing to the increasing use of central access devices. Other causes include benign teratoma, tuberculosis, silicosis, and sarcoidosis.

Pathophysiology

The superior vena cava (SVC) is the primary drainage vein for blood return from the head, neck, and upper extremities. It is a relatively thin-walled vein that is particularly vulnerable to obstruction from adjacent tumor invasion or thrombosis. The obstruction leads to elevated venous pressure, although collateral veins partially compensate. This is one reason for the relatively slow onset of the classic symptoms of SVCS. In fact, 75% of patients have signs and symptoms for more than 1 week before seeking medical attention.[15]

Treatment

Desired Outcomes

❸ *The primary goal of treatment of SVCS is to relieve the obstruction of the SVC by treating the underlying malignancy.* In the case of SVCS caused by thrombosis, the goal is to dissolve the thrombus and prevent further clot formation. Resolution of the obstruction will rapidly relieve symptoms and restore normal SVC function. The final goal of therapy is to avoid potentially fatal complications of SVCS, such as cerebral edema from rapid increases in intracranial pressure and intracranial thrombosis or bleeding.

TABLE 96–6. Tumors Most Commonly Associated with Superior Vena Cava Syndrome

Cause	Frequency (%)
Lung cancer	65–80
Lymphoma	10
Mediastinal tumors	10
Germ cell tumors	
Thymoma	
Metastatic solid tumors	5–10
Breast cancer	

Data from ref. 15.



Clinical Presentation and Diagnosis

General

- Presentation depends on the degree of SVC obstruction.
- Almost complete obstruction is necessary to demonstrate classic symptoms.

Signs and Symptoms

- Facial, neck, and upper extremity edema; dyspnea; cough, dilated upper extremity veins; and orthopnea are most common.
- Less common—hoarseness, dysphagia, dizziness, headache, lethargy, chest pain
- Patients with elevated intracranial pressure may have mental status changes.
- Patients with airway obstruction may have shortness of breath.

Diagnostic Tests

Tissue biopsy to determine underlying cause (if unknown), chest x-ray, computed tomographic (CT) scan, bronchoscopy, and mediastinoscopy

General Approach to Treatment

Since most SVCSs are not immediately life-threatening, a tissue diagnosis (if unknown) to specifically identify the underlying malignancy is critical because treatment approaches vary considerably according to tumor histology. Thus therapy typically can be withheld until a tissue diagnosis is established. While biopsy results are pending, supportive measures such as head elevation, diuretics, corticosteroids, and supplemental oxygen may be used.

Nonpharmacologic Therapy

Radiation therapy is the treatment of choice for chemotherapy-resistant tumors such as non–small cell lung cancer (NSCLC) or in chemotherapy-refractory patients with SVCS. Between 70% and 90% of patients will experience relief of symptoms. Radiation therapy also may be combined with chemotherapy for chemotherapy-sensitive tumors such as SCLC and lymphoma. In the rare emergency situations of airway obstruction or elevated intracranial pressure, empirical radiotherapy prior to tissue diagnosis should be used. In most patients, symptoms resolve within 1 to 3 weeks.

Surgical options for the management of SVCS include stent placement and surgical bypass. SVC stenting may provide longer-term relief of symptoms than radiotherapy; thus it is used often in the palliative-care setting when chemotherapy has failed.[16] One disadvantage of SVC stenting is the need for anticoagulation, especially in patients at high risk for thrombosis. The role of surgical bypass is limited to patients with complete SVC obstruction or patients who are refractory to chemotherapy and radiotherapy; thus it is rarely indicated.

Pharmacologic Therapy

Cytotoxic chemotherapy is the treatment of choice for chemotherapy-sensitive tumors such as SCLC and lymphoma. As indicated earlier, chemotherapy also may be combined with radiotherapy, especially in patients with lymphoma who have bulky mediastinal lymphadenopathy.

Corticosteroids play a key role in the management of SVCS, particularly in cases of lymphoma, because these tumors inherently respond to corticosteroid therapy. They are also helpful in the setting of respiratory compromise. Corticosteroids benefit patients who are receiving radiation therapy by reducing local radiation-induced inflammation and increased intracranial pressure. Dexamethasone 4 mg intravenously or by mouth every 6 hours is a frequently used regimen. The dosage should be tapered on completion of radiation therapy or resolution of symptoms.

The role of diuretics in the management of SVCS is controversial. While patients may derive symptomatic relief from edema, complications such as dehydration and reduced venous blood flow may exacerbate the condition. If diuretics are used, furosemide is used most frequently with diligent monitoring of the patient's fluid status and blood pressure.

In the case of thrombosis-related SVCS, anticoagulation is controversial because there is a lack of survival benefit. However, thrombolytics (e.g., alteplase) and anticoagulation with heparin and warfarin may be beneficial in patients with thrombosis owing to indwelling catheters if it is used within 7 days of onset of symptoms, although catheter removal may be required.

Outcome Evaluation

The major measure of outcome of treatment of SVCS is the relief of symptoms, regardless of the therapy used. SVC stenting provides rapid relief of symptoms within 1 to 7 days of stent placement.[15] Patients who receive chemotherapy and/or radiotherapy generally will experience symptom relief within 1 to 2 weeks. Monitor the patient for relief of symptoms by

- Daily physical assessment of signs and symptoms
- Daily monitoring of fluid status
- For corticosteroid use, serum glucose, insomnia, fluid retention, GI upset, mental status changes, signs and symptoms of infection daily

Repeat CT scans of the chest after the first cycle of chemotherapy, surgical stenting, or radiotherapy to assess tumor response.

NEUROLOGIC COMPLICATIONS

Spinal Cord Compression

Although not typically life-threatening, spinal cord compression is a true oncologic emergency because delays in treatment by mere hours may lead to permanent neurologic dysfunction. It is therefore incumbent on practitioners to



Patient Care and Monitoring

1. Does the patient have a known cancer at presentation? Assess the patient's symptoms at presentation to determine the need for emergent treatment versus disease-specific treatment following tissue diagnosis.
2. Review biopsy results to determine optimal chemotherapy and/or radiation regimen.
3. For patients receiving corticosteroids, monitor for adverse effects and drug interactions. Does the patient need GI prophylaxis for long-term treatment? Slowly taper once symptoms improve and/or radiation is completed.
4. Evaluate the patient for drug interactions, allergies, and adverse effects with chemotherapy and/or corticosteroid therapy.

quickly recognize the signs and symptoms to facilitate rapid management strategies.

Epidemiology and Etiology

Around 20,000 cancer patients experience spinal cord compression in the United States every year, most of which involves the thoracic spine (approximately 70%). Cancers that inherently metastasize to bone (e.g., breast, prostate, and lung) are the most frequent etiologies identified. Most spinal cord compression occurs in patients with a known malignancy; however, 8% to 34% occurs as the initial presentation of cancer, especially in patients with non-Hodgkin's lymphoma, multiple myeloma, and lung cancer.[17]



Clinical Presentation and Diagnosis

General

- Once neurologic deficits appear, progression to irreversible paralysis may occur within hours to days.
- Around 10% to 38% of patients present with multiple sites of spinal involvement.

Signs and Symptoms

- Back pain is present in more than 90% of patients.
  - Initially localized and increases in intensity over several weeks
  - Aggravated by movement, supine positioning, coughing, sneezing, neck flexion, straight-leg raise, Valsalva maneuver, and palpation of spine
- Sensory deficit
  - Cervical spine compression may lead to quadriplegia
  - Thoracic spine compression may lead to paraplegia
  - Upper lumbar spine compression may lead to bowel and bladder dysfunction (constipation and urinary retention) and abnormal extensor plantar reflexes
- Weakness

Diagnostic Tests

- Magnetic resonance imaging (MRI) with gadolinium enhancement is the "gold standard."
- X-rays may be helpful to identify bone abnormalities.

Pathophysiology

The spinal cord emerges from the brain stem at the base of the skull and terminates at the second lumbar vertebra. The thoracic spine is most vulnerable to cord compression because of natural kyphosis and because the width of the thoracic spinal canal is the smallest among the vertebrae. Most spinal cord compression is due to adjacent vertebral metastases that compress the spinal cord or from pathologic compression fracture of the vertebra. This results in significant edema and inflammation in the affected area.

Treatment

Desired Outcome

❶ *Since patients with spinal metastases generally are incurable, the primary goal of treatment of spinal cord compression is palliation. The most important prognostic factor for patients presenting with spinal cord compression is the underlying neurologic status.* Only around 10% of patients who present with paralysis are able to ambulate following treatment, whereas 98% of ambulatory and 60% of nonambulatory patients are able to ambulate after treatment.[17] Therefore, the goals of treatment are recovery of normal neurologic function, local tumor control, pain control, and stabilization of the spine. Therapeutic options depend primarily on the following factors:

- Underlying malignancy
- Prior therapies
- Stability of the spine at presentation
- Overall patient prognosis

Nonpharmacologic Therapy

Radiation therapy generally is considered to be the treatment of choice for most patients. Exceptions to this include patients with prior radiation to the treatment site and patients with inherently radioresistant tumors (e.g., melanoma and renal cell carcinoma). The radiation field should include two vertebral bodies above and below the involved area.

Surgery for spinal cord compression typically involves either **laminectomy** for posterior lesions or decompression with fixation. Surgery is the treatment of choice for the following patients: (1) those with an unstable spine requiring

stabilization, (2) those with immediately impending sphincter dysfunction requiring rapid spinal decompression, (3) those who do not respond to or have received their maximum dose of radiotherapy, and (4) those with direct compression of the spinal cord owing to spinal bony fragments.[17] Recent evidence suggests that surgery followed by radiation therapy may be superior to radiotherapy alone in terms of increased ambulation time after treatment, maintenance of continence, and rates of nonambulatory patients becoming ambulatory.[18] Surgery also is useful for establishing a tissue diagnosis in cases of unknown malignancy. Overall, the risks and benefits of surgery must be weighed against the expected prognosis of the patient in light of the significant rehabilitation required after surgery.

Pharmacologic Therapy

Corticosteroids play a key role in the management of spinal cord compression. Dexamethasone is used most frequently to reduce edema, inhibit inflammation, and delay onset of neurologic complications. Dexamethasone has been shown to improve ambulation in combination with radiation as compared with radiation alone.[19] Significant controversy exists regarding the optimal dosing of dexamethasone. Loading doses of 10 to 100 mg followed by 4 to 24 mg four times daily have been used. Higher doses may be used in cases of rapidly progressing symptoms, but adverse effects including GI bleeding and psychosis are more severe. Steroids should be continued during radiation therapy and then tapered appropriately.

Pain management is also of critical importance in patients with spinal cord compression. While dexamethasone will provide some benefit, opioid analgesics also should be used and titrated rapidly to achieve adequate pain control.

Outcome Evaluation

Patients who receive definitive treatment with radiation and/or surgery generally derive benefit within days. Monitor patients for

- Improved symptoms of sensory loss using physical examination every 4 hours until symptoms improve and then daily
- Improved autonomic system function, including urine and bowel control, every 4 hours until symptoms improve and then daily
- Improved pain control using detailed pain assessment every 2 to 4 hours during initial titration and then daily thereafter
- For corticosteroid use, serum glucose, insomnia, fluid retention, GI upset, mental status changes, and signs and symptoms of infection daily

Complications of Brain Metastases

Brain metastases are among the most feared complications of cancer and generally carry a poor prognosis. One serious consequence of brain metastases is elevated intracranial pressure, which can rapidly lead to fatal intracranial herniation and death. Rapid identification of the signs and symptoms of brain metastases is critical to improve long-term outcome and avoid mortality.

Epidemiology and Etiology

Brain metastasis is the most common neurologic complication seen in patients with cancer. Approximately 170,000 patients develop brain metastases in the United States each year.[20] Many malignancies are frequently associated with brain metastases (Table 96–7). While melanoma is the tumor type most likely to metastasize to the brain, brain metastases owing to lung and breast cancers are seen more often because they are among the most common cancers. In addition, brain metastasis may be diagnosed at the same time as the primary malignancy in around 20% of cases.[22] Around 80% of brain metastases occur in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brain stem.

Pathophysiology

A delicate balance of normal pressure is maintained in the brain and spinal cord by brain, blood, and cerebrospinal fluid (CSF) volume. Since the brain is contained within a confined space (skull), any foreign mass contained within that space causes adverse sequelae. This results in either destruction or displacement of normal brain tissue with associated edema. Most brain metastases occur through hematogenous spread of the primary tumor, and around 80% of patients will have multiple sites of metastases within the brain.



Patient Care and Monitoring

1. Does the patient have a known cancer at presentation? Determine the need for surgery to make the tissue diagnosis, and treat the compression.
2. What is the neurologic status of the patient at presentation? A detailed physical examination and history are keys to determine long-term outcome.
3. For patients receiving corticosteroids, monitor for adverse effects and drug interactions. Does the patient need GI prophylaxis for long-term treatment? Slowly taper once symptoms improve and/or radiation is completed.
4. Provide patient education regarding when to take medications and the importance of compliance, and promptly report symptoms of recurrence.
5. Refer patient to physical therapy for rehabilitation to help regain optimal neurosensory function.

TABLE 96–7. Cancers Most Frequently Associated with Brain Metastases

Type of Cancer	Frequency (%)
Lung cancer	18–64
Breast cancer	2–21
Melanoma	4–16
Colorectal cancer	2–11
Hematologic malignancies (i.e., leukemia)	Approximately 10 (primarily owing to leptomeningeal spread)

Data from ref. 21.

Treatment

Desired Outcomes

Therapeutic modalities used for the management of brain metastases may be divided into symptomatic management and definitive management. ❺ *The goals of treatment of brain metastases are to manage symptoms by reducing cerebral edema, treat the underlying malignancy both locally and systemically, and improve survival.*

General Approach to Treatment

Patients with brain metastases have a poor prognosis. Untreated patients generally have a median survival of 1 month. The choice of treatment depends primarily on the status of the patient's underlying malignancy and the number and sites of brain metastases. The primary definitive treatments for brain metastases are surgery and radiation therapy. Pharmacologic modalities are used primarily to control symptoms, although cytotoxic chemotherapy plays a limited role in the management.



Clinical Presentation and Diagnosis

General

- Almost all patients with brain metastases are symptomatic.
- New cerebral neurologic symptoms in a cancer patient should initiate evaluation for brain metastases.
- Other causes of brain lesions, including hemorrhage, infection, and infarction, should be ruled out.

Signs and Symptoms

- Mental status changes (most common) leads to loss of consciousness, irritability, confusion
- Hemiparesis, aphasia, **papilledema**, weakness, seizure, nausea and vomiting
- Headache may be of gradual onset or sudden in the case of hemorrhage.

Diagnostic Tests

- MRI with contrast enhancement is the "gold standard."
- CT scans may be used in patients with pacemakers but may miss small metastases.

Nonpharmacologic Therapy

Radiation therapy is the treatment of choice for most patients with brain metastases. Most patients receive whole-brain radiation because the majority of brain metastases are multifocal. Another method known as *stereotactic radiosurgery* provides intense focal radiation, typically using a **linear accelerator** or **gamma knife,** in patients who cannot tolerate surgery or have lesions that are surgically inaccessible (e.g., in the brain stem).

Surgery plays a key role in the management of patients with brain metastases, particularly patients whose systemic disease is well controlled and in those with solitary lesions. Surgery also may benefit patients with multiple metastatic sites who have a single dominant lesion with current or impending neurologic sequelae.

In cases of elevated intracranial pressure (ICP) owing to cerebral herniation, mechanical hyperventilation to decrease the arterial P_{CO_2} down to 25 mm Hg (3.33 kPA) acutely decreases ICP by causing cerebral vasoconstriction. Elevation of the patient bed also may quickly reduce the ICP. It should be noted that these strategies only relieve symptoms and that definitive therapy is still required.

Pharmacologic Therapy

Corticosteroids are a mainstay in the management of brain metastases. They reduce edema that typically surrounds sites of metastasis, thereby reducing ICP. A loading dose of dexamethasone 10 mg followed by 4 mg by mouth or intravenously every 6 hours typically is used. Symptom relief may occur shortly after the loading dose, although the maximum benefit may not be seen for several days (after definitive therapy).

Mannitol is an agent that may be used in patients with impending cerebral herniation. Mannitol is an osmotic diuretic that shifts brain osmolarity from the brain to the blood. Doses of 100 g (1–2 g/kg) as an intravenous bolus should be used. Repeated doses typically are not recommended because mannitol may diffuse into damaged brain tissue, leading to rebound increased ICP.[21]

Twenty percent of patients with brain metastases may present with seizures and require anticonvulsant therapy. Phenytoin is the most frequently used agent, with a loading dose of 15 mg/kg followed by 300 mg by mouth daily (titrated to therapeutic levels between 10 and 20 mcg/mL). Diazepam 5 mg intravenously may be used for rapid control of persistent seizures. Prophylactic anticonvulsants have been used frequently, but a recent meta-analysis did not support their use.[23] Thus, because adverse effects and drug interactions are common, the routine use of prophylactic anticonvulsants is not recommended.

Outcome Evaluation

The success of therapy is based on the ability to decrease symptoms, treat the underlying sites of disease within the

brain, and prolong survival. Monitor parameters of symptom improvement by

- Frequent assessment of symptoms (i.e., mental status and sensory and motor function) every 4 hours until symptoms improve and then daily.
- For corticosteroid use, monitor serum glucose, insomnia, fluid retention, GI upset, mental status changes, signs and symptoms of infection daily.

UROLOGIC COMPLICATIONS

Hemorrhagic Cystitis

Hemorrhagic cystitis is defined as acute or insidious bleeding from the lining of the bladder. Although therapy with certain medications is the most common cause, it is also the most preventable. Once it occurs, hemorrhagic cystitis causes significant morbidity and mortality rates of between 2% and 4%. This section will focus on preventative strategies for chemotherapeutic agents, which rely heavily on pharmacotherapeutic approaches.

Epidemiology and Etiology

Numerous etiologies have been linked to hemorrhagic cystitis[24] (Table 96–8). Of these, the oxazaphosphorine alkylating agents (i.e., cyclophosphamide and ifosfamide) are implicated most frequently. Incidence rates vary considerably but generally range between 18% and 40% with ifosfamide and 0.5% and 40% with high-dose cyclophosphamide.[25] Chronic low-dose oral cyclophosphamide, typically as used in autoimmune disorders and chronic lymphocytic leukemia, also is associated infrequently with hemorrhagic cystitis.

Twenty percent of patients receiving pelvic irradiation may experience hemorrhagic cystitis, especially with concurrent cyclophosphamide. Viral infections commonly associated with this condition occur most frequently in bone marrow transplant recipients who also may receive cyclophosphamide.

TABLE 96–8. Primary Causes of Hemorrhagic Cystitis

Pharmacologic	Nonpharmacologic
Cyclophosphamide	Pelvic irradiation
Chronic low doses	Viral infection
High doses used in BMT	Cytomegalovirus
Ifosfamide	Papovavirus
Intravesicular thiotepa	Herpes simplex virus
Chronic oral busulfan	Adenovirus
Anabolic steroids	

BMT, bone marrow transplantation.
Data from ref. 24.

Pathophysiology

Cyclophosphamide- or ifosfamide-induced damage to the bladder wall is caused primarily by their metabolite known as *acrolein*. Acrolein causes sloughing and inflammation of the bladder lining, leading to hemorrhage. This is most common when urine output is low because higher concentrations of acrolein come into contact with the bladder urothelium for longer periods of time.



Patient Care and Monitoring

1. Assess patient symptoms for prompt referral for radiation or surgery.
2. For patients receiving corticosteroids, monitor for adverse effects and drug interactions. Does the patient need GI prophylaxis for long-term treatment? Slowly taper once symptoms improve and/or radiation or surgery is completed.
3. Evaluate the patient for drug interactions, allergies, and adverse effects with phenytoin or corticosteroid therapy.
4. Instruct patients receiving phenytoin about the symptoms of elevated serum concentrations (e.g., nystagmus, blurred vision, dizziness, drowsiness, and lethargy).
5. Provide patient education regarding when to take medications, the importance of compliance, and promptly reporting symptoms of recurrence (e.g., mental status changes and seizures).



Clinical Presentation and Diagnosis

General

Presentation may be mild (microscopic hematuria) or severe (massive hemorrhage) and develops during or shortly after chemotherapy infusion.

Signs and Symptoms

- Suprapubic pain and cramping, urinary urgency and frequency, dysuria and burning, hematuria
- Urinary retention leading to **hydronephrosis** and renal failure may occur if large blood clots obstruct the ureters or bladder outlet.

Laboratory Tests

- Urine dipsticks for blood
- Urinalysis reveals more than three RBCs per high-power field and microscopic hematuria.
- CBC with differential, PT/INR, aPTT, BUN, creatinine.

Prevention

❻ *The use of effective prevention strategies can decrease the incidence of hemorrhagic cystitis to less than 5% in patients receiving cyclophosphamide or ifosfamide. There are three methods to reduce the risk: administration of mesna, hyperhydration, and bladder irrigation with catheterization.* Mesna is the primary method used with ifosfamide, whereas all three strategies are used with cyclophosphamide.

Mesna is a thiol compound that is oxidized rapidly in the bloodstream after administration to dimesna, which is inactive. However, once filtered through the kidneys, dimesna is reduced back to mesna, which binds to acrolein, leading to inactivation and excretion. The American Society of Clinical Oncology (ASCO) has published evidence-based guidelines for the dosing and administration of mesna[25] (Table 96–9). The dose of oral mesna must be double the intravenous dose owing to oral bioavailability of between 40% and 50%. Because the half-life of mesna (approximately 1.2 hours) is much shorter than that of ifosfamide or cyclophosphamide, prolonged administration of mesna beyond the end of the chemotherapy infusion is critical (Fig. 96–2). Patients should receive at least 2 L of intravenous fluids beginning 12 to 24 hours before and ending 24 to 48 hours after the last dose of chemotherapy.

Continuous bladder irrigation by catheterization uses normal saline at 250 to 1000 mL/hour to flush acrolein from the bladder. Hyperhydration with normal saline at 3 L/m^2 per day with intravenous furosemide to maintain urine output greater than 100 mL/hour also has been used with cyclophosphamide. Mesna is equivalent to both strategies in patients receiving high-dose cyclophosphamide and avoids the discomfort and infection risk with catheterization and the intensity of hyperhydration. Thus mesna is the preventative method of choice.

Treatment

Desired Outcome

If hemorrhagic cystitis occurs, the goals of treatment are to decrease exposure to the offending etiology, establish and maintain urine outflow, avoid obstruction and renal compromise, and maintain blood and plasma volume. Restoration of normal bladder function is the ultimate goal following acute treatment.

General Approach to Treatment

The treatment of hemorrhagic cystitis first involves discontinuation of the offending agent. Agents such as anticoagulants and inhibitors of platelet function also should be discontinued. Intravenous fluids should be administered aggressively to irrigate the bladder. Blood and platelet transfusions may be necessary to maintain normal hematologic values. Pain should be managed with opioid analgesics. Local **intravesicular** therapies may be necessary if hematuria does not resolve (Fig. 96–3).

Nonpharmacologic Therapy

A large-diameter multihole urethral catheter should be inserted to facilitate saline lavage and evacuation of blood clots. Surgical removal of blood clots under anesthesia may be required if saline lavage is ineffective. Active bleeding from isolated areas may be cauterized with an electrode or laser. In severe cases that are unresponsive to local or systemic pharmacologic intervention,

TABLE 96–9. ASCO Guidelines for the Use of Mesna with Ifosfamide and High-Dose Cyclophosphamide

Chemotherapy Schedule	Dosing Schedule for Mesna	Comments
Low-dose ifosfamide 2 g/m^2 per day	Oral: 100% of total daily dose of ifosfamide given 20% IV 15 minutes before and 40% PO 2 and 6 hours after start of ifosfamide	Available in 400-mg tablets. Peak urinary thiol concentrations with oral mesna is at 3 hours. If patient vomits within 2 hours of administration, repeat dose orally or intravenously.
Standard-dose ifosfamide 2.5 g/m^2/day	Bolus: 60% of total daily dose of ifosfamide given IV in 20% increments 15 minutes before and 4 and 8 hours after start of ifosfamide Infusion: 60% of total daily dose of ifosfamide given 20% IV 15 minutes before and 40% by continuous infusion during and for 12–24 hours after end of ifosfamide	Peak urinary thiol concentrations with intravenous mesna is at 1 hour. Compatible with ifosfamide and cyclophosphamide by Y-site administration or when admixed in the same bag.
High-dose ifosfamide Greater than 2.5 g/m^2 per day	Lack of evidence for dosing, however higher doses for longer duration recommended based on longer half-life of ifosfamide at high doses	
Standard-dose cyclophosphamide	Use of mesna is not routinely necessary.	
High-dose cyclophosphamide (bone marrow transplant)	Bolus: 40% of cyclophosphamide dose given IV at hours 0, 3, 6, and 9 after cyclophosphamide Infusion: 100% of cyclophosphamide dose given by continuous infusion until 24 hours after cyclophosphamide	Should be combined with saline diuresis (1.5 liters/m^2 per day of normal saline).

ASCO, American Society of Clinical Oncology; IV, intravenously; PO, by mouth.
Data from ref. 25.

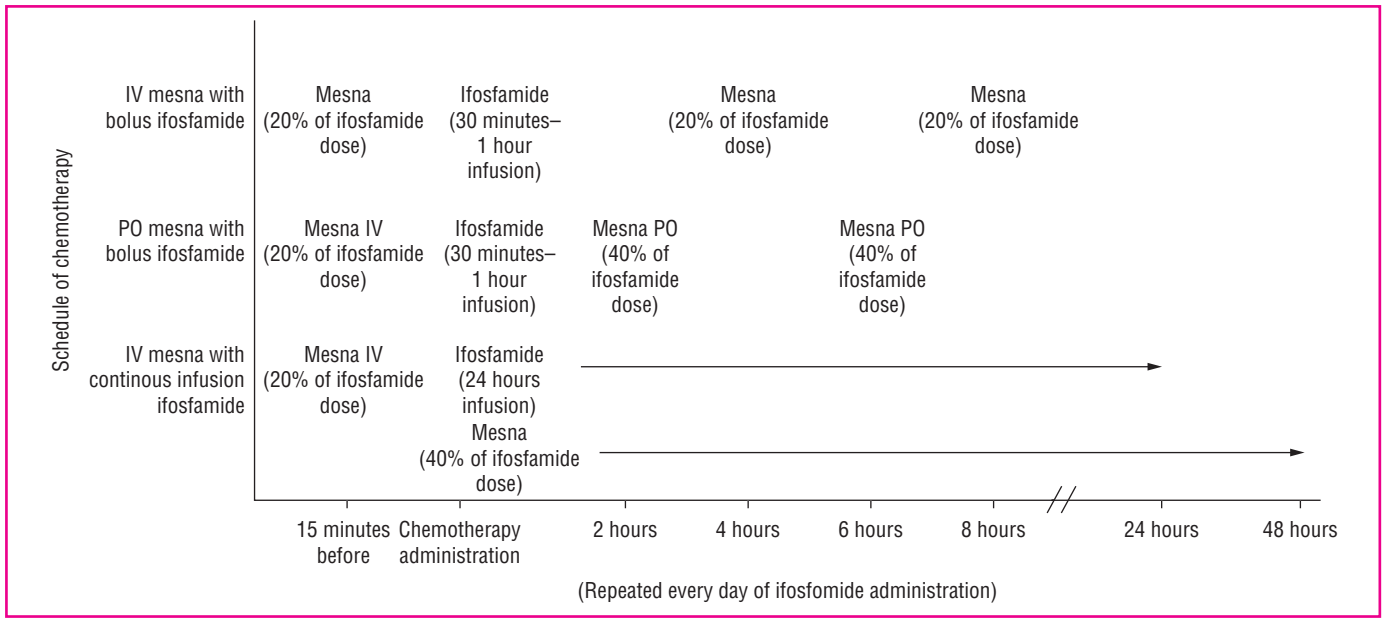


FIGURE 96–2. Examples of mesna administration with ifosfamide. IV, intravenous. PO, by mouth.

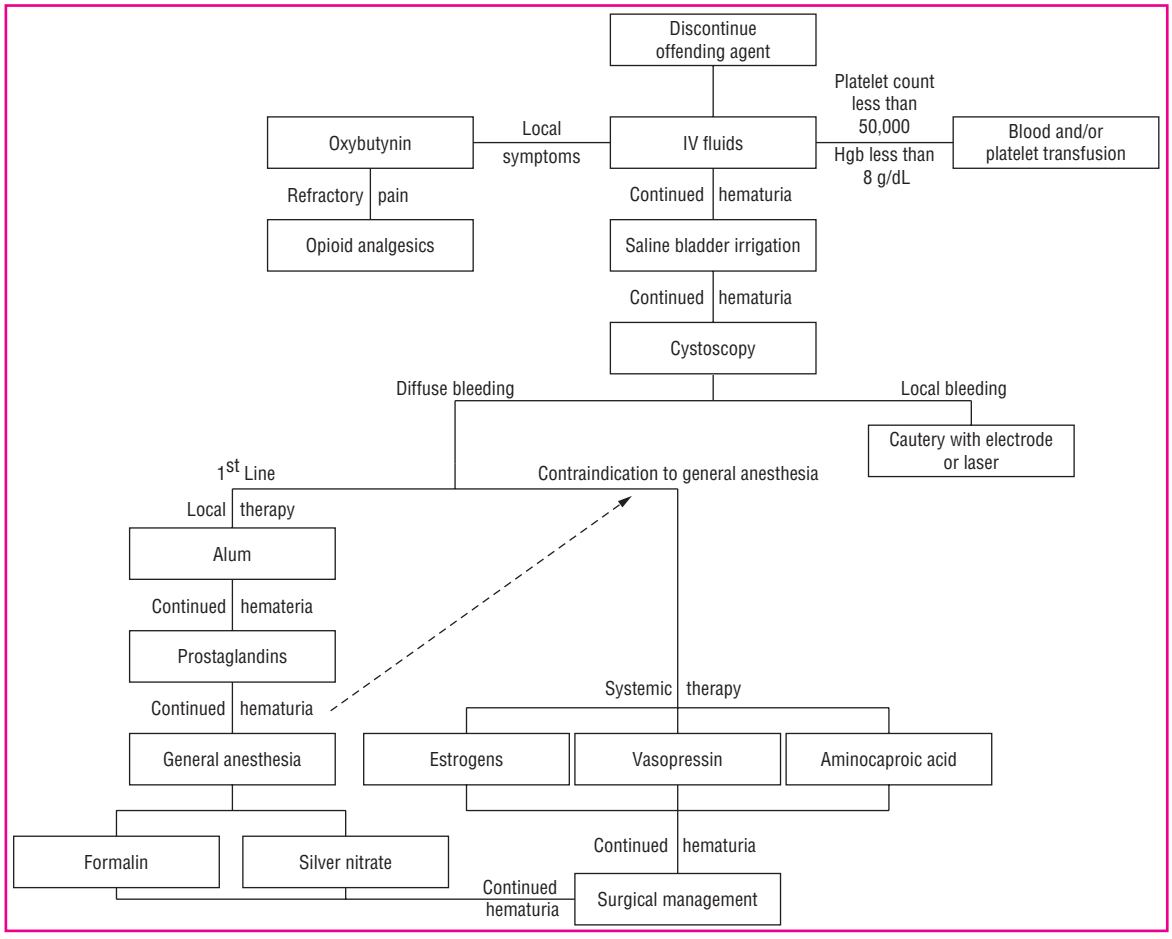


FIGURE 96–3. Treatment of hemorrhagic cystitis. IV, intravenous. (Data from ref. 24.)



Patient Care and Monitoring

1. Assess the patient receiving ifosfamide or cyclophosphamide at least daily for the development of hematuria.
2. Ensure administration of adequate hydration and proper doses of mesna.
3. Counsel the patient receiving oral mesna on the importance of compliance, when to take the doses, and to immediately report any episodes of vomiting for intravenous readministration.
4. Assess the quantity of urinary bleeding, and promptly refer to a urologist for local or surgical management.
5. Patients receiving systemic treatment should be monitored every 4 hours for resolution of hematuria. Promptly refer to urologist for refractory hematuria.
6. Evaluate the patient for drug interactions, allergies, and adverse effects with chemotherapy, mesna, or systemic therapies for management.

urinary diversion with percutaneous **nephrostomy** or surgical removal of the bladder may be required.

Pharmacologic Therapy

Many agents administered either locally or systemically are used in the treatment of hemorrhagic cystitis.[24] Local one-time administration of hemostatic agents such as alum, prostaglandins, silver nitrate, and formalin may be used; however, general anesthesia is required, especially with formalin. Systemic agents including estrogens, vasopressin, and aminocaproic acid may be used in patients who are refractory to local therapy, although they introduce the risk of systemic side effects. These agents should be continued until bleeding stops.

Antispasmodic agents such as oxybutynin 5 mg by mouth two to three times daily may be used for bladder spasms. In patients with refractory pain, opioid analgesics should be titrated to adequate pain control.

Outcome Evaluation

Monitor the patient for resolution of hematuria after each successive therapeutic intervention. Frequency of monitoring is based on the severity of hemorrhaging. Monitor urinary output and serum chemistries (including sodium, potassium, chloride, blood urea nitrogen, and serum creatinine) daily for renal dysfunction. Check the CBC at least daily to monitor hemoglobin and platelet count.

METABOLIC COMPLICATIONS

Hypercalcemia of Malignancy

Hypercalcemia is the most common metabolic abnormality experienced by patients with cancer. Once hypercalcemia occurs, it is associated with a very poor prognosis owing to the frequent association with advanced or metastatic disease.[26]

Epidemiology and Etiology

Hypercalcemia occurs in 10% to 30% of patients with cancer during the course of their disease. The most common tumor types associated with hypercalcemia are breast cancer; squamous cell carcinomas of the head, neck, and lung; and renal cancer. Hematologic malignancies such as multiple myeloma and, rarely, lymphomas are other causes of hypercalcemia.

Pathophysiology

Around 99% of calcium is contained in the bones, whereas the other 1% resides in the extracellular fluid. Of this extracellular calcium, approximately 40% is bound to albumin, and the remainder is in the ionized, physiologically active form. Normal calcium levels are maintained by three primary factors: parathyroid hormone, 1,25-dihydroxyvitamin D, and calcitonin. Parathyroid hormone increases renal tubular calcium resorption and promotes bone resorption. The active form of vitamin D, 1,25-dihydroxyvitamin D, regulates absorption of calcium from the GI tract. Calcitonin serves as an inhibitory factor by suppressing osteoclast activity and stimulating calcium deposition into the bones.

The delicate balance maintained by these factors is altered in patients with cancer by two principal mechanisms: tumor production of **humoral** factors that alter calcium metabolism (humoral hypercalcemia) and local osteolytic activity from bone metastases.[27] Humoral hypercalcemia causes around 80% of all hypercalcemia cases and is mediated primarily by systemic secretion of parathyroid hormone–related protein



Patient Encounter 2, Part 1

LP is a 58-year-old man with newly diagnosed stage IIIA non–small cell lung cancer who presents to the clinic complaining of loss of appetite, excess thirst, nausea and vomiting, and confusion × 2 days. The medication history lists NKDA, hydrochlorothiazide 50 mg by mouth daily for hypertension, and naproxen 500 mg by mouth twice daily for arthritis.

- What risk factors for hypercalcemia are exhibited in this patient?
- Are there any presenting signs or symptoms that are consistent with possible hypercalcemia?

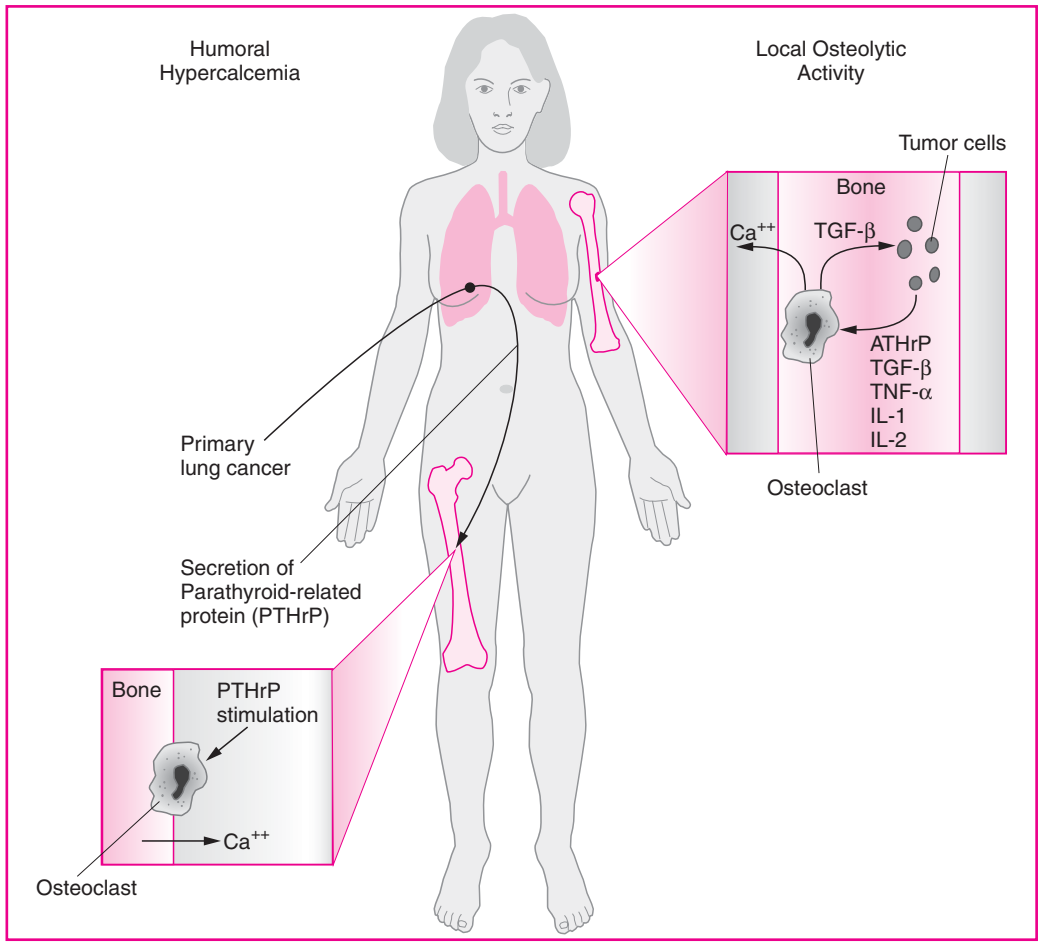


FIGURE 96–4. Pathophysiology of the hypercalcemia of malignancy. PTHrP, parathyroid hormone–related protein; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor alpha; Ca^{2+}, calcium; IL-1, interleukin 1; IL-2, interleukin 2.

(PTHrP). This protein mimics the action of endogenous parathyroid hormone on bones. Local osteolytic activity causes 20% to 30% of hypercalcemia cases, although local osteolytic activity also may have a humoral component. Local production of various factors directly stimulates osteoclastic bone resorption, which releases growth factors and cytokines (e.g., transforming growth factor β) that are necessary for tumor growth. Thus these metastatic tumors perpetuate their own growth through this mechanism. Calcium is also released by the osteolytic activity, resulting in hypercalcemia (Fig, 96–4).



Clinical Presentation and Diagnosis

General

- Presence of symptoms depends not only on the calcium level but also on the rapidity of onset.
- Normal calcium level is 8.5 to 10.5 g/dL (2.1–2.6 mmol/L) (varies by lab).
- Serum calcium level *must* be corrected for albumin level using the following formula: Corrected calcium = (measured calcium – measured albumin) + 4.

Signs and Symptoms

Five primary organ systems may be affected:

- Gastrointestinal: anorexia, nausea, vomiting, and constipation
- Musculoskeletal: weakness, bone pain, fatigue, and ataxia
- Central nervous system: confusion, headache, lethargy, seizures, and coma
- Genitourinary: polydipsia, polyuria, and renal failure
- Cardiac: bradycardia, ECG abnormalities, and arrhythmias

Laboratory Tests

- Elevated corrected serum calcium level greater than or equal to 10.5 g/dL (2.6 mmol/L), serum albumin, low to normal serum phosphate
- Patient may have elevated BUN and serum creatinine.
- Elevated alkaline phosphatase may indicate bone destruction.
- ECG may indicate prolonged PR interval, shortened QT interval, and widened T wave.

Other Diagnostic Tests

Rule out other causes of hypercalcemia, including primary hyperparathyroidism, hyperthyroidism, vitamin D intoxication, and chronic renal failure.



Patient Encounter 2, Part 2

A chemistry panel is drawn from LP that reveals a serum calcium level of 12.4 g/dL (3.1 mmol/L) and a serum albumin level of 2.6 g/dL (26 g/L). An ECG is done that reveals a prolonged PR interval.

- What is LP's corrected calcium level?
- What treatment plan would you outline to manage LP's hypercalcemia based on the calcium level and his signs and symptoms?
- What changes (if any) would you make to LP's current medication regimen?

A third and less common mechanism is production of 1,25-dihydroxyvitamin D by tumor cells (usually lymphoma), which increases GI absorption of calcium and enhances osteoclastic bone resorption.

Treatment

Desired Outcome

❼ *The primary goal of treatment for hypercalcemia is to control the underlying malignancy. Therapies directed at lowering the calcium level are temporary measures that are useful until anticancer therapy begins to work.* The goals of calcium-lowering therapy are to (1) lower the corrected calcium to normal levels, (2) regain fluid and electrolyte balance, (3) relieve symptoms, and (4) prevent life-threatening complications. Patients who are refractory to available therapies may have calcium-lowering therapy withheld (usually resulting in coma and death), which may be a humane approach.[26]

General Approach to Treatment

❽ *Therapeutic options for the treatment of hypercalcemia should be directed toward the level of corrected serum calcium and the presence of symptoms* (Fig. 96–5). Hypercalcemia may be classified as mild [corrected calcium equal to 10.5–11.9 g/dL (2.6–3 mmol/L)], moderate [12–13.9 g/dL (3–3.5 mmol/L)], and severe [greater than 14 g/dL (3.5 mmol/L)].[26] ❽ *Adequate treatment of mild or asymptomatic hypercalcemia may be achieved on an outpatient basis with nonpharmacologic measures. Moderate to severe or symptomatic hypercalcemia almost always requires pharmacologic intervention.*

Nonpharmacologic Therapy

Calciuric therapy in the form of hydration is a key component of the treatment of hypercalcemia, regardless of severity or presence of symptoms.[28] Mild or asymptomatic patients may be encouraged to increase oral fluid intake (3–4 L/day). Patients with moderate to severe or symptomatic hypercalcemia should receive normal saline at 200 to 500 mL/hour according to dehydration and cardiovascular status. Patients should be encouraged to ambulate as much as possible because immobility enhances

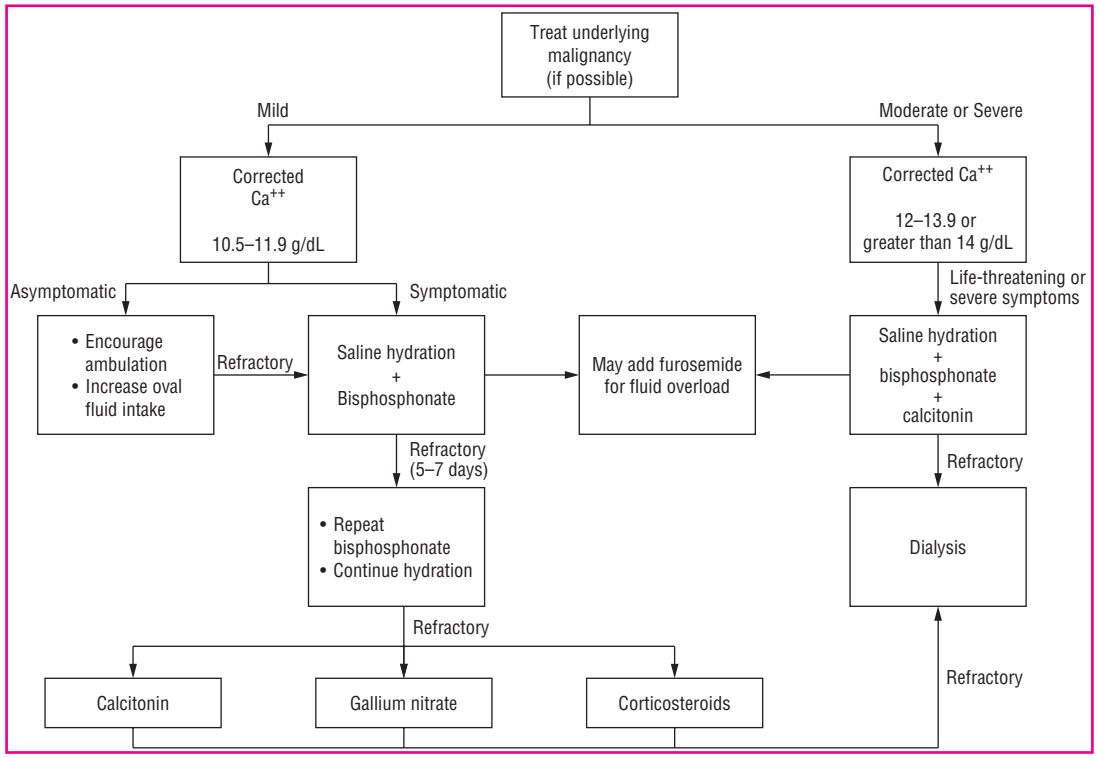


FIGURE 96–5.
Treatment algorithm for the hypercalcemia of malignancy.

bone resorption. Although calcium should be discontinued from parenteral feeding solutions, oral calcium supplementation minimally contributes to hypercalcemia unless it is mediated by vitamin D. In these cases, oral calcium should be discontinued. Finally, agents that may contribute to hypercalcemia (e.g., thiazide diuretics, vitamin D, and lithium) or decrease renal function (e.g., NSAIDs) should be discontinued. Dialysis may be used in refractory cases or in patients who cannot tolerate aggressive saline hydration.

Pharmacologic Therapy

Multiple pharmacologic interventions are available for the treatment of hypercalcemia (Table 96–10). Furosemide 20 to 40 mg/day may be added to hydration once rehydration has been achieved to avoid fluid overload and enhance renal excretion of calcium. Although effective in relieving symptoms, hydration and diuretics are temporary measures that are useful until the onset of antiresorptive therapy; thus hydration and antiresorptive therapy should be initiated simultaneously.

The antiresorptive therapy of choice for hypercalcemia of malignancy is a bisphosphonate. Because of poor oral bioavailability, only intravenous agents should be used. Pamidronate and zoledronic acid are used most commonly and are potent inhibitors of osteoclast activity.[29] The choice of bisphosphonate is a difficult one; zoledronic acid is more efficacious in terms of response rate and longer duration of normocalcemia but is approximately four times more expensive.[30] Regardless of selection, the bisphosphonates should be administered at diagnosis owing to their delayed onset of action.

Calcitonin is the drug of choice in cases of emergent hypercalcemia (e.g., in patients with life-threatening ECG changes, arrhythmias, or CNS effects) owing to its rapid onset of action. Calcitonin inhibits osteoclast activity and decreases renal tubular calcium resorption. Corticosteroids are useful in patients with steroid-responsive malignancies, such as lymphomas or multiple myeloma, and may delay **tachyphylaxis** to calcitonin. Gallium nitrate also was recently reapproved for treatment, although the 5-day administration regimen and risk of nephrotoxicity limit its use.

Outcome Evaluation

The long-term success of therapy for hypercalcemia is determined primarily by the success of treatment of the underlying malignancy. In the short term, monitor patients for relief of

TABLE 96–10. Treatment Options for Hypercalcemia of Malignancy

	Agent	Dosage	Onset	Duration	Reduction in Serum Calcium Concentration	Comments
Calciuric therapy	Intravenous normal saline	200–500 mL/hour	24–48 hours	2–3 days	0.5–2 mg/dL	Avoid fluid overload, monitor electrolytes.
	Furosemide	20–40 mg IV	4 hours	2–3 days	—	Monitor for hypokalemia, dehydration.
Antiresorptive therapy	Pamidronate	60–90 mg IV over 2–24 hours[a]	24–72 hours	3–4 weeks	Greater than 1 mg/dL	Nadir not seen until after 4–7 days; may cause fever, renal dysfunction; pamidronate less expensive.
	Zoledronic acid	4 mg IV over 15 minutes	24–48 hours	4+ weeks	Greater than 1 mg/dL	
	Corticosteroids	Prednisone (or equivalent) 50–100 mg daily	5–7 days	3–4 days	0.5–3 mg/dL	Monitor for hyperglycemia, insomnia, immunosuppression.
	Calcitonin	4–8 IU/kg SQ or IM q6–12 hours	2–4 hours	1–3 days	2–3 mg/dL	Salmon-derived formulation preferred; 1-unit test dose recommended; can be given in renal failure; may cause flushing, nausea.
	Gallium nitrate	100–200 mg/m^2 CIV daily for 5 days	24–48 hours	—	—	Do not administer if creatinine is greater than 2.5 mg/dL (221 µmol/L); may cause renal failure.

[a]60 mg of pamidronate may be used in smaller patients or in those patients with mild hypercalcemia or renal dysfunction. May use longer infusion time in patients with renal dysfunction.
IU, international units; IV, intravenously; SQ, subcutaneously; IM, intramuscularly; CIV, continuous intravenous infusion.
Data from refs. 26 and 28.



Patient Care and Monitoring

1. Determine the status of the patient's underlying malignancy. Has this patient been treated for his or her underlying malignancy? Has the patient received any prior therapy for hypercalcemia? Is calcium-lowering therapy still warranted?
2. Assess the patient's symptoms to determine the need for laboratory studies. Determine if absence of symptoms in the presence of mild hypercalcemia warrants conservative outpatient management.
3. Obtain a complete history of prescription, nonprescription, and natural drug products. Avoid or discontinue agents that increase calcium levels, impair excretion of calcium, or decrease renal function.
4. Determine the need for long-term maintenance therapy with monthly bisphosphonates. Is the patient beginning definitive therapy for a responsive malignancy?
5. Counsel the patient to avoid excessive oral calcium intake in vitamin D–mediated hypercalcemia.
6. Evaluate the patient for adverse drug reactions, allergies, and drug interactions when starting calcium-lowering therapy.

symptoms and restoration of fluid balance. Monitor the serum calcium level, serum albumin, serum blood urea nitrogen (BUN) and creatinine, and electrolytes daily during therapy. Assess the fluid balance by daily ins and outs, weights, and signs of fluid overload. Monitor the ECG in patients with cardiac manifestations until normalized. Repeat doses of bisphosphonate after 5 to 7 days if the patient does not become normocalcemic. Reassess patient status in terms of refractoriness to treatment to determine if treatment should be withheld.

Tumor Lysis Syndrome

Although not as common as hypercalcemia, tumor lysis syndrome may cause significant morbidity and mortality if adequate prophylaxis and treatment are not instituted. Tumor lysis syndrome is the result of rapid destruction of malignant cells with subsequent release of intracellular contents into the circulation.



Patient Encounter 3, Part 1

HT is a 55-year-old man with newly diagnosed acute myeloid leukemia. The patient is asymptomatic at this time. Laboratory results reveal the following significant findings:

- WBC count $39 \times 10^3/\mu L$ ($39 \times 10^9/L$)
- Serum potassium 4.9 mEq/L (4.9 mmol/L)
- Serum phosphorous 4.2 mg/dL (1.4 mmol/L)
- Serum calcium 7.6 mg/dL (1.9 mmol/L)
- Uric acid 9.1 mg/dL (541 µmol/L)

In addition, the patient has a serum creatinine of 1.6 mg/dL (141 µmol/L) and a BUN of 21 mg/dL (7.5 mmol/L). His LDH is normal.

- What risk factors does HT have for tumor lysis syndrome?
- Why is the serum uric acid elevated and renal function decreased?

Epidemiology and Etiology

The overall incidence of tumor lysis syndrome is unknown but has been linked to a number of risk factors[31] (Table 96–11). Tumor lysis syndrome typically occurs in malignancies with high tumor burdens or high proliferative rates. Thus children are affected most frequently because they frequently have aggressive malignancies. Tumor lysis syndrome typically is induced by cancer treatment modalities, including chemotherapy, hormonal therapy, radiation, biologic therapy, and corticosteroids, although some patients may present spontaneously before treatment.

TABLE 96–11. Risk Factors for Tumor Lysis Syndrome

Disease Related
High-risk
Acute lymphoblastic leukemia
High-grade non-Hodgkin's lymphoma (i.e. Burkitt's)
Intermediate risk
Chronic lymphocytic leukemia (especially bulky lymphadenopathy)
Acute myeloid leukemia (especially white blood cell count greater than $50/mm^3$)
Multiple myeloma
Low risk
Low- and intermediate-grade non-Hodgkin's lymphoma
Hodgkin's disease
Chronic myeloid leukemia (blast crisis)
Rare
Breast cancer
Small cell lung cancer
Testicular cancer
Patient Related
Decreased urinary output, dehydration, or renal failure
Preexisting hyperuricemia
Acidic urine
White blood cell count greater than $50 \times 10^3/\mu L$ ($50 \times 10^9/L$)
Lactate dehydrogenase (LDH) levels greater than 1500 IU/L (1500 U/L or 25 uKat/L)
High tumor sensitivity to treatment modalities

IU, international unit.
Data from refs. 31 and 32.



Clinical Presentation and Diagnosis

General

- Patients present primarily with lab abnormalities.
- Normal uric acid is equal to 2 to 8 mg/dL (119–476 µmol/L).
- Most often occurs within 12 to 72 hours of initiation of cytotoxic therapy.

Signs and Symptoms

- Most patients are asymptomatic.
- Patients may develop edema, fluid overload, and oliguria that may progress to anuria with acute renal failure.
- Some patients with hyperuricemia may have nausea, vomiting, and lethargy.
- Hyperkalemia leads to lethargy, muscle weakness, **paresthesia,** ECG changes, bradycardia
- Hypocalcemia leads to muscle cramps, **tetany**, irritability, paresthesias, arrhythmias

Laboratory Tests (Adults)

- Serum uric acid level greater than 8 mg/dL (476 µmol/L)
- Serum potassium greater than 6 mEq/L (6 mmol/L)
- Serum phosphorous greater than 4.5 mg/dL (1.45 mmol/L)
- Serum calcium less than 7 mg/dL (1.75 mmol/L)
- Elevated BUN and creatinine once renal dysfunction develops
- Or a change of greater than 25% from baseline in any of these lab values[32]

Pathophysiology

Patients with tumor lysis syndrome experience a wide range of metabolic abnormalities. The massive cell lysis that occurs leads to the release of intracellular electrolytes, resulting in hyperkalemia and hyperphosphatemia. High concentrations of phosphate bind to calcium, leading to hypocalcemia and calcium phosphate precipitation in the renal tubule. Purine nucleic acids are also released that are subsequently metabolized to uric acid through multiple enzyme-mediated steps (Fig. 96–6). Uric acid is poorly soluble at urinary acidic pH, leading to crystallization in the renal tubule. The precipitation of uric acid and calcium phosphate leads to metabolic acidosis, facilitating further uric acid crystallization. Acute renal failure may be the end result.

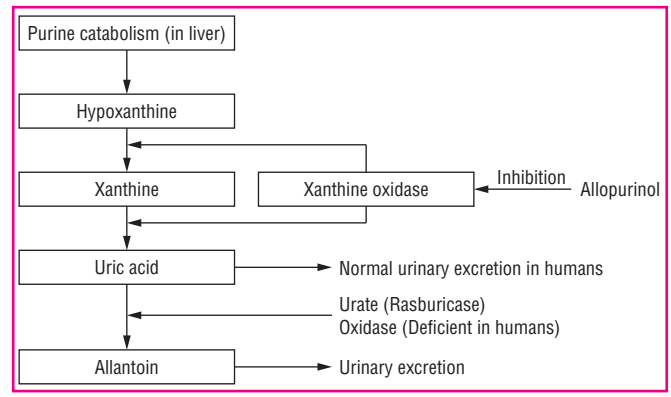


FIGURE 96–6. The role of allopurinol and rasburicase in the enzymatic degradation of purine nucleic acids.



Patient Encounter 3, Part 2

Chemotherapy with 7+3 (cytarabine for 7 days + idarubicin for 3 days) is ordered for HT. You also determine that HT is taking lisinopril 10 mg by mouth daily for hypertension.

- When should tumor lysis syndrome prophylaxis begin for HT?
- What strategies would you use for tumor lysis syndrome prophylaxis for HT?
- If tumor lysis syndrome develops, how would you modify your management approach?

Treatment

Desired Outcomes

❾ *The primary goals of management of tumor lysis syndrome are (1) prevention of renal failure and (2) prevention of electrolyte imbalances. Thus the best treatment for tumor lysis syndrome is prophylaxis to enable delivery of cytotoxic therapy for the underlying malignancy.* For patients who present with or develop tumor lysis syndrome despite prophylaxis, treatment goals include (1) decrease uric acid levels, (2) correct electrolyte imbalances, and (3) prevent compromised renal function. These goals should be achieved in a cost-effective manner.

General Approach to Treatment

Prevention of tumor lysis syndrome generally is achieved by increasing the urine output and preventing accumulation of uric acid. Prophylactic strategies should begin immediately on presentation, preferably 48 hours prior to cytotoxic therapy. Treatment modalities primarily increase uric acid solubility, address electrolyte disturbances, and support renal output.

Nonpharmacologic Therapy

Vigorous intravenous hydration with dextrose 5% in water with half-normal saline at 3 L/m^2 per day to maintain a urine output of 100 mL/m^2 per hour or more is necessary, unless the patient presents with acute renal dysfunction. Alkalinization of the urine to a pH of 7.0 or more with 50 to 100 mEq/L of sodium bicarbonate has been used to promote uric acid solubility for excretion. This measure is controversial because xanthine and hypoxanthine are less soluble at alkaline pH, potentially leading to crystallization, especially during and after allopurinol therapy[32] (see Fig. 96–6). Medications that increase serum

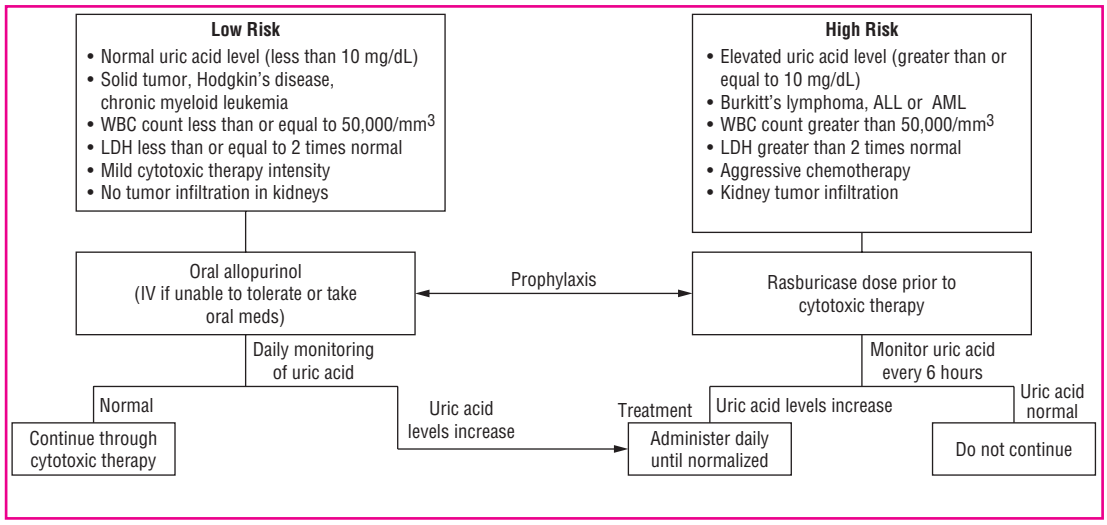


FIGURE 96–7. Prophylaxis and treatment of hyperuricemia associated with tumor lysis syndrome. ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; IV, intravenous. (Data from refs. 32 and 33.)

potassium (e.g., ACE inhibitors and spironolactone) or block tubular resorption of uric acid (e.g., probenecid and thiazides) should be discontinued. Nephrotoxic agents such as amphotericin B or aminoglycosides also should be avoided. Hemodialysis may be required in patients who develop anuria or uncontrolled hyperkalemia, hyperphosphatemia, hypocalcemia, acidosis, or volume overload.

Pharmacologic Therapy

Pharmacologic prevention strategies for tumor lysis syndrome are aimed at low- and high-risk patients (Fig. 96–7). Allopurinol is a xanthine oxidase inhibitor that is used for prevention only because it has no effect on preexisting elevated uric acid. Rasburicase is a recombinant form of urate oxidase that is useful for both prevention and treatment but is extremely expensive (Table 96–12). Although the approved dose is 0.2 mg/kg per day for 5 days, recent studies using abbreviated courses (1–3 days) and/or lower doses (0.05–0.1 mg/kg per day) may be equally efficacious with significantly reduced cost.[32] Since uric acid levels generally fall within 4 hours of the first dose, one dose may be administered with frequent, serial monitoring of the uric acid level for repeat dosing if necessary (see Fig. 96–7). Of note, rasburicase continues to break down uric acid in blood samples drawn from patients. This can be avoided by immediately placing the sample in an ice bath for processing to avoid falsely lowered uric acid levels.

Electrolyte disturbances that develop in patients with tumor lysis syndrome should be managed aggressively to avoid renal failure from hyperphosphatemia and hypocalcemia and cardiac signs from hyperkalemia. One exception pertains to the use of intravenous calcium for hypocalcemia. Adding calcium may cause further calcium phosphate precipitation in the presence of hyperphosphatemia and should be used cautiously.

TABLE 96–12. Comparison of Allopurinol and Rasburicase

Drug	Dosing	2005 AWP[a]	Comments
Oral allopurinol (Zyloprim®)	Adult: 600–800 mg/day in 2–3 divided doses Child: 10 mg/kg per day or 200–300 mg/m^2 per day	$0.48/day (generic)	Adjust dose for renal impairment. Avoid drug interactions (mercaptopurine). Monitor for skin rash.
Intravenous allopurinol (Aloprim®)	Adult: 200–400 mg/m^2 per day Child: 200 mg/m^2 per day	$625–$1250/day	As above. Reserve for patients who cannot tolerate or take oral medications. Maximum dose = 600 mg/day.
Rasburicase (Elitek®)	0.2 mg/kg per day for up to 5 days	$12,000/day	Lower doses and abbreviated schedules may be used to decrease cost (0.05–0.1 mg/kg per day). May rarely cause nausea and vomiting. Contraindicated in patients with G6PD deficiency lead to hemolytic anemia. Rare cases of hypersensitivity and antibody formation.

[a]Normalized for a 70-kg patient or body surface area of 1.73m^2; all costs are estimated and may vary.
G6PD, glucose-6-phosphate dehydrogenase, AWP, average wholesale price.
Data from ref. 34.



Patient Care and Monitoring

1. Assess patient risk factors prior to onset of treatment.
2. Discontinue or avoid medications that affect renal function or contribute to electrolyte abnormalities. Obtain a complete medication history.
3. Evaluate the patient for drug interactions, allergies, and adverse effects of allopurinol or rasburicase.

Outcome Evaluation

The most successful outcome in tumor lysis syndrome is prevention. Monitor the patient who presents with normal lab values every day for serum uric acid, electrolytes (i.e., Na, K, Ca, Mg, Cl, and PO_4), BUN, creatinine, and urine output. Monitor the patient for signs of fluid overload during aggressive hydration. Continue hydration and prophylaxis until 2 to 3 days after cytotoxic therapy. In patients undergoing urinary alkalinization with sodium bicarbonate, assess the urine pH every 6 hours and maintain above 7. For patients who present with or develop signs of tumor lysis syndrome, monitor these parameters every 6 hours until stable. Order an ECG for patients with hyperkalemia, and monitor serially until resolution. Adjust the dose of allopurinol and other renally eliminated medications for patients who develop renal dysfunction. In patients receiving rasburicase, monitor the hemoglobin and hematocrit for signs of hemolytic anemia.

MISCELLANEOUS

Chemotherapy Extravasation

Extravasation generally is defined as leakage of intravenous fluids into the interstitial tissue. It is one of the most feared complications of the administration of cytotoxic chemotherapy. While extravasation does not cause death, significant morbidity may result from local tissue destruction, and immediate management is necessary.

Epidemiology and Etiology

The incidence of chemotherapy extravasation generally is reported to be between 0.5% and 6% of all chemotherapy-related adverse events.[35] A number of risk factors have been identified for chemotherapy extravasation (Table 96–13).

TABLE 96–13. Risk Factors for Chemotherapy Extravasation

Presence of multiple venipunctures (common in cancer patients)
Poor needle insertion technique
Poor catheter location (dorsum of the hand, antecubital fossa)
Inability to communicate symptoms (children, sedated patients, language barrier between patient and nurse)
Presence of peripheral neuropathy
Nurse experience and training
Young age or elderly patients (small or fragile veins)
Gross obesity



Patient Encounter 4, Part 1

JM is a 32-year-old woman who was recently diagnosed with stage IIIB Hodgkin's disease. She comes to the clinic to receive her first dose of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy. She currently does not have a central access device; therefore, she will receive her chemotherapy via peripheral vein.

- Which chemotherapy agent(s) will JM receive is(are) considered to be vesicants? Irritants? Nonvesicants?
- What techniques and prevention strategies should be employed to decrease the risk of an extravasation?
- What symptoms or signs should you watch for during chemotherapy administration?

Chemotherapy agents generally are classified into three groups: vesicants, irritants, and nonvesicants[36] (Table 96–14). Either vesicants or irritants may cause local symptoms, but vesicants cause local tissue necrosis on extravasation, whereas irritants do not. The degree of tissue injury depends on the concentration and amount of fluid extravasated. It is important to note that some agents are well-known vesicants. For many agents, however, only isolated case reports of tissue necrosis exist. Therefore, it is imperative to use caution when administering any chemotherapeutic agent, especially new or investigational agents that have unknown vesicant properties.

TABLE 96–14. Chemotherapeutic Agents with Vesicant or Irritant Properties

Vesicants	Irritants
Common	
Anthracyclines	Camptothecins
Daunorubicin	Irinotecan
Doxorubicin	Topotecan
Epirubicin	Carmustine
Idarubicin	Cyclophosphamide
Dactinomycin	Dacarbazine
Mechlorethamine	Epipodophyllotoxins
Mitomycin C	Etoposide
Vinca alkaloids	Teniposide
Vincristine	Fluorouracil
Vinblastine	Gemcitabine
Vinorelbine	Ifosfamide
Rare[a]	Melphalan
Cisplatin	Pentostatin
Liposomal doxorubicin	Streptozocin
Mitoxantrone	
Oxaliplatin	
Taxanes	
Docetaxel	
Paclitaxel	

[a]Agents for which there are isolated case reports of local tissue necrosis.
Data from ref. 36.



Clinical Presentation and Diagnosis

General

- Anthracycline, mechlorethamine, and vinca alkaloid extravasations typically cause immediate pain.
- Patients may be asymptomatic at the time of extravasation but may return within days to weeks with signs of tissue damage (particularly with mitomycin C).
- Exposure to ultraviolet light may worsen some lesions.

Signs and Symptoms

- Local pain (burning, tingling, stinging), swelling, erythema, induration
- Lack of blood return
- Ulceration may not develop until after 1 to 2 weeks or longer.

Diagnostic Tests

Usually based on clinical history and presenting symptoms, but tissue biopsy may reveal definitive findings.

Pathophysiology

The mechanism of tissue injury is related to the pharmacodynamic characteristics of the extravasated drug. These agents may be classified into DNA-binding and non-DNA-binding. Examples of DNA-binding agents include the anthracyclines, mechlorethamine, and mitomycin C. These agents first cause cell death through interactions with DNA, then are released into the surrounding tissue, and are taken up by adjacent cells. This repeating cycle is perpetuated by the lipophilic nature of these drugs, resulting in chronic, slow-healing tissue injury owing to long tissue retention. Doxorubicin in particular may remain in tissues for weeks to months.[36]

Non-DNA-binding agents include the vinca alkaloids and etoposide. These agents tend to cause injury in the pattern of a thermal burn and are cleared more easily from interstitial spaces. Thus they are more readily neutralized and tend to have a better healing prognosis.

Prevention

⓾ *Chemotherapy extravasation may be avoided in many cases by the use of successful prevention strategies. The most important preventative measure is proper patient education.* Patients must be instructed to promptly report any local symptoms not only during administration but also days to weeks later. Another key factor is the exclusive use of highly trained personnel who are trained to administer chemotherapeutic drugs. The Oncology Nursing Society has developed guidelines for the administration of vesicant drugs, as summarized in Table 96–15.[37] Although placement of a central venous catheter is recommended, extravasations still may occur owing to dislodged or poorly placed needles or nicked catheters.

TABLE 96–15. Prevention Strategies for Chemotherapy Extravasation[37]

Central venous catheters should be placed for vesicant administration whenever possible, especially in high-risk patients.
Avoid the dorsum of the hand, antecubital fossa, and limbs with significant lymphedema.
Use uncovered plastic cannulas or a butterfly needle for peripheral administration.
Always test the line with intravenous fluids before chemotherapy administration, and observe the site for swelling.
Check for blood return prior to and frequently during administration.
If venipuncture is repeated, should be proximal to prior needle insertion site.
Vesicants given via peripheral vein should be given by intravenous push rather than by infusion to enable immediate cessation and withdrawal of fluids if extravasation occurs.

Treatment

Desired Outcome

Once extravasation occurs, the primary goals of treatment are (1) avoid further tissue damage by using appropriate nonpharmacologic and pharmacologic strategies and (2) promptly refer patients for surgery if required. Optimal pharmacologic and nonpharmacologic treatment of the extravasation will allow the cancer patient to continue with his or her chemotherapy (Table 96–16).

Nonpharmacologic Therapy

If extravasation occurs, the infusion should be stopped immediately, with aspiration of fluid from the site, needle, and tubing as much as possible. The affected limb or area should be elevated (if possible). The site should be documented photographically as well as the time, date, site, patient complaints, and estimated volume of extravasated drug.[36] Both hot and cold packs have been used to manage extravasations, but use of the proper therapy for certain agents is critical. For example, warm compresses have been shown to worsen doxorubicin extravasations, whereas cold packs may exacerbate vinca alkaloid



Patient Encounter 4, Part 2

Despite adequate precautions, midway through her doxorubicin administration, JM complains of intense burning around the catheter site, and the site appears to be swollen and erythematous.

- What nonpharmacologic management strategies should be employed immediately?
- What pharmacologic management strategy would you recommend to manage this potential extravasation?

TABLE 96–16. Management of Chemotherapy Extravasation

Drug	Application of Heating or Cooling	Pharmacologic Antidote	Dose	Comments
Anthracyclines	Cold packs	DMSO 50–99%	Apply 1–2 mL to area of skin twice the size of lesion every 6–8 hours for 7–14 days	Allow to air dry. Do not cover
		Alternative: Dexrazoxane	1000 mg/m^2 IV within 5 hours of extravasation followed by 1000 mg/m^2 on day 2,500 mg/m^2 day 3	Promising new agent; expensive, may not be reimbursed by payors.
Mitomycin C	Cold packs	DMSO 50–99%	As above	
Mechlorethamine	Cold packs	Sodium thiosulfate	Prepare 1/6 M solution by adding 4 mL of 10% solution to 6 mL sterile water; inject 2 mL for each mg of mechlorethamine. Follow with 1 mL SQ (0.1 mL doses clockwise around area); may repeat every 3–4 hours if needed.	Sodium thiosulfate must be diluted prior to administration.
Vinca alkaloids	Hot packs	Hyaluronidase	Inject 1–6 mL of 150 units/mL concentration (150–900 units) through IV line or SQ if removed; may repeat every 3–4 hours if needed	Dilute with normal saline.
Paclitaxel	Cold packs	Hyaluronidase	As above	Hot packs paradoxically shown to worsen lesions in some case reports.

DMSO, dimethylsulfoxide; SQ, subcutaneously; IV, intravenously.
Data from ref. 36.

lesions. Pressure should not be applied to the area because this may facilitate spread. Finally, patients should be referred to a plastic surgeon if pain persists or ulceration develops despite treatment.

Pharmacologic Therapy

Therapeutic modalities to treat extravasation events consist of specific antidotes to halt or decrease the severity of local tissue necrosis. It should be noted that only one-third of extravasation events will lead to local tissue necrosis, and most studies of antidotes are in animal models or isolated case reports. Antidotes either disperse or bind the chemotherapy agent and accelerate the removal of the agent from the tissues. Specific antidotes and their uses are presented in Table 96–16.

Dimethylsulfoxide (DMSO) is the antidote of choice for anthracycline and mitomycin C extravasations. It readily penetrates tissues and increases diffusion in the tissue area. In addition, DMSO is a free-radical scavenger that functions to block this principal mechanism of anthracycline- and mitomycin C–mediated tissue injury. DMSO generally is well tolerated but may cause some mild burning and redness. Dexrazoxane is a free-radical scavenger typically used for cardioprotection from anthracyclines. Promising results have been seen with large-volume extravasations and in a mouse model.[38]

Hyaluronidase is the antidote of choice for vinca alkaloid and high-concentration epipodophyllotoxin extravasations. Hyaluronidase breaks down hyaluronic acid, which functions as "tissue cement." This promotes absorption of the extravasated drug away from the local site. Hyaluronidase also may be used for paclitaxel extravasations, but there are conflicting reports regarding its efficacy.[39] Hyaluronidase should not be used with anthracycline extravasations because enhancement of local spread may occur.

The antidote of choice for mechlorethamine extravasations is sodium thiosulfate. This agent binds alkylating agents, resulting in neutralization to inactive compounds that are then excreted. Sodium thiosulfate also may be effective for high-concentration cisplatin or dacarbazine extravasations.

Outcome Evaluation

The primary outcome is the prevention of extravasation events using proper administration techniques. Instruct patients to promptly report any symptoms of extravasation. If extravasation occurs, select the proper antidote and thermal application for immediate administration. Promptly refer the patient for plastic surgery if pain persists or ulceration develops.



Patient Care and Monitoring

1. On diagnosis, determine the need for administration of chemotherapy with vesicant properties. Refer the patient for surgical placement of a central access device.
2. Ensure proper training and certification of all personnel in institutions who administer chemotherapeutic agents.
3. Educate the patient regarding signs and symptoms of extravasation and instruct to *immediately* relate to caregiver.
4. Educate the patient to report increasing pain promptly, spread of the lesion, or ulceration.
5. Educate the patient regarding proper application of hot or cold packs as well as topical antidotes. Should the area be allowed to air dry or be covered?
6. Evaluate the patient for allergies and adverse effects of pharmacologic antidotes.

ABBREVIATIONS

ACE: angiotensin converting enzyme inhibitor
AIDS: acquired immune deficiency syndrome
ANC: absolute neutrophil count
AWP: average wholesale price
BMT: bone marrow transplantation
BUN: blood urea nitrogen
CBC: complete blood count
CIV: continuous intravenous
CNS: central nervous system
CSF: colony-stimulating factor
CT scan: computed tomographic scan
DMSO: dimethylsulfoxide
DNA: deoxyribonucleic acid
ECG: electrocardiogram
FDA: Food and Drug Administration
G6PD: glucose-6-phosphate dehydrogenase
GCSF: granulocyte colony-stimulating factor
GI: gastrointestinal
GMCSF: granulocyte macrophage-colony stimulating factor
ICP: intracranial pressure
IM: intramuscular
IV: intravenous
LDH: lactate dehydrogenase
MRI: magnetic resonance imaging
NKDA: no known drug allergies
NSAID: nonsteroidal anti-inflammatory drug
NSCLC: non–small cell lung cancer
PCP: *Pneumocystis jiroveci* pneumonia (formerly *Pneumocystis carinii*)
PTHrP: parathyroid-related protein
RBC: red blood cell
SCLC: small cell lung cancer
SVCS: superior vena cava syndrome
SQ: subcutaneous
T_{max}: maximum temperature recorded in 24 hours
WBC: white blood cell

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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97 Parenteral Nutrition

Michael D. Kraft and Imad F. Btaiche



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. List appropriate indications for the use of parenteral nutrition (PN).
2. Describe the components of PN and their role in nutrition support.
3. Explain the pharmaceutical and compounding issues with PN.
4. Develop a PN prescription and a plan to initiate PN based on patient-specific factors.
5. Describe the etiology and risk factors for substrate intolerance, including hyperglycemia, hypoglycemia, hyperlipidemia, and azotemia, in patients receiving PN.
6. Describe the etiology and risk factors for the refeeding syndrome in patients receiving PN.
7. Describe the etiology and risk factors for liver complications and metabolic bone disease in patients receiving PN.
8. Design a plan to monitor, prevent, and treat PN–associated complications.
9. Design a plan to monitor and correct electrolyte, vitamin, and trace-element abnormalities in patients receiving PN.

Key Concepts

❶ Parenteral nutrition (PN), also called total parenteral nutrition (TPN), is the intravenous administration of fluids, macronutrients, electrolytes, vitamins, and trace elements for the purpose of weight maintenance or gain, to preserve or replete lean body mass and visceral proteins, and to support anabolism and nitrogen balance *when the oral/enteral route is not feasible or adequate.*

❷ Amino acids are provided to preserve or replete lean body mass and visceral proteins and to promote protein anabolism and wound healing.

❸ Dextrose (D-glucose) is the major immediate energy source in PN and is vital for cellular metabolism, body protein preservation, and cellular growth.

❹ Intravenous lipid emulsions are used as an energy source in PN and to prevent or treat essential fatty acid deficiency.

❺ PN should not be used to treat acute fluid abnormalities. Rather, PN should be adjusted to minimize worsening of underlying fluid disturbances.

❻ Electrolytes, vitamins, and trace elements are essential for numerous biochemical and metabolic functions and should be added to PN daily unless otherwise not indicated.

❼ PN can be administered via a small peripheral vein [as peripheral PN (PPN)] or via a larger central vein (as central PN).

❽ PN admixtures can be prepared by mixing all components into one bag [3-in-1 admixture or a total nutrient admixture (TNA)] or by mixing and infusing dextrose, amino acids, and all other components together and infusing intravenous lipid emulsion separately (2-and-1 admixture).

❾ PN is associated with significant complications with both short- and long-term therapy.

❿ Patients receiving PN should have specific laboratory values checked to assess electrolyte status, organ function, and nutritional status, and these parameters should be monitored as indicated clinically.

Maintaining adequate nutritional status, especially during periods of illness and metabolic stress, is an important part of patient care. Malnutrition in hospitalized patients is associated with significant complications, including increased infection risk, poor wound healing, prolonged hospital stay, and increased mortality, especially in surgical and critically ill patients.[1] *Specialized nutrition support* refers to the administration of nutrients via the oral, enteral, or parenteral route for therapeutic purposes.[1] ❶ *Parenteral nutrition (PN), also*

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called total parenteral nutrition (TPN), is the intravenous administration of fluids, macronutrients, electrolytes, vitamins, and trace elements for the purpose of weight maintenance or gain, to preserve or replete lean body mass and visceral proteins, and to support anabolism and nitrogen balance when the oral/enteral route is not feasible or adequate. PN is a potentially lifesaving therapy in patients with intestinal failure but also may be associated with significant complications.

DESIRED OUTCOMES AND GOALS

Specialized nutrition support is aimed at meeting nutritional needs, improving energy and protein balance, promoting growth or weight maintenance, and improving healing, particularly in malnourished patients. Goals of providing specialized nutrition support include:

- Weight maintenance (potentially weight gain in malnourished patients and growing children)
- Preservation (or repletion) of lean body mass and visceral proteins
- Support of anabolism and nitrogen balance
- Correction or avoidance of fluid and electrolyte abnormalities
- Correction or avoidance of vitamin and trace element abnormalities
- Avoidance of further nutritional deficiencies

INDICATIONS

Parenteral nutrition can be a lifesaving therapy in patients with intestinal failure, but the oral or enteral route is preferred when providing nutrition support ("when the gut works, use it"). Compared with PN, enteral nutrition generally is associated with fewer infectious complications (e.g., pneumonia, intraabdominal abscess, and catheter-related infections) and potentially improved outcomes.[1–3] However, if used in appropriate patients (i.e., patients with questionable intestinal function or when the intestine cannot be used), PN can be used safely and effectively and may improve nutrient delivery.[4] Indications for PN are listed in Table 97–1.[1]

TABLE 97–1. Indications for Parenteral Nutrition[1,a]

Bowel obstruction
Physical/mechanical (e.g., tumor compressing intestinal lumen)
Functional (e.g., postoperative ileus)
Major small bowel resection (e.g., short bowel syndrome)
Adult patients with less than 100 cm small bowel distal to the ligament of Treitz without a colon
Adult patients with less than 50 cm of small bowel if the colon is intact
Diffuse peritonitis
Gastrointestinal fistulas if enteral nutrition cannot be provided above or below the fistula
Pancreatitis—if patients have failed enteral nutrition beyond the ligament of Treitz or cannot receive enteral nutrition (e.g., due to obstruction)
Severe intractable vomiting
Severe intractable diarrhea
Preoperative nutrition support in patients with moderate to severe malnutrition who cannot tolerate enteral nutrition and in whom surgery can be delayed safely for at least 7 days

[a]When adequate oral or enteral nutrition is not possible for 5–10 days in patients with malnutrition or critical illness or for 7–14 days in most other cases.

PN COMPONENTS

PN should provide a *balanced* nutritional intake, including macronutrients, micronutrients, and fluid. Macronutrients, including amino acids, dextrose, and intravenous lipid emulsions, are important sources of structural and energy-yielding substrates. A balanced PN formulation includes 10% to 20% of total daily calories from amino acids, 50% to 60% of total daily calories from dextrose, and 20% to 30% of total daily calories from intravenous lipid emulsion. Micronutrients, including electrolytes, vitamins, and trace elements, are required to support essential biochemical reactions. Parenteral nutrition also provides a significant source of fluids. Patients require individual adjustments of PN components based on their nutritional requirements, underlying disease state(s), degree of metabolic stress, clinical status, and organ function.

Amino Acids

Amino acids are the building blocks of body proteins. There is no excess storage form of protein in the body, so amino acids are an essential component of the PN admixture. ❷ *Amino acids are provided to preserve or replete lean body mass and visceral proteins and to promote protein anabolism and wound healing.* Amino acids are a source of calories with a caloric value of 4 kcal/g.

Crystalline amino acid bulk solutions are supplied by various manufacturers in various concentrations (e.g., 3.5%, 5%, 7%, 8.5%, 10%, 15%, and 20%). Different formulations are tailored for specific age groups (e.g., adults and infants) and disease states (e.g., renal and liver disease). Specialized formulations for patients with renal failure contain higher proportions of essential amino acids. Formulas for patients with hepatic encephalopathy contain higher amounts of branched-chain and lower amounts of aromatic amino acids. However, these specialized formulations should not be used routinely in clinical practice because their efficacy has not been clearly demonstrated. Crystalline amino acid solutions have an acidic pH (pH ≈ 5–7) and may contain inherent electrolytes (e.g., sodium, potassium, acetate, and phosphate).

Dextrose

❸ *Dextrose (D-glucose) is the major immediate energy source, and it is vital for cellular metabolism, body protein*



Patient Encounter, Part 1

AA is 45-year-old woman admitted to the hospital with chief complaints of fever, abdominal pain, nausea, and vomiting for 2 days. She also reports decreased appetite and decreased oral intake for the past 3 to 4 days. The patient was discharged 2 weeks ago after having a small bowel resection for recurrent bowel obstruction.

MH
Recurrent intestinal **strictures,** intestinal obstructions, type II diabetes mellitus

SH
Small bowel resections (greater than 100 cm of small intestine remaining, colon intact)

FH and SH
Non-contributory

Meds prior to admission
Glipizide XL 5 mg orally daily

PE
Height 168 cm (5 ft, 6 in), weight 60 kg (132 lbs), temperature 38.9°C (102°F), heart rate 98 beats/minute, blood pressure 98/55 mm Hg, respiratory rate 30 breaths/minute, alert and oriented × 3, mucous membranes and skin appear cool and dry, **tachycardic, tachypneic,** lungs clear

Abd: slightly tense, diffuse abdominal pain

Diagnoses
Possible intestinal leak/perforation, diffuse peritonitis, **sepsis,** mild dehydration, and hypovolemic hypotonic hyponatremia

Plan
Admit to the surgical intensive-care unit for resuscitation and treatment.

- Would PN be indicated in this patient?
- What other patient data should be collected to help formulate a PN prescription?

preservation, and cellular growth. Several body tissues depend primarily on dextrose as an energy source, including the central nervous system, red blood cells, and the renal medulla.

Dextrose used in PN compounding typically is provided as a 70% stock solution (70 g/100 mL), although some institutions use a 50% stock solution. The final dextrose concentration in the PN solution typically should not exceed 35%. Hydrous dextrose provides 3.4 kcal/g (14.2 kJ/g). A dextrose infusion rate of 2 mg/kg per minute should be sufficient to suppress gluconeogenesis and prevent protein breakdown in adults.[5] Continuous dextrose infusion rate in adult patients generally should not exceed 4 to 5 mg/kg per minute in most hospitalized patients.[6,7]

Intravenous Lipid Emulsions

❹ *Intravenous lipid emulsions have two main clinical uses: prevent or treat essential fatty acid deficiency and provide an energy source.* Intravenous lipid emulsions currently marketed in the United States consist of long-chain triglycerides. Lipid particles consist of a triglyceride core surrounded by a layer of egg phospholipids (emulsifiers). These particles carry a negative charge on their surface that creates repulsive electrostatic forces between droplets and maintains the stability of the emulsion. Glycerol is added to the emulsion to adjust the tonicity, and water is the solvent. The stability of intravenous lipid emulsions can be affected by several factors. The negative charges on the surface of the lipid particles can be disrupted by cations, especially divalent cations such as calcium and magnesium or iron[8] which can exist in divalent or trivalent form, and possibly by pH changes, particularly acidic pH. Disruption of the negative charges can diminish the repulsive electrostatic forces and impair stability of the lipid emulsion. Lipid particles also can aggregate and form larger particles. **Creaming** of the emulsion occurs when these particles form and migrate to the surface of the emulsion but can be reversed with mild agitation. If these particles continue to aggregate, **coalescence** may occur and destabilize the emulsion. Once an emulsion has coalesced, it should not be infused into a patient because this can result in the formation of fat emboli. If coalescence continues, irreversible separation of the emulsion can occur (**oiling out** or breaking of the emulsion).

Intravenous lipid emulsions differ in their concentration (10%, 20%, and 30%), caloric density, natural source of lipids, and ratio of phospholipids to triglycerides (PL:TG). Table 97–2 shows a comparison of commercially available intravenous lipid emulsions in the United States. The 10%, 20%, and 30% lipid emulsions provide 1.1 kcal/mL (4.6 kJ/mL), 2 kcal/mL (8.4 kJ/mL), and 3 kcal/mL (12.6 kJ/mL) with a PL:TG of 0.12, 0.06 and 0.04 respectively. The lower PL:TG indicates a lower phospholipid content and translates to a better clearance of the 20% and 30% lipid emulsions compared with the 10% lipid emulsion.[9] The 30% lipid emulsion is only approved for infusion in a TNA and should not be infused directly into patients.

Intravenous lipid emulsion particles are hydrolyzed in the bloodstream by the enzyme **lipoprotein lipase** to release free fatty acids and glycerol. Free fatty acids then are be taken up into adipose tissue for storage (triglycerides), oxidized to energy in various tissues (e.g., skeletal muscle), or recycled in the liver to make lipoproteins.

The essential fatty acids in humans are linoleic acid (C-18:2 N-6) and α-linolenic acid (C18:3 N-3). Arachidonic acid (C20:4 N-6) is also essential but can be synthesized from linoleic acid. Administration of 2% to 4% of total daily calories as linoleic acid should be adequate to prevent **essential fatty acid deficiency** in adults (e.g., infusion of 500 mL of 20% intravenous lipid emulsion once weekly).[7] Biochemical evidence of essential fatty acid deficiency can develop in about 2 to 4 weeks in adult patients receiving lipid-free PN, and clinical manifestations generally appear after an additional

TABLE 97–2. Comparison of Intravenous Lipid Emulsions

Brand Names	Liposyn II®		Liposyn III®			Intralipid®		
Source	Soybean and safflower oil		Soybean oil			Soybean oil		
Concentration (%)	10%	20%	10%	20%	30%	10%	20%	30%
Linoleic acid (%)	65.8	65.8	54.5	54.5	54.4	50	50	50
Linolenic acid (%)	4.2	4.2	8.3	8.3	8.3	9	9	9
Phospholipids (egg yolk) (%)	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
PL:TG ratio[a]	0.12	0.06	0.12	0.06	0.04	0.12	0.06	0.04
Caloric density (kcal/mL)	1.1	2	1.1	2	3	1.1	2	3

[a]PL:TG ratio, phospholipid: triglyceride ratio.

1 to 2 weeks.[10] Symptoms may include hair loss, thinning of skin, and skin **desquamation.**

Intravenous lipid emulsions are also a source of calories. The typical daily dose in adults is approximately 0.5 to 1 g/kg per day. In the absence of hypertriglyceridemia, substituting a portion of dextrose calories with lipid calories may be beneficial in situations where dextrose infusion may lead to complications (e.g., hyperglycemia). Some examples include patients with diabetes mellitus or pancreatic disease and patients under severe stress (e.g., trauma or burns) who are at risk for hyperglycemia. The maximum of dose of lipid emulsions is 2.5 g/kg per day,[7] or 60% of total daily calories, although doses this high are used rarely in practice.

Complications and safety concerns related to the administration of intravenous lipid emulsions include severe hypertriglyceridemia, infection, **anaphylactic** reactions, and infusion-related reactions. Patients with hypertriglyceridemia, renal dysfunction, hepatic dysfunction, **pancreatitis,** and severe metabolic stress may have reduced lipid clearance and are at high risk of developing hypertriglyceridemia. Patients with hyperglycemia are also at risk of developing hypertriglyceridemia. In general, intravenous lipid emulsions should be withheld in adult patients with a serum triglyceride concentration of 400 mg/dL (4.52 mmol/L) or more and used cautiously in critically ill patients, especially those with sepsis.

Patients without malnutrition who receive PN may have a higher incidence of infectious complications than patients who do not receive PN.[11] However, conflicting data exist on the incidence of infectious complications in patients receiving PN with or without intravenous lipid emulsions. Intravenous lipid emulsions support the growth of common bacterial and fungal pathogens, but bacterial growth is slower in TNAs than in intravenous lipid emulsions alone.[12,13] This may be due to the acidic pH of amino acid solutions and osmolarity of PN formulations. Furthermore, a 0.22-micron bacterial retention filter cannot be used on the infusion line because the average size of lipid particles is approximately 0.5 micron. Therefore, strict aseptic techniques must be used when handling intravenous lipid emulsions to minimize the risk of PN contamination and possible infectious complications. The Centers for Disease Control and Prevention (CDC) recommends that infusion of intravenous lipid emulsions separately from PN be completed within 12 hours of initiation. Because TNAs support microbial growth at a slower rate than intravenous lipid emulsions, the CDC recommends that TNA infusion be completed within 24 hours of initiation.

Patients with allergy to eggs or legumes (e.g., soy beans, broad beans, and lentils) may have cross-sensitivity with intravenous lipid emulsions and are at risk for allergic reactions. Infusion-related adverse effects also may occur with rapid infusion of intravenous lipid emulsions, including fever, chills, headache, palpitations, dyspnea, chest tightness, and nausea. Although these reactions are rare, patients should be monitored for adverse events related to lipid infusion. Extending the infusion time (e.g., 12–24 hours) can minimize infusion-related adverse events and improves lipid clearance. If a 24-hour lipid infusion is used separately from PN, then two lipid containers should be used, with each container infused over 12 hours.

Fluid

❺ *PN generally should not be used to treat acute fluid abnormalities. Rather, PN should be adjusted to minimize worsening of underlying fluid disturbances, taking into account other fluids the patient is receiving.* Daily maintenance fluid requirements for adults can be estimated with the following equation:

$$\text{Total daily maintenance fluid requirements} = 1500\ \text{mL} + \{20\ \text{mL/kg} \times [\text{wt (kg)} - 20]\}^{*}$$

For patients with fluid deficits, it is safer and more cost-effective to correct fluid abnormalities using standard intravenous fluids (e.g., sodium chloride 0.9% in water, dextrose 5% in water, and lactated Ringer's solution). Minimizing fluid volume in PN may be indicated in patients with fluid overload, such as critically ill patients who receive large-volume resuscitation fluids, patients with oliguric (urine output less than 400 mL/day) or anuric (urine output less than 50 mL/day) renal failure, and those with congestive heart failure. It is reasonable to

*For elderly patients (e.g., greater than 60 years old), use 15 mL/kg for every kilogram above 20 kg.

provide total daily fluid requirements (both maintenance needs and abnormal/extrarenal losses) in the PN admixture in patients who depend on long-term PN. However, caution should be exercised when the PN solution is diluted to an extent that may alter the stability and compatibility of a concentrated solution. Diluting a PN admixture may affect the physical and chemical properties of the admixture (e.g., the pH, which could affect lipid emulsion stability and calcium-phosphate compatibility); therefore, stability and compatibility data should be confirmed first.

Electrolytes

❻ *Electrolytes are involved in many metabolic and homeostatic functions, including enzymatic and biochemical reactions, maintenance of cell membrane structure and function, neurotransmission, hormone function, muscle contraction, cardiovascular function, bone composition, and fluid homeostasis.* The causes of electrolyte abnormalities in patients receiving PN may be multifactorial, including altered absorption and distribution; excessive or inadequate intake; altered hormonal, neurologic, and homeostatic mechanisms; altered excretion via gastrointestinal and renal losses; changes in fluid status and fluid shifts; and medications.

Electrolytes that are included routinely in PN admixtures include sodium, potassium, phosphorus (as phosphate), calcium, magnesium, chloride, and acetate. When determining electrolytes in PN admixtures, the patient's renal function always must be taken into account. Typical daily electrolyte maintenance requirements for adults with normal renal function are listed in Table 97–3.

Sodium

Sodium is the most abundant extracellular cation in the body and is the major osmotically active ion in the extracellular fluid. Sodium concentration determines the distribution of water in the extracellular space, and sodium disorders can be caused by many factors. Patients with abnormal gastrointestinal losses (e.g., gastric, **ostomy,** and **fistula** losses) have increased sodium requirements. Patients with fluid overload and hypervolemic hypotonic hyponatremia may require sodium and fluid restriction. Sodium in PN can be provided in the forms of chloride, acetate, and phosphate salts. One millimole (mmol) of sodium phosphate provides 1.33 mEq of elemental sodium. Total sodium concentration in PN should not exceed 154 mmol/L (the equivalent of normal saline). PN is not used to treat sodium disturbances but rather to minimize worsening of any underlying disorders.

Potassium

Potassium is the second most abundant cation in the body and is found primarily in the intracellular fluid. Potassium has many important physiologic functions, including regulation of cell membrane electrical action potential (especially in the myocardium), muscular function, cellular metabolism, and glycogen and protein synthesis. Potassium in PN can be provided as chloride, acetate, and phosphate salts. One millimole of potassium phosphate provides 1.47 mEq of elemental potassium. Generally, the concentration of potassium in peripheral PN (PPN) admixtures should not exceed 80 mEq/L (80 mmol/L). While it is safer to also stick to the 80 mEq/L (80 mmol/L) limit for administration through a central vein, the maximum recommended potassium concentration for infusion via a central vein is 150 mEq/L (150 mmol/L).[14] Patients with abnormal potassium losses (e.g., loop or thiazide diuretic therapy) may have higher requirements, and patients with renal failure may require potassium restriction.

Phosphorus and Calcium

Phosphorus and calcium are essential electrolytes involved in many physiologic processes and biochemical reactions.

TABLE 97–3. Approximate Daily Maintenance Electrolyte Requirements for Adults[7]

Electrolyte	Approximate Daily Maintenance Requirements	Electrolyte Salts Used in PN
Sodium	1–2 mEq/kg	Chloride, acetate, phosphate
Potassium	1–2 mEq/kg	Chloride, acetate, phosphate
Phosphorus	20–40 mmol	Sodium phosphate, potassium phosphate
Calcium	10–15 mEq	Gluconate
Magnesium	8–20 mEq	Sulfate
Chloride	[a]	Sodium, potassium
Acetate	[a]	Sodium, potassium
Conversions	1 mmol potassium phosphate = 1.47 mEq potassium 1 mmol sodium phosphate = 1.33 mEq sodium	

[a]As needed to maintain acid-base balance; linked to amounts of sodium and potassium provided (as chloride and acetate salts).

Phosphorus is provided as sodium or potassium phosphate in PN. Approximately 10 to 15 mmol of phosphate are needed per 1000 kilocalories to maintain normal serum phosphorus concentrations (provided the patient is well nourished and has normal renal function).[15] Patients with renal insufficiency may require phosphorus restriction.

The Food and Drug Administration (FDA) published a safety alert in 1994 in response to two deaths associated with calcium-phosphate precipitation in PN.[16] Autopsy reports from these patients revealed diffuse **microvascular pulmonary emboli** containing calcium-phosphate precipitates. Because calcium and phosphate can bind and precipitate in solution, caution must be exercised when mixing these two electrolytes in PN admixtures. Several factors can affect calcium-phosphate solubility, including

- *pH.* Largely affected by the final amino acid concentration, to a lesser extent by the dextrose concentration (unless the final amino acid concentration is very low); the lower the solution pH, the less chance there is for precipitation; monobasic phosphates predominate at low pH, leaving fewer free dibasic phosphates for precipitation with divalent calcium; monobasic calcium phosphate is more soluble than dibasic calcium phosphate.
- *Amino acid concentration.* Primary factor that affects pH of the PN admixture; the higher the concentration of amino acids, the higher is the amount of calcium and phosphate that can remain in solution (phosphate likely binds with amino acids and less is available to bind with calcium), therefore lowering the risk of calcium-phosphate precipitation.
- *Calcium salt.* Calcium gluconate is the preferred salt in PN because it is has a low dissociation in solution with lesser free calcium available at a given time to bind phosphate (as opposed to calcium chloride, which dissociates rapidly in solution).
- *Time.* More calcium and phosphate will dissociate over time, increasing the risk for calcium-phosphate precipitation.
- *Temperature.* As temperature increases, more calcium and phosphate dissociate and increase the risk of calcium-phosphate precipitation.
- *Order of mixing.* Calcium and phosphate should be separated when mixing PN admixtures (e.g., add phosphate first, then all other PN components, and then add calcium last); if calcium is added before all other components are in the bag, including lipid emulsion, then the volume in the bag at the time calcium is added must be used to determine the maximum calcium that can be added.

Magnesium

Magnesium is the second most abundant intracellular cation. Magnesium serves as an essential cofactor for numerous enzymes and in many biochemical reactions, including reactions involving adenosine triphosphate (ATP).[17] Magnesium disorders can be multifactorial and can be related to renal function, disease state, and medication therapy. Magnesium in PN typically is provided as magnesium sulfate (1 g magnesium sulfate = 8.1 mEq of elemental magnesium).

Chloride and Acetate

Concentration limits for chloride and acetate in PN typically are linked to limitations for sodium and potassium. The usual ratio of chloride:acetate in PN is about 1:1 to 1.5:1. Chloride and acetate primarily play a role in acid-base balance. Acetate is converted to bicarbonate at a 1:1 molar ratio. This conversion appears to occur mostly outside the liver. Bicarbonate *never* should be added to or coinfused with PN solutions. This can lead to the release of carbon dioxide and potentially result in the formation of calcium or magnesium carbonate (very insoluble salts).

Vitamins

❻ *The water-soluble and fat-soluble vitamins in the parenteral multivitamin mix are essential cofactors for numerous biochemical reactions and metabolic processes. Parenteral multivitamins are added daily to the PN.* Patients with chronic renal failure are at risk for vitamin A accumulation and potential toxicity. Serum vitamin A concentrations should be measured in patients with renal failure when vitamin A accumulation is a concern. Previously, vitamin K was administered either daily or once weekly because intravenous multivitamin formulations did not contain vitamin K. However, manufacturers have reformulated their parenteral multivitamin products to provide 150 mcg of vitamin K in accordance with FDA recommendations. There is a parenteral multivitamin formulation available without vitamin K (e.g., for patients who require warfarin therapy), but standard compounding of PN formulations should include a parenteral multivitamin that contains vitamin K unless otherwise clinically indicated.

Trace Elements

❻ *Trace elements are essential cofactors for numerous biochemical processes. Trace elements that are added routinely to PN include zinc, selenium, copper, manganese, and chromium.* There are various commercial parenteral trace element formulations that can be added to PN admixtures (e.g., MTE-5®). Zinc is important for wound healing, and patients with high-output fistulas, diarrhea, burns, and large open wounds may require additional zinc supplementation. Patients may lose as much as 12 to 17 mg zinc per liter of gastrointestinal (GI) output (e.g., from diarrhea or enterocutaneous fistula losses); however, others have demonstrated that 12 mg/day may be adequate to maintain these patients in positive zinc balance.[18] Patients with chronic diarrhea, malabsorption, and short-gut syndrome may have increased selenium losses and may require additional selenium supplementation. Patients with severe **cholestasis** should have copper and manganese

restricted to avoid their accumulation and toxicity because both elements undergo biliary elimination. Chromium is an important cofactor for glucose metabolism, and patients with chromium deficiency may exhibit glucose intolerance; however, this is a rare cause of hyperglycemia. Monitor trace-element concentrations regularly, deficiency or toxicity especially in patients at risk for.

PN Additives

Heparin

Heparin (0.5–1 unit/mL) may be added to PN admixtures for three reasons:

- To maintain catheter patency
- To reduce **thrombophlebitis**
- To enhance lipid particle clearance by acting as a cofactor for the lipoprotein lipase enzyme

The benefit and necessity of adding heparin to PN are unclear. There are also concerns about the stability/compatibility of intravenous lipid emulsions with heparin added at concentrations above 1 unit/mL. Heparin should be omitted in patients with active bleeding, **thrombocytopenia,** heparin-induced thrombocytopenia (HIT), or heparin allergy.

Regular Insulin

Regular insulin may be added to PN admixtures for glycemic control. The dose of insulin depends on the severity of hyperglycemia and daily insulin requirements. Generally, once the patient is receiving PN at goal, about 70% of the total insulin administered over the previous 24 hours as sliding scale (or continuous infusion) can be added to the next PN admixture. The insulin dose should be adjusted based on frequent capillary blood glucose evaluation. Caution should be used when insulin is added to PN to avoid hypoglycemia. Adding insulin to PN rather than administering as a continuous intravenous infusion does not provide the flexibility of frequent titration of the insulin dose to the desired target blood glucose concentration. As such, severe uncontrolled hyperglycemia is best treated with a continuous insulin infusion.

Histamine-2-Receptor Antagonists

Intravenous histamine-2-receptor antagonists such as ranitidine, famotidine, and cimetidine are compatible with PN and can be added to the daily PN for prevention of stress-related mucosal damage and peptic ulcer disease. This provides a continuous acid suppression and reduces nursing time by avoiding intermittent scheduled infusions.

Human Albumin

Human albumin is a colloid used as a plasma volume expander and is *not* a source of nutrition. Albumin should be administered separately from PN because it may be incompatible and may increase microbial growth and infectious risk when mixed in the PN admixture.

Iron Dextran

Iron-deficiency anemia in chronic PN patients may be due to underlying clinical conditions and the lack of iron supplementation in PN. Parenteral iron therapy becomes necessary in iron-deficient patients who cannot absorb or tolerate oral iron. Parenteral iron should be used with caution owing to infusion-related adverse effects. A test dose of 25 mg of iron dextran should be administered first, and the patient should be monitored for adverse effects for at least 60 minutes. Intravenous iron dextran then may be added to lipid-free PN at a daily dose of 100 mg until the total iron dose is given. Iron dextran is not compatible with intravenous lipid emulsions at therapeutic doses and can cause oiling out of the emulsion. Other parenteral iron formulations (e.g., iron sucrose and ferric gluconate) have not been evaluated for compounding in PN and should not be added to PN formulations.

NUTRITION ASSESSMENT AND NUTRITIONAL REQUIREMENTS

The first step before delivering specialized nutrition support is to perform a nutritional assessment and determine nutrient requirements based on the patient's nutritional status and clinical conditions. Collect subjective and objective data to determine a patient's level of nutrition, to identify patients with malnutrition or at risk for malnutrition, and to identify risk factors that may put a patient at risk for nutrition-related problems.[1] A nutrition assessment should include:[1,19]

- Patient history
- Physical assessment including height, weight, ideal body weight (IBW), and recent weight loss (intentional or unintentional)
- Physical examination of the musculoskeletal system (e.g., biceps, triceps, quadriceps, temporalis, deltoid, and interosseus muscles) for loss of muscle mass, and examination of the skin and mucous membranes for abnormalities (e.g., noting dry or flaky skin, bruising, edema, ascites, poorly healing wounds) and loss of subcutaneous fat
- Changes in eating habits and/or changes in GI function
- Presence and severity of underlying disease(s)
- Serum proteins (i.e., albumin concentration) because hypoalbuminemia at baseline or prior to hospitalization may be indicative of malnutrition and associated with poor outcome

There are several approaches and methods to conducting a nutrition assessment, but one approach that has been validated is the Subjective Global Assessment (SGA).[1] Application of the SGA requires gathering the data just listed and assessing these parameters (i.e., weight change, change in diet, GI symptoms, functional capacity, and physical examination)

TABLE 97–4. Estimating Daily Nutritional Requirements in Adults[1,7,19]

Determining Energy Expenditure	
Harris-Benedict equations[a]	Men: BEE = 66.42 + 13.75 (W) + 5 (H) – 6.78 (A) Women: BEE = 655.1 + 9.65 (W) + 1.85 (H) – 4.68 (A) W = weight in kg, H = height in cm, A = age in years Energy expenditure then should be multiplied by a stress factor to estimate the total energy expenditure (TEE): Bed rest ≈ 1.2 × BEE Ambulatory ≈ 1.3 × BEE Anabolic ≈ 1.5 × BEE Energy requirements should also be increased ~ 12% with each degree of fever above 37°C (98.6°F).
Energy expenditure per body weight (i.e., kcal/kg)[a]	Range of ~ 20–35 kcal/kg per day Maintenance ~ 20–25 kcal/kg per day Repletion/postoperative wound healing/critical illness/sepsis/ ~ 25–30 kcal/kg per day Anabolic//trauma/burns ~ 30–35 kcal/kg per day

Determining Protein Requirements

Patient Clinical Condition	Daily Protein Requirements[b]
Maintenance/non-stressed	0.8–1 g/kg
Repletion	1.3–1.5 g/kg
Trauma, sepsis, critical illness	1.5–2 g/kg
Burns	1.5–2.5 g/kg
Hepatic failure with encephalopathy	0.5–1 g/kg
Renal failure predialysis	0.6–0.8 g/kg
Renal failure receiving intermittent hemodialysis (IHD)	1.1–1.3 g/kg
Renal failure receiving continuous ambulatory peritoneal dialysis (CAPD)	1.2–1.3 g/kg
Renal failure receiving continuous renal replacement therapy (CRRT)	1.5–2.5 g/kg

[a]Use AdjBW in significantly obese patients.
[b]Protein requirements based on ideal body weight (IBW); use AdjBW in obese patients.

and then assigning a subjective rating (A = well nourished; B = moderately malnourished or suspected of being malnourished; C = severely malnourished).[19]

After performing a nutrition assessment, estimate the patient's daily caloric and protein needs (Table 97–4). Indirect calorimetry involves measuring oxygen consumption and carbon dioxide production to determine the daily energy expenditure (EE). This is a valuable method to determine energy requirements, but it is technically very difficult, requires expensive equipment and trained personnel to use, and therefore is not feasible in all institutions. Over 200 separate equations have been developed to determine EE for adults, but the Harris-Benedict equations are some of the most widely used. These equations take into account a patient's sex, weight, height, and age to determine basal EE (BEE), and then a "stress factor" can be applied to estimate the daily total EE (TEE). Alternatively, EE can be estimated based on EE per body weight (i.e., kilocalories per kilogram). However, dry weight or admission weight should be used, and this estimation may not be appropriate in patients who are obese or in elderly patients. There is debate over the best method to use for patients who are obese (e.g., over 130% of IBW), but it is reasonable to use an adjusted body weight (AdjBW) in order to avoid overfeeding:

$$\text{AdjBW} = \text{IBW} + [0.25 \times (\text{actual weight} - \text{IBW})]$$

Protein requirements must be based on the patient's nutrition assessment and appropriate amounts provided (based on IBW or AdjBW for obese patients) to facilitate anabolism and wound healing, and avoid adverse effects (e.g., azotemia and uremia).

PREPARING THE PN PRESCRIPTION: ADMINISTRATION, COMPOUNDING, AND PHARMACEUTICAL ISSUES

After performing a nutrition assessment and estimating nutritional requirements, determine the optimal route to provide specialized nutrition support (e.g., oral, enteral, or parenteral). If PN is deemed necessary, venous access (i.e., peripheral or central; see below) for PN infusion must be obtained. Finally, formulate a PN prescription, and administer PN according to proper safety guidelines.

Route of PN Administration: Peripheral Versus Central Vein Infusion

❼ *PN can be administered via a smaller peripheral vein (e.g., cephalic or basilic vein) or via a larger central vein (e.g., superior vena cava).* Peripheral PN (PPN) is infused via a peripheral vein and generally is reserved for short-term administration (up to 7 days) when central venous access is not available. PN formulations are hypertonic, and infusion via a peripheral vein can cause thrombophlebitis. Factors that increase the risk of **phlebitis** include high solution osmolarity, extreme pH, rapid infusion rate, vein properties, catheter material, and infusion time via the same vein.[20] The osmolarity of PPN admixtures should be limited to 900 mOsm/L or less to minimize the risk of phlebitis. The approximate osmolarity of a PN admixture can be calculated from the osmolarities of individual components:

- Amino acids = 10 mOsm/g (or 100 mOsm/1% final concentration in PN)
- Dextrose = 5 mOsm/g (or 50 mOsm/1% final concentration in PN)
- Sodium (chloride, acetate, and phosphate) = 2 mOsm/mEq
- Potassium (chloride, acetate, and phosphate) = 2 mOsm/mEq
- Calcium gluconate = 1.4 mOsm/mEq
- Magnesium sulfate = 1 mOsm/mEq

PPN admixtures should be coinfused with intravenous lipid emulsion when using the 2-and-1 PN because this may decrease the risk of phlebitis. Infectious and mechanical complications may be lower with PPN compared with central venous PN administration. However, because of the risk of phlebitis and osmolarity limit, PPN admixtures have low macronutrient concentrations and therefore require large fluid volumes to meet a patient's nutritional requirements. Given these limitations, every effort should be made to obtain central venous access and initiate central PN when it is unlikely a patient will tolerate enteral or oral nutrition within 5 to 7 days.

Central PN refers to the administration of PN via a large central vein, and the catheter tip must be positioned in the vena cava. Central PN allows the infusion of a highly concentrated, hypertonic nutrient admixture. The typical osmolarity of a central PN admixture is about 1500 to 2000 mOsm/L. Central veins have much higher blood flow, and the PN admixture is diluted rapidly on infusion, so phlebitis is usually not a concern. Patients who require PN administration for longer periods of time (greater than 7 days) should receive central PN. One limitation of central PN is the need for placement of a central venous catheter and an x-ray to confirm placement of the catheter tip. Central venous catheter placement may be associated with complications, including **pneumothorax,** arterial injury, **air embolus,** venous thrombosis, infection, **chylothorax,** and **brachial plexus** injury.[1,20]

Type of PN Formulation: 3-in-1 versus 2-and-1

❽ *PN admixtures can be prepared by mixing all components into one bag, or instead, intravenous lipid emulsion may be infused separately (via a Y-site infusion or through a separate intravenous catheter). When all components are mixed together, this is referred to as a 3-in-1 admixture or a total nutrient admixture (TNA).*[21] *When dextrose, amino acids, and all other components are mixed together without intravenous lipid emulsion, this is referred to as a 2-and-1 admixture.* With a 2-and-1 PN, intravenous lipid emulsion can be infused separately on a daily or intermittent basis. Once lipid emulsion is added, the TNA becomes an emulsion. There are various advantages and disadvantages to using either 3-in-1 or 2-and-1 PN (Table 97–5).

A primary concern when administering PN is safety. The FDA published a safety alert in 1994 in response to two deaths associated with TNA infusion.[16] Autopsy reports from these patients revealed diffuse microvascular pulmonary emboli containing calcium-phosphate precipitates. The FDA provided

TABLE 97–5. Advantages and Disadvantages of Using 3-in-1 (TNA) or 2-and-1 PN Admixtures

	3-in-1 (TNA)	2-and-1
Advantages	Simplified regimen for patient Increased patient compliance at home Decreased labor Decreased costs Decreased risk of contamination (due to less manipulation) Minimize infusion-related reactions from intravenous lipid emulsions Decreased vein irritation (especially with PPN)	Improved stability compared to TNA Increased number of compatible medications Decreased bacterial growth compared to TNA Easier visual inspection Can use 0.22-micron bacterial retention filter Cost savings if unused (i.e. not spiked) intravenous lipid emulsion can be reused
Disadvantages	Decreased stability compared to 2-in-1 PN Cannot use 0.22-micron bacterial retention filter Increased bacterial growth compared to 2-in-1 PN Visual inspection is difficult Limited compatibility with medications	Increased labor and costs (if intravenous lipid emulsion infused separately) Increased vein irritation, especially if PPN is not coinfused with intravenous lipid emulsion

PPN, peripheral parenteral nutrition; TNA, total nutrient admixture.

recommendations for safe infusion of PN admixtures containing calcium and phosphate:

- A 0.22-micron air-eliminating filter should be used for infusion of non-lipid-containing PN.
- A 1.2-micron in-line filter should be used for the infusion of 3-in-1 PN (i.e., a TNA) because it can remove large and unstable lipid droplets as well as particulate matter.[22]

Another concern is the coinfusion of intravenous medications with PN admixtures. Many intravenous medications have limited compatibility with 3-in-1 formulations but may be coinfused with a 2-and-1 formulation.[23,24] Some medications can be coinfused at the Y-site, few medications can be mixed directly into the PN solution or coinfused with intravenous lipid emulsion, and some cannot be mixed or coinfused with the PN admixture.[23,24] Always consult compatibility data before adding a medication to a PN admixture or coinfusing with PN. Medications that are compatible should be added to PN only if it is reasonable and safe (i.e., based on toxicity profile, pharmacokinetic/pharmacodynamic considerations).

Formulating a PN Admixture and Regimen

After completing a full nutrition assessment (e.g., SGA),[1,19] estimating the patient's daily fluid, calorie, and protein requirements (Table 97–4), and determining if PN is indicated (Table 97–1), develop a PN prescription.



Patient Encounter, Part 2

AA was diagnosed with an intestinal leak at the previous surgical site, diffuse peritonitis, sepsis, mild dehydration, and hypovolemic hypotonic hyponatremia.

Laboratory data

Na =130 mEq/L (130 mmol/L), K = 3.4 mEq/L (3.4 mmol/L), Cl = 104 mEq/L (104 mmol/L), HCO_3 = 21 mEq/L (21 mmol/L), BUN = 14 mg/dL (5 mmol/L), serum creatinine = 0.6 mg/dL (53 µmol/L), blood glucose = 177 mg/dL (9.8 mmol/L), Ca = 3.96 mEq/L (1.98 mmol/L), ionized Ca = 2.34 mEq/L (1.17 mmol/L), Mg = 1.72 mEq/L (0.86 mmol/L), phosphorus = 2.1 mg/dL (0.68 mmol/L), WBC count = 14,400/mm^3 (14×10^9/L), hemoglobin = 11.2 mg/dL (112 g/L or 6.9 mmol/L), hematocrit = 42% (0.42), and platelets = 164,000/mm^3 (164×10^9/L)

AA was taken to the operating room for an **exploratory laparotomy,** repair of the intestinal leak, and small bowel resection. Postoperatively, a nasogastric (NG) tube was placed and drained 800 to 1000 mL/day on postoperative days 1 and 2. The surgeons placed a central venous catheter and wanted to start the patient on central PN given her diagnoses of diffuse peritonitis, intestinal leak, evidence of poor intestinal function (given high NG tube output), and history of recurrent bowel obstructions. Refer to Table 97–6 for recommendations on formulating a goal PN prescription for AA.



Patient Encounter, Part 3

The surgical team plans to initiate the PN prescription you recommended for AA. How should this PN admixture be initiated and titrated to goal?

Day 1: Start at approximately 50% of the goal (i.e., initiate at 40 mL/hour or 960 mL/day) with a maximum of 2 mg/kg per minute of dextrose.

Initiating PN

Exercise caution when initiating PN to avoid hyperglycemia and fluid and electrolyte abnormalities. Once the goal daily volume is determined, infuse the PN admixture over 24 hours. For safety, initiate PN at a lower infusion rate (e.g., ~50% of goal for 24 hours) on day 1 with no more than 150 to 200 g of dextrose per day. Then titrate PN up to goal infusion rate, provided that glycemic control is maintained and the patient does not experience any significant fluid or electrolyte abnormalities. Monitor electrolytes daily and correct as needed, and monitor severely malnourished patients for refeeding syndrome (see "Complications of PN").

Cycling PN

PN should be administered over 24 hours in most hospitalized patients to minimize glucose, fluid, and electrolyte abnormalities. However, administering PN via an intermittent infusion, or *cycling PN*, may be advantageous in certain patients and situations. Cycling PN typically involves administering the same goal PN volume usually over 12 hours rather than over 24 hours. Taper PN to the goal cycle over 2 to 4 days (e.g., 24 hours, then 18 hours the next day, then 14 hours the next day, and then 12 hours the next day). Titrate the PN infusion rate up over 1 to 2 hours to goal rate and then taper down over 1 to 2 hours at the end of the cycle to avoid reactive hypoglycemia. Most home infusion pumps can be programmed to cycle a given PN volume automatically over a given time. However, the pharmacist may have to develop an appropriate PN cycle if the infusion pump cannot be programmed (e.g., in the inpatient setting or in long-term care facilities).

Cyclic PN has the following advantages:

- It helps to limit PN-associated liver cholestasis by avoiding continuous compulsive nutrient overload on the liver.[25]
- It improves the quality of life of patients receiving home PN by allowing the patient time off of PN to engage in normal daily activities.

TABLE 97–6. Patient Encounter, Part 2, Developing a Goal PN Prescription

PN Component	Formulation and Considerations
Fluid	Adjust PN to provide minimal amount of fluid, then take into consideration other fluid sources (e.g., other IV fluids) and adjust to meet daily maintenance fluid needs Safer and more cost-effective to adjust IV fluids rather than PN 1500 mL + (20 mL/kg × 40 kg) = 1500 mL + 800 mL = 2300 mL/day
Goal calorie and protein requirements	Perform a subjective global assessment Take into consideration the patient's current clinical status, diagnoses, medications, etc. Total daily calories ~25–30 kcal/kg per day, or ~1500–1800 kcal/day Protein ~1.5–2 g/kg per day of ideal body weight (~89–118 g protein/day) This patient has sepsis, diffuse peritonitis, and recent surgical procedures, target ~1800 kcal/day and ~110 g protein/day
Intravenous lipid emulsion	Typical intravenous lipid emulsion should provide ~20–30% of total daily calories Can be an alternative source of calories in patients with diabetes or hyperglycemia—consider increasing calories from intravenous lipid emulsion in these patients (e.g., 30% of total daily calories) Total daily goal calories ≈ 1800 kcal/day 1800 kcal/day × 0.3 = 540 kcal/day 540 kcal/day to be provided from intravenous lipid emulsion $\frac{540 \text{ kcal/day}}{2 \text{ kcal/mL}}$ ~ 270 mL of 20% intravenous lipid emulsion/day (11.25 mL/hour × 24 hours, so round to 11 mL/hour) 11 mL/hour × 24 hours = 264 mL/day of 20% intravenous lipid emulsion = 528 kcal/day
Amino acids	Amino acids: goal of ~110 g/day 440 kcal/day (should provide ~10–20% of total daily calories) If using a 10% stock amino acid solution: $110 \text{ g} \times \frac{100 \text{ mL}}{10 \text{g}} = 1100 \text{ mL}$ of 10% stock solution
Dextrose	Dextrose infusion rate should be ~3–4 mg/kg per minute, should comprise ~50–60% of total daily calories Since this patient has type 2 diabetes mellitus, consider a goal of ~3 mg/kg per minute Provide remainder of total daily calories as dextrose: Total daily goal calories ≈ 1800 kcal/day 1800 kcal/day –528 kcal/day (from intravenous lipid emulsion) 1272 kcal/day –440 kcal/day (from amino acids) 832 kcal/day to make up with dextrose. $\frac{832 \text{ kcal/day}}{3.4 \text{ kcal/g}} \approx 245$ g dextrose/day If using a 70% stock dextrose solution: $245 \text{ g} \times \frac{100 \text{ mL}}{70 \text{ g}} = 350 \text{ mL}$ 245 g/day × 3.4 kcal/g ≈ 833 kcal/day As a double-check, convert to mg/kg/minute: 245 g dextrose/day × 1000 mg/1 g × 1 day/1440 minute = 170.1 mg/minute $\frac{170.1 \text{ mg/minute}}{60 \text{ kg}} \approx 2.8$ mg/kg per minute
Final goal PN formulation (if using a 3-in-1 preparation)	Fluid: 264 mL from lipid emulsion, 1100 mL from amino acids, 350 mL from dextrose; assume approximately 100 mL for electrolytes, multivitamin, trace elements, and any additives Total fluid = 264 mL + 1100 mL + 350 mL + 100 mL = 1814 mL/day, or ~ 76 mL/hour Dextrose = 245 g/day (833 kcal/day); or 135 g/L (13.5% final concentration) Amino acids = 110 g/day (440 kcal/day); or 60 g/L (6% final concentration) 20% intravenous lipid emulsion = 264 mL/day (528 kcal/day); or 2.9% final concentration ~ 1801 kcal/day and 110 g amino acids/day ~ 30 kcal/kg/day; ~1.83 g amino acids/kg per day
Electrolytes	Daily doses based on daily maintenance requirements, renal function, gastrointestinal losses, acid-base status, concomitant drug therapy, nutritional and anabolic status Patient has hyponatremia, hypokalemia, hypomagnesemia, and hypophosphatemia, also has low serum bicarbonate concentration, could be component of metabolic acidosis due to sepsis

(*Continued*)

TABLE 97–6. Patient Encounter, Part 2, Developing a Goal PN Prescription (*Continued*)

PN Component	Formulation and Considerations
Electrolytes (*continued*)	Sodium chloride/acetate ≈ 275 mEq/day initially (or ~154 mEq/L, given that the patient has hypovolemic hypotonic hyponatremia, likely from vomiting and gastric/NG tube losses); may require adjustment as hyponatremia corrects (e.g., change to ~70–80 mEq/L) Potassium chloride/acetate ≈ 90 mEq/day initially (~1.5 mEq/kg/day given the patient has hypokalemia and normal renal function); may require adjustment after serum potassium corrects Assess arterial blood gas measurement (if available) and determine appropriate amounts of chloride and acetate (i.e., consider increasing acetate amount if found with metabolic acidosis) Sodium phosphate ≈ 35–40 mmol/day initially (given the patient has hypophosphatemia and normal renal function); may require adjustment after serum phosphorus corrects Calcium gluconate ≈ 10 mEq/day initially Magnesium sulfate ≈ 10–15 mEq/day initially
Vitamins	Provide standard parenteral multivitamin (containing water- and fat-soluble vitamins) in PN daily; assess for any possible deficiencies, otherwise no indication for additional supplemental vitamins
Trace elements	Provide standard parenteral trace element preparation (containing zinc, copper, manganese, chromium, and selenium) daily in PN Assess patient for any possible adjustments needed (e.g., delete copper and manganese from PN if the patient has evidence of severe cholestasis, supplemental zinc and selenium for any GI or fistula losses) or potential deficiencies
Additives	Consider other medications the patient may be receiving Consider adding histamine-2-receptor antagonist to PN if indicated Consider adding regular insulin to PN if the patient continues to exhibit hyperglycemia and requires exogenous insulin for blood glucose control

Concerns with cycling PN include hyperglycemia with high infusion rates, reactive hypoglycemia, and fluid and electrolyte abnormalities. Reactive hypoglycemia can be minimized by tapering down PN over 1 to 2 hours before disconnecting. Typically, the nadir will occur around 30 to 60 minutes or even a little over an hour after the PN is stopped. Random capillary blood glucose concentrations should be checked 4 hours into the PN cycle (~2 hours after reaching goal rate), 15 to 60 minutes after PN stops, and intermittently during the PN cycle as needed for glycemic control.

Transition to Oral or Enteral Nutrition

The goal is to transition the patient to enteral or oral nutrition and taper off PN as soon as feasible clinically. When initiating enteral or oral nutrition, monitor the patient for glucose, fluid, and electrolyte abnormalities. Perform calorie counts to determine the adequacy of nutrition via the oral or enteral route. When the patient is tolerating more than 50% of total estimated daily calorie and protein requirements via the oral or enteral route, wean PN by about 50%. PN can be stopped once the patient is tolerating more than 75% of total estimated daily calorie and protein requirements via the oral or enteral route, assuming that intestinal absorption is maintained.

AMERICAN SOCIETY FOR PARENTERAL AND ENTERAL NUTRITION SAFE PRACTICES OF PN

Because serious and sometimes fatal adverse events have occurred with inappropriate use of PN, the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) has published an updated safe practice guidelines for PN.[7] These practice guidelines provide a tool and reference for health professionals for the safe and efficacious use of PN. The guidelines represent the standards of practice as they relate to PN prescribing, compounding, stability, compatibility, labeling, administration, and quality assurance. Although application of these guidelines is voluntary, pharmacists who handle PN should review these guidelines and apply them as they fit in light of the circumstances of their practice sites and individual patient conditions.

COMPLICATIONS OF PN

❾ *PN therapy is associated with significant complications, both with short- and long-term therapy. Many complications are related to overfeeding (Table 97–7). Metabolic complications include hyperglycemia, hypoglycemia, hyperlipidemia,* ***hypercapnia,*** *electrolyte disturbances, refeeding syndrome, and acid-base*

TABLE 97–7. Consequences of Overfeeding

Source of Overfeeding	Consequences
Dextrose	Hyperglycemia, hypertriglyceridemia, hepatic steatosis, hypercapnia; hyperglycemia may cause fluid and electrolyte disturbances and increased infection risk
Intravenous lipid emulsions	Hypertriglyceridemia, hyperlipidemia, hepatic steatosis
Amino acids	Azotemia
Total calories	Hepatic steatosis, cholestasis, hypercapnia

disturbances. Long-term metabolic complications include liver toxicity, vitamin abnormalities, trace element abnormalities, and metabolic bone disease. Other complications include infectious and mechanical complications that relate to venous catheters.

Hyperglycemia

Hyperglycemia is one of the most common complications associated with PN therapy. The rate of dextrose oxidation may be reduced in patients with stress and hypermetabolism (e.g., surgery, organ failure, and sepsis), patients with diabetes or acute pancreatitis, and patients receiving certain medications (e.g., corticosteroids, **vasopressors,** octreotide, and tacrolimus).[26,27] Uncontrolled hyperglycemia can lead to fluid and electrolyte disturbances, **hyperglycemic hyperosmolar nonketotic syndrome,** hypertriglyceridemia, and increased risk of infection.[28]

Hyperglycemia in critically ill patients may be more a reflection of illness severity than from dextrose infusions, provided that the patient is not being overfed.[29] Critical illness is associated with increased endogenous glucose production (due to increased glycogenolysis and gluconeogenesis) and insulin resistance. Therefore, critically ill patients have lower tolerance for dextrose infusion compared nonstressed patients. In patients with hyperglycemia, it is reasonable to initiate PN with a continuous dextrose infusion rate of approximately 2 mg/kg per minute until glycemic control is achieved and then advance to goal.[5] Dextrose infusion rate typically ranges between approximately 3 and 4 mg/kg per minute but should not exceed 5 mg/kg per minute in the adult stressed patient.[1,6] Adjusted body weight should be used in obese patients rather than actual weight. A portion of calories can be provided with intravenous lipid emulsion rather than dextrose to help decrease hyperglycemia, provided that the patient does not have hypertriglyceridemia or sepsis. Overfeeding (with dextrose and with total calories) always must be avoided.

Hyperglycemia can impair cellular and humoral host defenses and can lead to the development of nosocomial and wound infections.[28] Historically, hyperglycemia has been defined as blood glucose concentrations of more than 200 to 220 mg/dL (11.1–12.21 mmol/L), and concentrations of 150 to 200 mg/dL (8.3–11.1 mmol/L) were considered "acceptable" in critically ill patients. More recent data suggest that tighter glucose control (e.g., 80–110 mg/dL or 4.4–6.1 mmol/L) with intensive insulin therapy may improve patient outcomes and reduce mortality.[30] It also appears that the benefits observed are due to glycemic control rather than to the dose of insulin.[31] Achieving a goal serum glucose concentration of 80 to 110 g/dL (4.4–6.1 mmol/L) may be a challenge while avoiding hypoglycemia. The exact goal range for optimal glucose control and reduction in hyperglycemia-associated complications is still debated, but an upper threshold for serum glucose concentration of 145 mg/dL (8.0 mmol/L) has been suggested as acceptable.[32] The use of regular insulin as a continuous infusion rather than adding insulin to PN may reduce the risk of prolonged hypoglycemia because the insulin drip can be readily titrated as insulin requirements change.

Hypoglycemia

Hypoglycemia can occur in patients when PN is interrupted suddenly (reactive hypoglycemia), especially when patients are treated with insulin or as a result of insulin overdosing in PN.[1] It is essential to prevent hypoglycemia and, if it occurs, to identify and treat it promptly. Reactive hypoglycemia typically is rare and usually can be avoided by tapering PN over 1 to 2 hours before discontinuation rather than abruptly stopping the infusion (especially if the patient is receiving insulin in PN or if the patient is not receiving oral or enteral nutrition). Reactive hypoglycemia generally occurs within 15 to 60 minutes after stopping PN (especially in neonatal patients), although it can occur later than this after discontinuing PN.[1] Capillary blood glucose concentrations should be monitored about 15–60 minutes after stopping PN infusion in order to detect any potential hypoglycemia. If PN is interrupted abruptly (e.g., due to lost intravenous access), infusing dextrose 10% in water at the same rate as PN should prevent hypoglycemia. In patients with poor venous access, reduce the PN infusion rate to half for 1 hour before discontinuing. Another alternative to prevent reactive hypoglycemia is to provide a glucose source via the oral route (by mouth or sublingually) when feasible. Monitor capillary blood glucose concentrations regularly in patients receiving insulin in PN, and adjust insulin doses accordingly.

Hyperlipidemia

Patients receiving intravenous lipid emulsion may be at risk for hyperlipidemia and hypertriglyceridemia. Hyperglycemia can lead to hypertriglyceridemia and is the most common cause of hypertriglyceridemia in patients receiving PN. Hyperlipidemia in patients receiving PN may lead to a reduction in pulmonary gas diffusion and pulmonary vascular resistance (especially in patients with underlying pulmonary and vascular disease).[33] Severe hypertriglyceridemia (especially when serum triglyceride concentrations exceed 1000 mg/dL or 11.3 mmol/L) can precipitate acute pancreatitis.[34] Hypertriglyceridemia may develop as a result of increased fatty acid synthesis due to hyperglycemia or impaired lipid clearance or in patients with history of hyperlipidemia, obesity, diabetes, alcoholism, renal failure, liver failure, multiorgan failure, sepsis, pancreatitis, or as a result of medications (e.g., propofol, corticosteroids, cyclosporine, and sirolimus).[35] Propofol is formulated in a 10% lipid emulsion (which is not cleared as effectively as the 20% or 30% lipid emulsions) and may lead to hypertriglyceridemia. It also has been proposed that propofol could have direct effects on lipid metabolism, given that hypertriglyceridemia associated with propofol infusion has been observed with lipid doses that are lower than those typically given in PN.[35,36]

A higher PL:TG ratio in the 10% lipid emulsion has been proposed to cause the appearance of the abnormal lipoprotein X particles [rich in phospholipids (~60%) and cholesterol (~25%), small amounts of triglycerides] in the blood.[9,35] Lipoprotein X

may compete with lipid particles for metabolism by lipoprotein lipase. Therefore, intravenous lipid emulsions with a lower PL:TG ratio (i.e., 20% or 30% lipid emulsions) have improved clearance compared with emulsions with a higher PL:TG ratio (i.e., 10% lipid emulsion)[9,35] and should be used, especially in patients with hypertriglyceridemia. Lipid clearance may be improved by newer formulations of mixed medium- and long-chain triglycerides; however, these products are not yet approved for use in the United States.

Monitor serum triglyceride concentrations regularly during PN therapy (e.g., at the initiation of PN, then once or twice per week initially, and thereafter depending on clinical condition). If a patient develops hypertriglyceridemia, identify and correct the underlying cause(s) if possible (e.g., treatment of hyperglycemia or reduction of dextrose and/or lipid dose). Prolonging the infusion of intravenous lipid emulsion (e.g., over 24 hours) may improve clearance; however, this may require hanging two containers daily because each container of lipid emulsion should infuse for only 12 hours based on USP Chapter 797 and infection-control policies and practices. If a patient is receiving propofol, take into account the calories administered from the 10% lipid emulsion in propofol (1.1 kcal/mL or 4.6 kJ/mL). For safety reasons, intravenous lipid emulsion should be withheld in patients receiving propofol. It also should be held when the serum is lipemic or when serum triglyceride concentrations are greater than 400 mg/dL (4.5 mmol/L). When this occurs, restart intravenous lipid emulsions when the serum triglyceride concentration is approximately 200 to 400 mg/dL (2.3–4.5 mmol/L) (or less), and administer only two to three times per week to prevent essential fatty acid deficiency.

Hypercapnia

Hypercapnia (abnormally high concentration of carbon dioxide in the blood) can develop as a result of overfeeding with both dextrose and total calories.[1,37] Excess carbon dioxide production and retention can lead to acute respiratory acidosis. The excess carbon dioxide also will stimulate compensatory mechanisms, resulting in an increase in respiratory rate in order to eliminate the excess carbon dioxide via the lungs. This increase in respiratory workload can cause respiratory insufficiency that may require mechanical ventilation. Reducing total calorie and dextrose intake would result in resolution of hypercapnia if due to overfeeding.

Acid-Base Disturbances

Acid-base disturbances associated with PN usually are related to the patient's underlying condition(s). However, acid-base abnormalities may develop as a result of changes in chloride or acetate concentrations in PN admixtures. Because acetate is converted to bicarbonate in the body, excessive acetate salts in PN can lead to metabolic alkalosis; excessive chloride salts in PN can lead to metabolic acidosis. PN should not be used to treat or correct the underlying disorder. However, adjusting chloride or acetate salts in the PN admixture may help to prevent these acid-base disorders or minimize worsening of any underlying acid-base disorders.

Liver Complications

The incidence of liver complications associated with PN ranges from approximately 7% to 84%, and end-stage liver disease develops in as many as 15% to 40% of adult patients on long-term PN.[35] Patients often develop a mild increase in liver enzymes within 1 to 2 weeks of initiating PN, but this generally resolves when PN is discontinued. Severe liver complications include hepatic steatosis (fat deposition in liver), **steatohepatitis** (a severe form of liver disease characterized by hepatic inflammation that may progress rapidly to liver fibrosis and cirrhosis), cholestasis, and **cholelithiasis.**[35]

Hepatic steatosis usually is a result of excessive administration of carbohydrates and/or lipids, but deficiencies of carnitine, choline, and essential fatty acids also may contribute. Hepatic steatosis can be minimized or reversed by avoiding overfeeding, especially from dextrose and lipids.[35,38] Carnitine is an important amine that transports long-chain triglycerides into the mitochondria for oxidation, but carnitine deficiency in adults is extremely rare and is mostly a problem in premature infants and patients receiving chronic dialysis. Choline is an essential amine required for synthesis of cell membrane components such as phospholipids. Although a true choline deficiency is rare, preliminary studies of choline supplementation to adult patients' PN caused reversal of steatosis.

Cholestasis is a common problem in patients who are dependent on PN. Factors that predispose PN patients to cholestasis include overfeeding, lack of bowel stimulation, bowel rest (decrease in cholecystokinin secretion), long duration of PN, short bowel syndrome, bacterial overgrowth and translocation, and sepsis.[35] Patients may exhibit increased liver transaminases, increase alkaline phosphatase and gamma-glutamyl transferase concentrations, and mainly increased bilirubin concentrations with jaundice. The most sensitive marker of cholestasis is an increased serum conjugated bilirubin concentration of 2 mg/dL (greater than 34.2 μmol/L) or more.[35] Cholestasis generally is reversible if PN is discontinued before permanent liver damage occurs. Serum liver enzyme concentrations may take up to 3 months to return to normal after discontinuing PN. Steps to prevent cholestasis associated with PN include early initiation of enteral or oral feedings (even at a low or "trophic" rate), using a balanced PN formulation, avoiding overfeeding, cyclic PN infusion, and treating and avoiding sepsis.[35] Pharmacologic treatments include ursodeoxycholic acid (ursodiol), which may improve bile flow and reduce the signs and symptoms of cholestasis. However, ursodiol is only available in an oral dosage form, and absorption may be limited in patients with intestinal resections. If other measures are not successful, and bacterial

overgrowth is thought to be contributing to cholestasis, courses of oral metronidazole, oral gentamicin, or oral neomycin have been used to reduce bacterial overgrowth.

Cholelithiasis can develop as a result of decreased gallbladder contractility, especially in the absence of enteral or oral intake. Lack of intestinal stimulation reduces secretion of cholecystokinin, a peptide hormone secreted in the duodenum that induces gallbladder contractility. The best prevention of cholelithiasis is early initiation of enteral or oral feeding, as stated earlier (to stimulate secretion of cholecystokinin, gallbladder contraction and emptying, and intestinal motility).

Monitor liver function tests, including serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, conjugated bilirubin, unconjugated bilirubin, and gamma-glutamyl transferase at the initiation of PN therapy and regularly thereafter during PN therapy. The frequency of monitoring liver function tests depends on the presence or absence of liver disease. This varies from one to two times weekly in the acute setting to once weekly to once monthly in the stable home PN patient.

Manganese Toxicity

Manganese is a trace element that serves as a coenzyme in multiple biochemical reactions. Manganese usually is supplied in PN admixtures as part of the trace element package in an adult dose of 0.5 mg/day; however, this may be excessive for longer-term PN patients. Manganese accumulation can occur in patients with cholestasis, and the most common toxicity is neurotoxicity, but liver toxicity also may occur.[35] Neurologic symptoms associated with manganese toxicity include headache, somnolence, weakness, confusion, tremor, muscle rigidity, altered gait, and masklike face (a Parkinson's-like syndrome).[35] Conversely, some patients with hypermanganesemia may not exhibit symptoms of toxicity. Periodic measurement of blood manganese concentrations in patients on long-term PN is recommended. Patients with cholestasis receiving PN may require restriction of manganese to prevent accumulation.

Metabolic Bone Disease

Metabolic bone disease is a condition of bone demineralization leading to **osteomalacia, osteopenia,** or **osteoporosis** in patients receiving long-term PN. Metabolic bone disease, to some degree, may occur in as many as 40% to 100% of patients receiving long-term PN.[35] Often patients are asymptomatic, although symptoms can include bone pain, back pain, and fractures. Patients often will have increased serum alkaline phosphatase concentrations, low to normal parathyroid hormone (PTH) concentrations, normal 25-hydroxyvitamin D, low 1,25 dihydroxyvitamin D concentrations, hypercalcemia or hypocalcemia, and hypercalcuria.[39] Because patients may be asymptomatic, diagnosis can be incidental. Radiologic techniques commonly used in diagnosing bone disease include quantitative computed tomography (CT) and bone mineral density.[39]

Factors that can predispose patients to developing metabolic bone disease include deficiencies of phosphorus, calcium, and vitamin D; vitamin D and/or aluminum toxicity; amino acids and hypertonic dextrose infusions; chronic metabolic acidosis; corticosteroid therapy; and lack of mobility.[35,39] Calcium deficiency (due to decreased intake or increased urinary excretion) is one of the major causes of metabolic bone disease in patients receiving PN. Provide adequate calcium and phosphate with PN to improve bone mineralization and help to prevent metabolic bone disease. Administration of amino acids and chronic metabolic acidosis also appear to play an important role. Provide adequate amounts of acetate in PN admixtures to maintain acid-base balance.

Vitamin D toxicity has been suggested as a cause of metabolic bone disease. However, vitamin D deficiency results in bone loss, and data on vitamin D excess and metabolic bone disease remain controversial.

Aluminum toxicity appears to play a role in the development of metabolic bone disease in patients on long-term PN, possibly by impairing calcium bone fixation,[40] inhibiting the conversion of 25-hydroxyvitamin D to the active 1,25-dihydroxyvitamin D, and/or reducing PTH secretion.[35,41] Measure serum aluminum concentrations in PN patients with suspected metabolic bone disease to rule out aluminum toxicity. The FDA has been investigating the issue of aluminum contamination in parenteral products and issued a rule specifying acceptable aluminum concentrations in large-volume parenterals in 2000.[42] The rule further stated that the package insert ("Precautions") for large-volume parenterals used in making PN should indicate that the product contains no more than 25 mcg/L of aluminum and defined a safe upper limit for parenteral aluminum intake at less than 4 to 5 mcg/kg per day. This has required a great amount of effort by manufacturers to meet these limits and requires pharmacy policies for monitoring aluminum concentrations in PN admixtures.

Encourage patients on long-term PN to engage in regular low-intensity exercise. Yearly bone density measurements also should be performed on patients on long-term PN and when metabolic bone disease is suspected.

Refeeding Syndrome

Refeeding syndrome describes the metabolic derangements that occur during nutritional repletion of patients who are starved, underweight, or severely malnourished.[43] Hypophosphatemia and associated complications are the classic signs and symptoms, but refeeding syndrome encompasses a constellation of fluid and electrolyte abnormalities affecting multiple organ systems, including neurologic, cardiac, hematologic, neuromuscular, and pulmonary function. The most severe cases of refeeding syndrome have resulted in cardiac failure, seizures, coma, and death.[43–45] The reintroduction of carbohydrates/glucose drives metabolism back to using glucose as the predominant fuel source. This increases insulin secretion, creates a high demand for

the production of phosphorylated intermediates of glycolysis [e.g., ATP, and **2,3-diphosphoglycerate** (2,3-DPG)], inhibits fat metabolism, and causes an intracellular shift of phosphorus, potassium, and magnesium. These changes, in combination with preexisting low total body stores of phosphorus, potassium, and magnesium and enhanced cellular uptake of phosphorus during anabolic refeeding, result in hypophosphatemia, hypokalemia, and hypomagnesemia. Vitamin deficiencies (e.g., thiamine) also may exist or be precipitated during refeeding. High carbohydrate intake increases the demand for thiamine, an essential cofactor involved in carbohydrate metabolism. This can precipitate thiamine deficiency with its potential complications, including lactic acidosis and neurologic abnormalities,[43,46] as well as myocardial dysfunction and congestive heart failure. Other metabolic alterations that may occur include expansion of the extracellular water compartment, fluid imbalance, and fluid intolerance.

The primary goal is preventing refeeding syndrome when initiating PN in high-risk patients (e.g., patients with prolonged lack of adequate nutritional intake, significant weight loss, or moderate-severe malnutrition). When initiating nutrition support, the rule of thumb to prevent refeeding syndrome is to "start low and go slow." Initiate PN cautiously (e.g., approximately 25% of estimated nutritional needs on day 1), and gradually increase to goal over 3 to 5 days. Correct electrolyte abnormalities (e.g., hypophosphatemia, hypokalemia, and hypomagnesemia) before initiating PN, and provide supplemental phosphate, potassium, and magnesium in or outside of PN (if the patient has normal renal function). Well-nourished patients require 10 to 15 mmol of phosphate per 1000 kcal to avoid hypophosphatemia,[15] but patients with moderate to severe malnutrition who are at risk for refeeding syndrome will require more aggressive supplementation. Doses of intravenous phosphate as aggressive as 0.64 to 1 mmol/kg have been used to treat severe hypophosphatemia (provided the patient has normal renal function).[47,48] Vitamin supplementation also should be provided in addition to the multivitamin provided in PN. Provide supplemental oral or intravenous thiamine 100 mg/day and folic acid 1 mg/day for about a week. In addition, minimize fluid and sodium intake during the first few days of PN (e.g., total fluid of 1000 mL/day or less and sodium of 20 mEq/day or less).[49] Assess patients for fluid balance, signs of edema, fluid overload, and weight gain because any gain of more than 1 kg per week likely represents fluid retention.[49] Monitor patients closely for signs and symptoms of refeeding syndrome. Monitor vital signs (i.e., heart rate, blood pressure, and respiratory rate), mental status, and neurologic and neuromuscular function routinely during the first several days of PN until goal is reached. Monitor pulse oximetry and any electrocardiographic changes when indicated clinically.

Infectious Complications

Patients receiving central PN are at increased risk of developing infectious complications caused by bacterial and fungal pathogens.[1,50] Infections may be related to placement of a central venous catheter, contamination of a central venous catheter or intravenous site (catheter-related infection), and persistent hyperglycemia. Strict aseptic techniques must be used when placing the catheter, along with continuous care of the catheter and infusion site. Catheter-related bloodstream infections are a common complication in long-term PN patients, often requiring hospital admission for parenteral antimicrobial therapy and/or removal of the catheter. Contamination of the PN admixture is possible, although rare if protocols are followed for aseptic preparation of PN admixtures. Lack of use of the intestinal tract also may increase the risk of infection possibly by reducing gut immunity, leading to intestinal bacterial overgrowth and subsequent systemic bacterial translocation.

Mechanical Complications

Mechanical complications of PN are related to catheter placement and the system and equipment used to administer PN. A central venous catheter must be placed by a trained professional, and risks associated with placement include pneumothorax, arterial puncture, bleeding, hematoma formation, venous thrombosis, and air embolism.[1,20] Over time, the catheter may require replacement. Problems with the equipment include malfunctions of the infusion pump, intravenous tubing sets, and filters.

MONITORING PN THERAPY

⑩ When initiating PN, patients should have important baseline laboratory values checked to assess electrolyte status, organ function, and nutritional status (Table 97–8). Baseline laboratory monitoring should include

- Basic metabolic panel (i.e., sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, and calcium), phosphorus, and magnesium
- Liver function, including AST, ALT, alkaline phosphatase, lactate dehydrogenase (LDH), total and conjugated bilirubin; a comprehensive metabolic panel can be ordered (i.e., sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, AST, ALT, alkaline phosphatase, albumin, and total bilirubin), but phosphorus, magnesium, and fractionated



Patient Encounter, Part 4

The surgical team plans to initiate PN for AA as you have recommended. Laboratory data were listed previously.

- What other laboratory data or monitoring parameters should be obtained before initiating PN?
- How frequently should you monitor each of the various parameters after initiating PN?
- What potential complications of PN should you monitor for in this patient?

TABLE 97–8. Suggested Frequency of Monitoring Parameters in Hospitalized Patients Receiving Parenteral Nutrition

Parameters	Initial	Daily (Unstable)	2–3 × Weekly (Stable)	Weekly	As Indicated
Blood urea nitrogen, creatinine	X	X	X		
Sodium, potassium, chloride, bicarbonate	X	X	X		
Glucose	X	X	X		
Calcium, phosphorus, magnesium	X	X	X		
Albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase, total bilirubin, conjugated bilirubin	X			X	X
Prealbumin	X			X	X (once weekly)
Triglycerides	X			X	X
Red blood cell count, hemoglobin, hematocrit, white blood cell count ± differential, platelets, partial thromboplastin time	X				X
Prothrombin time/INR				X	X
Nitrogen balance					X
Zinc, selenium, chromium, copper, manganese, iron					X
Total iron-binding capacity, ferritin					X
Vitamin concentrations					X
Ammonia					X
Blood cultures					X
Weight	X	X	X		

or conjugated bilirubin are not included on this panel and must be ordered separately.

- Albumin, prealbumin, total protein, triglycerides
- Complete blood count (including hemoglobin, hematocrit, red blood cell count, and white blood cell count), and platelets with differential

⑩ *Thereafter, the preceding parameters and other nutritional parameters should be monitored routinely or as indicated* (Table 97–8). Random capillary blood glucose concentrations also should be monitored every 6 to 8 hours when initiating PN, and regular insulin should be administered to control glucose as needed (either by intermittent administration per sliding scale or as a continuous infusion).

SUMMARY AND CONCLUSION

PN is a specialized method of administering nutrition support but is associated with complications. Enteral nutrition is the preferred route of providing specialized nutrition support. However, PN can be a lifesaving therapy in patients who cannot receive oral or enteral nutrition. Administration of PN is associated with significant adverse effects, and patients must be monitored closely. Patients receiving PN therapy are at risk for metabolic, infectious, and mechanical complications. Optimal design of a PN regimen is essential to minimize the risk of adverse effects and complications, and patients must be monitored closely while receiving PN in order to optimize outcomes.

ABBREVIATIONS

AA:	amino acid(s)
ALT:	alanine aminotransferase
A.S.P.E.N.:	American Society for Parenteral and Enteral Nutrition
AST:	aspartate aminotransferase
ATP:	adenosine triphosphate
CT:	computed tomography
2,3-DPG:	2,3-diphosphoglycerate
FDA:	Food and Drug Administration
HIT:	heparin-induced thrombocytopenia
kcal:	kilocalorie(s)
LDH:	lactate dehydrogenase
mEq:	milliequivalents
mmol:	millimoles
mOsm:	milliosmoles
PL:	phospholipid(s)
PN:	parenteral nutrition
PPN:	peripheral parenteral nutrition
PTH:	parathyroid hormone
TG:	triglyceride(s)
TNA:	total nutrient admixture
TPN:	total parenteral nutrition

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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98 Enteral Nutrition

Sarah J. Miller



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Discuss how gut structure and function impact choice of feeding route and outcome of feeding.
2. Evaluate patient specific parameters to determine whether enteral nutrition (EN) is appropriate.
3. Compare clinical efficacy, complications, and costs of enteral nutrition (EN) versus parenteral nutrition (PN).
4. Choose an appropriate method of enteral nutrition (EN) delivery based on patient specific parameters.
5. Estimate kilocalorie and protein requirements of an enteral feeding candidate and design an enteral nutrition (EN) regimen to meet these.
6. Choose an appropriate category of enteral nutrition (EN) product given patient-specific parameters.
7. Formulate a monitoring plan for an enteral nutrition (EN) patient.
8. Select appropriate medication administration techniques for an enteral nutrition (EN) patient.

Key Concepts

❶ Enteral nutrition (EN) is the preferred route if the gut can be used safely in a patient who cannot meet nutritional requirements by oral intake.
❷ Enteral nutrition (EN) is associated with fewer infectious complications than parenteral nutrition (PN).
❸ For patients intolerant of gastric feedings or in whom the risk of aspiration is high, feedings delivered with the tip of the tube past the pylorus into the duodenum or, preferably, the jejunum are preferred.
❹ Standard enteral nutrition (EN) formulas are polymeric formulas; these are appropriate for most patients.
❺ When choosing an enteral nutrition (EN) formula, the patient's fluid status should dictate the caloric density selected.
❻ Clinical trial data supporting the use of specialty formulas in niche populations typically are unconvincing in terms of patient outcomes.
❼ The role of enteral immunonutrition in clinical practice remains controversial.
❽ Gastrointestinal complications are the most common complications of enteral nutrition (EN), limiting the amount of feeding that patients receive.
❾ An important practice to help prevent medication-related occlusion is adequate water flushing of the tube before, between, and after each medication is given through the tube.
❿ Compatibility of medications with an enteral nutrition (EN) formula and, conversely, an enteral nutrition (EN) formula with administered medications is of concern when administering medications through feeding tubes.

Enteral nutrition (EN) is broadly defined as delivery of nutrients via the gastrointestinal (GI) tract. This could include normal oral feeding as well as delivery of nutrients in a liquid form by a tube. Sometimes when the term *enteral nutrition* is used, only tube feedings are included; hence the terms *enteral nutrition* and *tube feedings* are often used synonymously. The bulk of this chapter will include information regarding delivery of feedings via tubes. Formulas for EN usually are delivered in the form of commercially prepared liquid preparations, although some products are produced as powders for reconstitution.

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It might be expected that EN via tubes would have been used widely before the development of **parenteral nutrition** (PN); however, this was not actually the case. EN via tubes inserted down the mouth or nose into the stomach and also via rectal tubes was used occasionally in the decades before the development of PN in the 1960s.[1] However, modern techniques for enteral access, both the placement of the tubes themselves and the materials for making pliable, comfortable tubes, had not yet been developed. Before the PN era, the formulas delivered by the tube route often were blenderized foods. The National Aeronautics and Space Administration effort in the United States in the 1960s led to the development of low-residue (monomeric) diets for astronauts. These diets were adapted for use in sick patients requiring EN. Nonvolitional feedings in patients who cannot meet nutritional requirements by oral intake thus include EN and PN; these techniques are collectively known as *specialized nutrition support* (SNS).

GASTROINTESTINAL TRACT STRUCTURE AND FUNCTION

Anatomy and Absorptive Function

With normal volitional feeding, food is ingested via the mouth. Here, the process of breaking down complex foodstuffs into simpler forms that can be absorbed subsequently by the small bowel begins. Solid food is chewed in the mouth, and enzymes begin the digestive process. The trigger for release of many of these substances is the presence of food in specific regions of the GI tract. The food then is swallowed and passes through the esophagus and the esophageal sphincter on its way to the stomach, where additional digestive enzymes and acid further break down the food. The stomach also serves a mixing and grinding function.

The food, now in a liquid form known as *chyme,* passes through the pyloric sphincter into the duodenum, where stomach acid is neutralized. There is wide variation in lengths of the components of the small intestine (i.e., duodenum, jejunum, and ileum) between individuals (Table 98–1). Most absorption of digested carbohydrate and protein occurs within the jejunum. Most fat absorption occurs within the jejunum and ileum. In the small bowel, breakdown of macronutrients (i.e., carbohydrate, protein, and fat) occurs both within the lumen of the gut and at the intestinal mucosal membrane surface. The absorptive units on the intestinal mucosal membrane are infoldings known as *villi.* These villi are made up of epithelial cells called *enterocytes.* Projections (striations) from these enterocytes called *microvilli* greatly increase the surface area of the small bowel and make up what is known as the *brush-border membrane.*

Digestive enzymes secreted by the pancreas play a role in food breakdown. The pancreas secretes large amounts of sodium bicarbonate that neutralize stomach acid. These substances flow from the pancreas through the pancreatic duct. The pancreatic duct typically joins with the hepatic duct to become the common bile duct that empties through the **sphincter of Oddi** into the duodenum. Bile secreted by the liver does not contain digestive enzymes, but bile salts help to emulsify fat and thus facilitate fat absorption. Bile flows through bile ducts into the hepatic duct and common bile duct. Bile is stored in the gallbladder until it is needed in the gut to aid fat digestion, at which time it empties through the cystic duct to the common bile duct to the duodenum. Pathways through which carbohydrate, protein, and fat are digested and absorbed through the small bowel are illustrated in Fig. 98–1.

After absorption in the small bowel, remaining undigested food passes from the ileum through the ileocecal valve to the colon. A major role of the colon is absorption of fluid. Some of the water and sodium absorption achieved by the colon is facilitated by short-chain fatty acids (SFCAs) formed from digestion of certain dietary fibers by colonic bacterial enzymes.

TABLE 98–1. Length of the Small Bowel in Adults

Segment	Length (ft)
Total	12–20
Duodenum	1
Jejunum	5–8
Ileum	7–12

Gut Immune Function

In addition to its roles in digestion and absorption, the gut plays significant immune roles in the body. The distal small bowel and colon host large numbers of bacteria and their endotoxins, and it is important that these organisms not gain access to the internal systems of the body. This function is known globally as the *gut barrier function* and can be divided into several components.[2] Normal flora of the gut comprise one component. The normal flora, particularly some of the anaerobes, help to prevent overgrowth of potential pathogens. A second component of the gut barrier includes mechanical factors. These include an epithelial mucus gel layer that prevents adherence of bacteria and peristalsis of the small bowel that prevents stasis of bacteria. **Gut-associated lymphoid tissue** (GALT), prominent in the small bowel, serves as a local immune system. Secretory immunoglobulin A produced at the mucosal surface prevents bacteria from invading the surface. Bile salts and the **reticuloendothelial system** of the liver are believed to bind bacterial endotoxin and help to clear it from the blood should it be absorbed into the portal circulation.

PATIENT SELECTION

In general, ❶ *if the gut can be used safely in a patient who cannot meet nutritional requirements by oral intake, then EN is the preferred route.* If the gut functions, EN is usually preferred

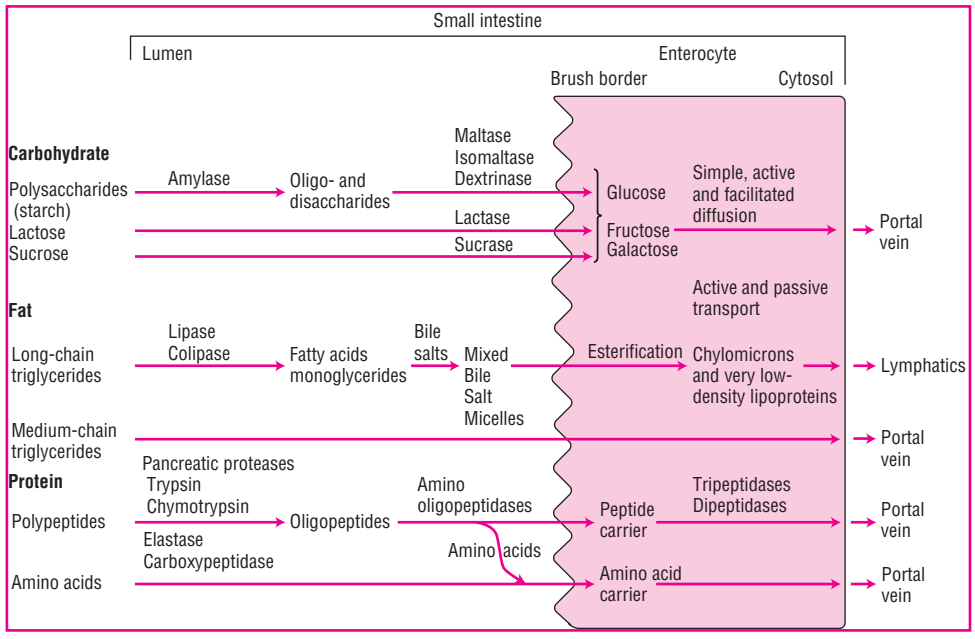


FIGURE 98–1. Schematic representation of carbohydrate, fat, and protein digestion. (From Kumpf VJ, Chessman KH. Enteral nutrition. In: DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: 2616.)

over PN. The timing of SNS (either EN or PN) is controversial, but definitive guidelines for these therapies state that SNS should be started when intake has been inadequate for 7 to 14 days or if inadequate oral intake is anticipated to last at least 7 to 14 days.[3] Prior nutritional status of the patient also should be considered. Previously well-nourished patients can better afford not being fed for longer periods of time than those who are previously poorly nourished. Methods for assessing nutritional status and designing SNS regimens are covered in Chapter 97. In general, hospitalized patients require 25 to 35 kcal/kg of body weight per day and 1 to 2 g protein per kilogram of body weight per day.

Indications

Many potential indications for EN exist (Table 98–2). PN was used extensively previously for many of these conditions. Advances in EN technology now allow many patients with these conditions to receive EN. EN is administered in both institutional (e.g., hospital and long-term care facility) and home settings.

Contraindications and Precautions

EN should not be used or should be used with extreme caution in certain conditions (Table 98–3). It is possible to use EN in some patients with these conditions depending on severity of illness, location of the abnormality, and experience of the practitioners delivering care. Controversy surrounds some of these contraindications and precautions. For example, whereas some clinicians will deliberately avoid enteral feedings in the hemodynamically unstable patient for fear of worsening intestinal ischemia, others believe that early feeding may facilitate intestinal perfusion and thus be beneficial.[4–6] Still others might avoid jejunal feedings in this setting but would be comfortable proceeding with cautious gastric feedings.

TABLE 98–2. Potential Indications for Enteral Nutrition

Neoplastic disease	**Gastrointestinal disease**
Chemotherapy	Inflammatory bowel disease
Radiation therapy	Short bowel syndrome
Upper gastrointestinal tumors	Esophageal motility disorder
Cancer cachexia	Pancreatitis
Organ failure	Fistulas
Hepatic	Gastroesophageal reflux disease
Renal	Esophageal atresia
Cardiac cachexia	**Neurologic impairment**
Pulmonary	Comatose state
Bronchopulmonary dysplasia	Cerebrovascular accident
Congenital heart disease	Demyelinating disease
Hypermetabolic states	Severe depression
Closed head injury	Failure to thrive
Burns	Cerebral palsy
Trauma	**Other indications**
Postoperative major surgery	Acquired immune deficiency syndrome
Sepsis	Anorexia nervosa
	Complications during pregnancy
	Geriatric patients with multiple chronic disease
	Organ transplantation
	Inborn errors of metabolism
	Cystic fibrosis
	Extreme prematurity

From DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: Table 138–4.

TABLE 98–3. Contraindications and Precautions for Enteral Nutrition

Severe hemorrhagic pancreatitis
Severe necrotizing pancreatitis
Necrotizing enterocolitis
Diffuse peritonitis
Small bowel obstruction
Paralytic ileus
Severe hemodynamic instability
Enterocutaneous fistulae
Severe diarrhea
Severe malabsorption
Severe gastrointestinal hemorrhage
Intractable vomiting

Enteral Versus Parenteral Feeding

With the advent of the technique of PN by a large central vein in the late 1960s, this modality of feeding quickly became popular. PN was used originally in the patients for whom it was designed (e.g., patients with inflammatory bowel disease or congenital bowel abnormalities), but it also was incorporated quickly into care of other types of patients such as the critically ill. The relative ease of administration of PN, along with the perception that critically ill patients had prolonged high-energy expenditures, led to complications of overfeeding. In the United States, where no intravenous fat emulsion was available commercially for several years during the 1970s, the impact of dextrose overfeeding was observed. Complications included hyperglycemia, carbon dioxide overproduction leading to delays in weaning from mechanical ventilation, and liver abnormalities owing to **hepatic steatosis.**

As complications of PN became evident, the pendulum began to swing toward EN in the late 1980s and early 1990s as clinical studies were published showing better clinical outcomes with EN compared with PN. Some of the potential advantages of EN over PN are included here. First, EN is expected to preserve the gut barrier function better than PN. This, in turn, could prevent **translocation** of bacteria and endotoxin from the gut lumen into the lymphatic system and systemic circulation, thus preventing infections. Studies from the same era support the contention that ❷ *EN is associated with fewer infectious complications than PN.*[7–9] EN is cited frequently as having a better overall safety profile than PN. Whereas PN is associated with more severe complications, such as pneumothorax and catheter sepsis, EN is associated with more nuisance complications, such as GI side effects that may delay or limit the delivery of nutrients. Another major frequently cited advantage of EN over PN is that EN is less expensive. It is true that EN formulas typically are cheaper and less labor-intensive to prepare than PN formulas. However, depending on the method of feeding tube placement, EN costs can mount if the tube must be placed by a radiologist or gastroenterologist rather than a nurse or if the tube must be replaced for some reason.

The arguments in support of EN over PN have been questioned.[10,11] Part of this questioning relates to the question of whether EN is really beneficial compared with PN or whether PN as it has been commonly administered may be detrimental. Overfeeding and hyperglycemia can occur easily with PN administration, and the potential harm of hyperglycemia, especially in the critical-care population, has been demonstrated poignantly in recent years.[12] A large high-profile study published in 1991 demonstrated in a mildly malnourished perioperative population that there were more infectious complications in patients randomized to receive PN compared with those randomized to receive no SNS; there was no difference in noninfectious complications between the two different feeding groups.[13] Only in severely malnourished perioperative patients were fewer noninfectious complications seen with PN feeding; in these patients, no difference in infectious complications was seen between groups. Whether EN truly prevents infections and improves clinical outcomes or whether PN is actually detrimental continues to be debated and is probably highly dependent on the specific patient population. However, at the present time, EN is preferred by most experts over PN when the gut is functional.

ROUTES OF ACCESS[14–16]

There are several access sites for EN (Fig. 98–2). The nasogastric (NG), orogastric (OG), nasoduodenal (ND), and nasojejunal (NJ) routes generally are for short-term use (less than 6 weeks), whereas gastrostomy, **percutaneous endoscopic gastrostomy** (PEG), jejunostomy, and **percutaneous endoscopic jejunostomy** (PEJ) tubes are preferred for longer-term treatment. The esophagostomy/pharyngostomy is used rarely. Both advantages and disadvantages exist for each of the EN routes (Table 98–4).

Gastric Feeding

Gastric feedings are used commonly. They require an intact gag reflex and normal gastric emptying for safety and success. Certain patients, such as those who have suffered head trauma, may not empty their stomachs efficiently and therefore may not be good candidates for gastric feedings. In these patients, it may be impossible to achieve a gastric tube feeding rate to provide adequate nutrients. In addition, pooling of the feeding formula in the stomach could increase the risk of aspiration of feeding into the lungs.

The NG route is used most commonly for short-term (less than 1 month) enteral access. Some institutions prefer the OG route because of less damage to the sinuses; the OG route is also useful in situations such as facial trauma, where nasopharyngeal damage prevents NG feeding. The major advantage of these routes is that the tubes can be placed quickly and inexpensively by the nurse at the bedside.

Gastrostomy tubes, where an incision is made directly through the abdominal wall, are indicated for patients who can tolerate gastric feedings but in whom long-term

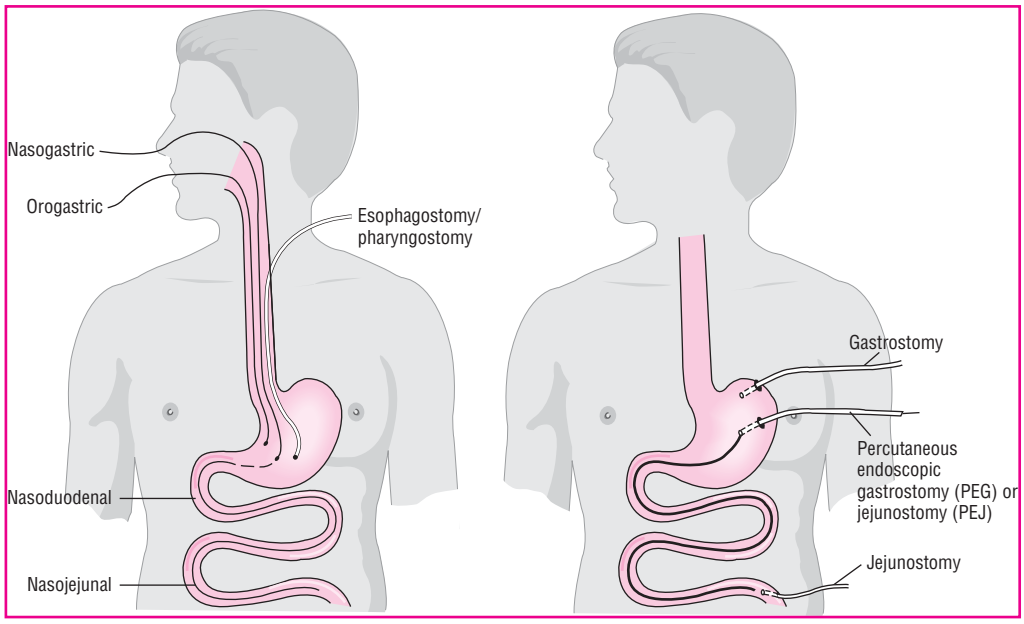


FIGURE 98–2. Access sites for tube feeding. (From Kumpf VJ, Chessman KH. Enteral nutrition. In DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed, New York: McGraw-Hill; 2005: 2619.)

(greater than 1 month) feedings are anticipated. The most commonly placed gastrostomy tubes are PEG tubes placed endoscopically. These tubes also can be placed laparoscopically or during an open procedure by a surgeon. Placement of a gastrostomy tube either endoscopically or surgically is more expensive than bedside OG or NG placement but does result in placement of a larger-bore tube.

An advantage of feeding into the stomach is that the feedings can be delivered in either an intermittent or continuous fashion. This is unlike feedings directly into the small bowel,

TABLE 98–4. Options and Considerations in the Selection of Enteral Access

Access	Indications	Tube Placement Options	Advantages	Disadvantages
Nasogastric or orogastric	Short-term Intact gag reflex Normal gastric emptying	Manually at bedside	Ease of placement Allows for all methods of administration Inexpensive Multiple commercially available tubes and sizes	Potential tube displacement Potential increased aspiration risk
Nasoduodenal or nasojejunal	Short-term Impaired gastric motility or emptying High risk of GER or aspiration	Manually at bedside Fluoroscopically Endoscopically	Potential reduced aspiration risk Allows for early postinjury or postoperative feeding Multiple commercially available tubes and sizes	Manual transpyloric passage requires greater skill Potential tube displacement or clogging Bolus or intermittent feeding not tolerated
Gastrostomy	Long-term Normal gastric emptying	Surgically Endoscopically Radiologically Laparoscopically	Allows for all methods of administration Large-bore tubes less likely to clog Multiple commercially available tubes and sizes Low-profile buttons available	Attendant risks associated with each type of procedure Potential increased aspiration risk Requires stoma site care
Jejunostomy	Long-term Impaired gastric motility or gastric emptying High risk of GER or aspiration	Surgically Endoscopically Radiologically Laparoscopically	Allows for early postinjury or postoperative feeding Potential reduced aspiration risk Multiple commercially available tubes and sizes	Attendant risks associated with each type of procedure Bolus or intermittent feeding not tolerated Requires stoma site care

GER, gastroesophageal reflux.
From DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: Table 138–5.

where continuous feedings must be used. Intermittent feedings into the small bowel result in GI intolerance in most patients.

Postpyloric Feedings

❸ *For patients intolerant of gastric feedings or in whom the risk of aspiration is high, feedings delivered with the tip of the tube past the pylorus into the duodenum or, preferably, the jejunum are preferred.* Feeding in this manner bypasses the problem of poor gastric emptying and adds another barrier (the pyloric sphincter) through which tube feedings must traverse before they are aspirated into the lungs. It should be noted that **postpyloric feedings** do not preclude the possibility of aspiration. In fact, many patients with this complication are not aspirating tube feeding formula but rather their own nasopharyngeal secretions.

ND and NJ feeding tubes can be placed by trained, experienced nurses at the bedside. Although such placements typically take more time than NG or OG placements, this is still an inexpensive method of placement. However, many institutions have not been able to achieve such placements consistently at the bedside. Therefore, in many institutions, ND or NJ placements are done in the radiology suite by a radiologist using fluoroscopy to visualize the advancement of the tube to the appropriate area. This procedure greatly increases the cost of EN therapy. NJ tubes generally are preferred over ND tubes; placement of the tip of the tube distal to the **ligament of Treitz** (located near the junction of the duodenum and the jejunum) may reduce the risk of aspiration further. Alternatively, during a laparotomy, the surgeon can place an ND or NJ tube.

Surgically placed jejunostomy tubes are an option; similar to surgically placed gastrostomy tubes, they are placed through an incision in the abdominal wall, precluding the need for a tube down the nose or mouth. These tubes frequently are placed during laparotomy following abdominal trauma. Alternatively, jejunal access can be obtained by placing a jejunal extension through a PEG tube; the resulting tube is sometimes referred to as a *PEJ tube.* Another option is to place a PEJ tube directly; this technique is a bit more technically difficult than PEG placement and may not be available in some settings.



Patient Encounter, Part 1

A 25-year-old man was involved in a motor vehicle accident in which he suffered several long bone fractures, a ruptured spleen, and a severe closed-head injury. This 5-ft, 10-in man was well nourished and weighed 75 kg before the accident. During the first surgery to repair his abdominal injuries, the surgeon placed a feeding jejunostomy tube. Following surgery, the patient was taken to the intensive-care unit, where he was mechanically ventilated and had an intracranial pressure monitor. He initially required significant amounts of vasopressor agents to maintain his blood pressure. The decision was made to delay dealing with the long bone fractures until he was more stable.

- What would this patient's estimated caloric and protein requirements be?
- What is the potential advantage of using EN rather than PN in this patient?
- Why is a jejunostomy tube a good access route for feeding this patient?
- Would it be prudent to start jejunal feedings immediately after the patient is admitted to the intensive-care unit following his abdominal surgery?

METHODS OF DELIVERY

Enteral feedings are delivered by several different methods. Continuous infusion must be used when duodenal or jejunal feedings are administered. For gastric feedings, bolus or intermittent feedings could be administered instead of continuous feedings. Each method has advantages and disadvantages.

In many hospitals, EN is delivered most commonly as a continuous infusion over 24 hours at a constant rate regulated by an infusion pump. A variation of continuous infusion is cyclic feeding, in which a constant rate is maintained by a pump over a certain number of hours daily. This method of administration is used more commonly in long-term care or home settings. Often EN is administered overnight, giving the patient "freedom" from the infusion pump during the day. This method may not be practical for patients with high nutritional needs because it may be difficult to increase the rate of feedings high enough while maintaining GI tolerance with limited infusion times.

Intermittent feedings are used more commonly in long-term care or home settings largely because they are easier to administer. Patients frequently are started with continuous feedings, transitioned to intermittent feedings given several times a day over about 30 to 45 minutes for each feeding, and eventually changed to bolus feedings, where the feeding is administered several times a day over less than 10 minutes per feeding. An advantage of intermittent feedings is that they may be administered by gravity flow adjusted with a roller clamp, although some institutions may use an infusion pump to administer them. Bolus feedings preclude the need for an infusion set or pump and can be administered using a 60-mL syringe, although, again, in some circumstances an infusion set and pump may be used. Intermittent and bolus feedings often are given in amounts of 240 to 480 mL per feeding, corresponding to one to two cans (8 oz each) of formula.

EN FORMULAS

A number of EN formulas are marketed commercially. Hospitals and long-term care facilities usually limit their formularies of EN formulas, stocking only a limited number of

products. A number of factors should be taken into account when devising a formulary.

Polymeric versus Oligomeric Formulas

One of the major criteria for categorizing various EN products is whether they contain more intact (polymeric) macronutrients or their macronutrient ingredients are present in simpler forms (oligomeric). ❹ *Standard EN formulas are polymeric formulas; these are appropriate for most patients.* Oligomeric formulas should be reserved for patients with GI dysfunction.

Polymeric formulas typically have low osmolality of 300 to 500 mOsm/kg. These formulas also usually supply essential vitamins and minerals in amounts similar to the Adequate Intakes or Recommended Dietary Allowances for these nutrients when the formula is delivered in amounts adequate to meet the macronutrient requirements of most patients. Many polymeric formulas are inexpensive relative to oligomeric formulas. Most polymeric formulas are lactose-free and gluten-free, as are most modern tube feeding products. Products designed to be used as oral supplements generally are polymeric and often have sucrose or other simple sugars added to improve taste.

The oligomeric formulas are also known as *chemically defined formulas.* This class of formulas can be subcategorized based on whether the formula contains all free amino acids (elemental formulas) or peptides (peptide-based) as the protein source. Some of these formulas contain a combination of free amino acids and small peptides. Actually, dipeptides and tripeptides in these formulas are absorbed more efficiently than free amino acids. Oligomeric formulas may be better tolerated than polymeric formulas for patients with defects in GI function and may be particularly useful in patients with severe pancreatic dysfunction or significantly decreased GI surface area (e.g., short bowel syndrome).

Oligomeric formulas typically are more expensive than polymeric formulas and have a higher osmolality because they contain more osmotically active particles. However, the osmolality of these products usually does not exceed 700 mOsm/kg, a value less than that of many oral medications or a regular diet. In the past, there was concern that higher-osmolality EN formulas could cause GI intolerance, particularly diarrhea. This led to dilution of these formulas by half or more with water and gradually increasing both the strength and rate of formula administration. This practice is unnecessary and probably served only to delay attainment of goal nutritional support from tube feedings. Sometimes enteral feedings are diluted to deliver extra water required by the patient; this practice generally is discouraged because of the potential risk of formula contamination. Instead, it is better to give extra water as boluses through the tube. If medications are administered through the feeding tube, generous amounts of water should be used to flush the tube before and after each medication; this practice helps to provide extra fluid to the patient and to prevent problems with occlusion of the feeding tube.

Oligomeric formulas usually are less palatable than polymeric formulas and are not designed for use as oral supplements. Many of the oligomeric formulas provide some fat calories as medium-chain triglycerides (MCTs), which are a fat source that is more readily metabolized by the body than the long-chain triglycerides (LCTs) typically found in polymeric formulas. The MCTs do not require bile salts or pancreatic enzymes for absorption. Some of the elemental formulas contain a very low proportion of fat (less than 10% of total calories), which makes them useful in certain situations where fat needs to be restricted. The carbohydrate source in oligomeric formulas is also less complex than in polymeric formulas, consisting of oligosaccharides rather than hydrolyzed starch.

Fiber Content

Another distinguishing factor of enteral formulas is whether or not a particular formula contains fiber. Both soluble and insoluble fibers may be included in the formula, with insoluble fiber exerting more effect on gut motility by drawing water into the intestine and decreasing transit time, thus preventing constipation. Soluble fiber can help to lower blood cholesterol levels, regulate blood sugar, and prolong gastric emptying. Cellulose gum is an example source of insoluble fiber. Oat fiber and guar gum provide primarily soluble fiber. Soy fiber provides primarily insoluble fiber but also some soluble fiber and is the most commonly used fiber source in tube feeding products. Fiber has been useful for regulating gut motility in some but not all clinical studies; it certainly can be useful in selected patients. Some patients may experience GI discomfort secondary to gas production with the introduction of fiber-containing formulas.

Fructooligosaccharides (FOSs) are a form of fiber receiving increasing attention. These pass through the stomach and small bowel undigested and are fermented by colonic bacteria to the SCFAs butyrate, propionate, and acetate. The SCFAs serve as a major fuel source for colonocytes and facilitate water and sodium reabsorption in the colon.[16] The FOSs fit in the category of substances called *prebiotics* that serve as fermentable substrates for the normal flora of the colon. The SCFAs are not added directly to EN products because they would be absorbed completely before reaching the colon; rather FOSs are added to some formulas, allowing bacterial degradation to form SCFAs.

Caloric Density

Enteral feeding formulas can be categorized based on caloric density. Standard caloric density is 1 to 1.3 kcal/mL. More calorically dense formulas containing 1.5 to 2 kcal/mL are also available and have a higher osmolality. ❺ *When choosing an EN formula, the patient's fluid status should dictate the caloric density selected.* Fluid-overloaded patients may benefit from more calorically dense formulas. It should be recognized that

as the caloric content of a formula increases, the amount of free water decreases. For example, whereas 1 kcal/mL formulas contain about 850 mL of free water per liter of formula, the 2 kcal/mL formulas contain about 710 mL of free water per liter of formula.[17]

Protein Content

The protein content of the EN formula is an important factor in choosing a formula. The standard protein content in EN formulas is up to about 15% of total kilocaloties as protein. High-protein formulas containing up to 25% of total calories as protein are available for highly stressed patients with elevated protein needs, as are low-nitrogen formulas containing less than 10% for use in patients requiring protein restriction. Thus a wide range of protein is available, from about 35 to 85 g/L.

Fat Content

As mentioned earlier, both MCTs and LCTs are used in tube feeding products. Corn, soy, and safflower oils have been the mainstay sources of fat in these products, providing mainly ω-6 polyunsaturated fatty acids (PUFAs). On the other hand, some newer EN products contain higher quantities of ω-3 PUFAs from sources such as fish oil [i.e., docosahexenoic acid (DHA) and eicosapentenoic acid or (EPA)]. Still other formulas contain higher quantities of monounsaturated fatty acids from canola oil and high-oleic safflower or sunflower oils. The essential fatty acid (EFA) content (mainly linoleic acid) of EN formulas is important because EFA deficiency can be induced if at least 1% to 4% of total calories are not supplied as EFA. It is important to note that MCT oil does not contain any EFA.

Specialty Formulas

Specialty formulas designed for use in specific clinical situations generally are much more expensive than standard polymeric formulas. ❻ *Strong clinical trial data supporting use of these specialty formulas in niche populations typically are unconvincing in terms of patient outcomes.*

Stress/Trauma Formulas

Historically, formulas aimed specifically for highly stressed, critically ill patients including those suffering significant trauma and those undergoing major surgical procedures, were enriched with branched-chain amino acids (BCAAs). The rationale for these products was that skeletal muscle BCAAs have been shown to be preferentially used for energy in the setting of critical illness. Thus provision of BCAAs was hoped to limit breakdown of muscle in these patients. Clinical data failed to support or refute the benefit of these formulas unequivocally in terms of clinical outcomes.[17]

The newer generation of enteral feeding formulas marketed for use in these populations covers a broad spectrum of characteristics (Table 98–5). Whereas some are polymeric, others are oligomeric to address the malabsorption that sometimes accompanies high stress. Some of the formulas marketed for use in critical illness are calorically dense (1.5–2 kcal/mL) to

TABLE 98–5. Enteral Feeding Formulas Marketed for Use in High Stress, Pulmonary Disease, and Trauma

Product Name/Manufacturer	kcal/mL	Protein (g/L)	Enriched Ingredients[a]	Selected Specialized Indications
Polymeric				
Impact®/Novartis	1	56	Arginine, nucleotides, ω-3 fatty acids	HS, TR
Impact 1.5®/Novartis	1.5	84	Arginine, nucleotides, ω-3 fatty acids	HS, TR
Impact with Fiber®/Novartis	1	56	Arginine, nucleotides, ω-3 fatty acids	HS, TR
TraumaCal®/Novartis	1.5	82		HS, TR
Nutrivent®/Nestle	1.5	67.5	55% total kcal as fat	PD
Respalor®/Novartis	1.5	75	40% total kcal as fat	PD
Novasource Pulmonary®/Novartis	1.5	75	40% total kcal as fat	PD
Pulmocare®/Ross	1.5	62.6	55% total kcal as fat	PD
Oxepa®/Ross	1.5	62.5	55% total kcal as fat	PD
Oligomeric				
Impact Glutamine®/Novartis	1.3	78	Arginine, nucoeotides, ω-3 fatty acids, glutamine	HS, TR
Crucial®/Nestle	1.5	94	Arginine, ω-3 fatty acids, MCT HS, TR	
Pivot 1.5 Cal®/Ross	1.5	93.8	Arginine, ω-3 fatty acids	HS
Alitraq®/Ross	1	52.5	Glutamine, MCT	HS, TR
Optimental®/Ross	1	51.3	ω-3 fatty acids	HS
IntensiCal®/Novartis	1.3	81		HS

[a]Formula considered enriched if following criteria met: arginine—greater than 10 g/1500 kcal; glutamine—greater than 10 g/1500 kcal; MCT—greater than 30% fat calories; ω-3 fatty acid—ratio of ω-6 to ω-3 less than or equal to 2:1.
CI, critical illness; HS, high stress; PD, pulmonary disease; TR, trauma; EPA, eicosapentenoic acid; GLA, γ-linolenic acid; MCT, medium chain triglycerides

address fluid restrictions sometimes seen in this population, whereas others are less calorically dense. Most of these products contain generous amounts of protein to address the high requirements of highly stressed patients (**nonprotein kilocalories to nitrogen ratios** typically between 75:1 and 125:1). Many of these products contain ingredients purported to increase immune function; the term *immunonutrition* is sometimes attached to these products.

Immune-enhancing ingredients present in some of the enteral feeding products include arginine, glutamine, ω-3 fatty acids, and nucleic acids. Few products contain all of these ingredients (see Table 98–5). Arginine is an important substrate for nitric oxide (NO) synthesis, and small amounts of NO have beneficial effects on immune function under certain conditions.[18] Thus arginine has been purported to have positive influence on lymphocyte and macrophage function. Glutamine is considered to be a conditionally essential amino acid in critical illness. This amino acid is a preferred fuel source for enterocytes of the small bowel. It has been suggested that supplementation with glutamine, either parenterally or enterally, may help to maintain the integrity of the gut mucosa. This might prevent translocation of bacteria and endotoxin from the gut lumen into the lymphatic system and the systemic circulation, although the importance of translocation in humans remains controversial. The ω-3 fatty acids, primarily from fish oils, are included in many immunonutrition products. The metabolites of ω-6 fatty acids include mediators such as prostaglandins, leukotrienes, and thromboxanes that are primarily proinflammatory and increase coagulation. On the other hand, the mediators produced from ω-3 fatty acids predominantly produce anti-inflammatory effects and decrease coagulation. Thus ω-3 fatty acids may help to preserve the antimicrobial capacity of critically ill patients by downregulating inflammation.[18] Finally, there are limited data supporting nucleic acids as immunomodulators. In addition, quantities of antioxidants (particularly vitamin C, vitamin E, and β-carotene) higher than those traditionally found in standard enteral formulas are added to some of the immunonutrition formulas to protect body systems including the immune system from damage by oxygen free radicals.[19] These oxygen free radicals may be produced in high quantities in the setting of injury or infection.

❼ *The role of enteral immunonutrition in clinical practice remains controversial.* A high-profile expert consensus conference held in 2004 concluded that certain populations, particularly malnourished patients undergoing GI surgery and trauma patients, will benefit from this therapy.[20–23] Noteworthy is the fact that this symposium was sponsored by the manufacturer of one of the leading immunonutrition products. Several meta-analyses of the commercial immunonutrition products and/or specific ingredients (e.g., arginine and glutamine) found in these products have been conducted.[24–28] In general, these analyses have found no benefit in terms of mortality from immunonutrition. However, several of them have concluded that infection rates, length of stay, and length of time on a ventilator appear to be decreased with these products. More research will be necessary to further delineate which subpopulations will most likely benefit from these therapies. The best timing (initiation and duration) of delivery also still needs to be determined. There is some concern that supplementation with arginine may be detrimental in septic patients.[28]



Patient Encounter, Part 2

By day 2 postoperatively, the patient's intracranial pressures were improving and he had been weaned off the vasopressor agents. He was still being mechanically ventilated and was requiring an insulin drip at 2 units/hour to keep his blood sugar below 150 mg/dL. He was started on an immune-enhancing enteral formula containing 1.3 kcal/mL and 80 g protein per liter; the beginning rate was 40 mL/hour to be advanced as tolerated to goal rate over 24 to 36 hours.

- What effect would the enteral feeding be expected to have on the patient's blood sugar?
- Is an immune-enhancing formula a good choice for this patient?
- Approximately what should be the goal rate for this patient using this enteral formula?

Pulmonary Formulas

Enteral feeding formulas designed for use in patients with chronic obstructive pulmonary disease or receiving mechanical ventilation contain higher amounts of fat (40%–55% of total kilocalories) than most formulas. The rationale for high fat content is that burning of fat for energy is associated with less carbon dioxide production compared with burning of carbohydrate. Less carbon dioxide production theoretically would be advantageous in patients with retention of this substance and might facilitate weaning from mechanical ventilation. Since part of the market targeted by the manufacturers of these products is mechanically ventilated patients, these products are included in Table 98–5 (e.g., Pulmocare®, Respalor®, Nutrivent®, and Oxepa®). Carbon dioxide retention owing to carbohydrate administration was a problem previously (particularly with PN) when feeding was overzealous. However, at the conservative calorie levels typically administered today, even the standard enteral formulas usually can be given without fear of excess carbon dioxide production.

One formula, Oxepa®, has been studied specifically in critically ill patients with acute respiratory distress syndrome (ARDS).[29] This high-fat formula contains high quantities of the ω-3 fatty acids (EPA) and γ-linolenic acid (GLA). γ-Linolenic

TABLE 98–6. Enteral Feeding Formulas Marketed for Use in Diabetes and Stress-Induced Hyperglycemia

Product Name/ Manufacturer	kcal/mL	% kcal as Fat	% kcal as Carbohydrate	Fiber (g/L)
Glytrol®/Nestle	1	42	40	15.2
Glucerna®/Ross	1	49	34.3	14.4
Diabetisource AC®/Novartis	1.2	44	36	10
Resource Diabetic®/Novartis	1.06	40	36	12.8
Choice DM®/Novartis	1.06	43	40	14.4

acid is metabolized to a prostaglandin with vasodilatory properties. Eicosapentenoic acid (EPA) is converted to prostaglandins and leukotrienes with primarily an anti-inflammatory profile. This formula also contains large quantities of antioxidants. Patients receiving this formula received fewer days of mechanical ventilation and stayed in the intensive-care unit a shorter time than patients receiving a high-fat enteral feeding product as a control.[29] More research should be conducted to confirm the findings of this single study.

Diabetic Formulas

Similar to the pulmonary formulas, formulas designed for the patient with diabetes or stress-induced hyperglycemia are relatively high in fat and low in carbohydrate (Table 98–6). The macronutrient content of these products does not follow the recommendations of the American Diabetes Association for patients with diabetes (lower carbohydrate content and higher fat content than recommended), which could be an issue especially if the formulas are used for more than a couple of weeks. These formulas typically contain fiber (primarily soluble) because it plays some role in glycemic control. They also may contain fructose and monounsaturated fatty acids. Data support improved blood sugar control with use of these formulas in patients with diabetes.[30] There is increasing recognition of the importance of maintenance of euglycemia in various clinical settings including intensive care.[12] Therefore, whether or not a diabetic EN formula is chosen, avoidance of overfeeding and maintenance of good glycemic control with insulin or other hypoglycemic medications are important in these populations.

Renal Formulas

Each of the major manufacturers of EN products markets more than one specialty formula for use in renal failure (Table 98–7). These products uniformly have high caloric density (2 kcal/mL) in light of the need to decrease fluid in this situation. The products vary widely in amounts of nutrients of interest in renal failure patients such as protein, potassium, phosphorus, and magnesium. Products low in protein (20–35 g/L) may be appropriate in chronic renal failure patients not yet receiving dialysis. On the other hand, removal of protein by dialysis, coupled with the hypercatabolic, hypermetabolic condition seen in many patients with acute renal failure, makes use of higher-protein formulas (70–85 g/L) appropriate in these situations. Note that of the products listed in Table 98–7, two manufacturers market a low- and a high-protein product designed for use in renal failure. The potassium, phosphorus, and magnesium contents of EN formulas designed for use in renal failure tend to be lower than in standard formulas because these renally excreted electrolytes can accumulate during renal failure.

Historically, elemental formulas designed for renal failure were enriched with essential amino acids (EAAs) and contained lesser amounts of nonessential amino acids (NEAAs) than standard formulas. Theoretically, EAAs could combine with urea nitrogen in the synthesis of NEAAs, thus leading to a decrease in blood urea nitrogen (BUN). The only situation in which such formulas may be appropriate is in patients with

TABLE 98–7. Enteral Feeding Products Designed for Use in Renal Failure

Product Name/Manufacturer	Protein/L	Characteristics
Renalcal®/Nestle Nutrition	34.4	Enriched with EAAs, arginine, histidine; incomplete[a] formula due to negligible electrolytes and lack of fat soluble vitamins
Nutrirenal®/Nestle Nutrition	70	Complete formula[b] with lower amounts of potassium, phosphate, and magnesium than standard formulas; similar to Nepro®, Novasource Renal®, and Magnacal Renal®
Nepro®/Ross	70	Complete formula similar to Nutrirenal®, Novasource Renal®, and Magnacal Renal®
Novasource Renal®/Novartis	74	Complete formula similar to Nutrirenal®, Nepro®, and Magnacal Renal®
Magnacal Renal®/Novartis	75	Complete formula similar to Nutrirenal®, Nepro®, and Novasource Renal®
Suplena®/Ross	30	Complete formula with low amounts of protein for patients not yet receiving dialysis

[a]Incomplete formula—contains insufficient amounts of one or more essential nutrients.
[b]Complete formula—contains all nutrients in amounts sufficient to meet needs of most patients in a volume equal to or less than that usually administered.

chronic renal failure who are not candidates for dialysis. Even in this setting, the use of these products should be limited to no more than 2 or 3 weeks owing to the risk of increased serum ammonia levels.[3] These EAA-enriched formulas have been supplanted largely by polymeric formulas with a protein content similar to standard EN formulas. The main difference between these products and standard EN formulas is reduced potassium, phosphate, and magnesium concentrations.

Hepatic Formulas

Specialized formulas for patients with hepatic insufficiency are limited in number. These products are enriched with BCAAs while containing a reduced quantity of aromatic amino acids (AAAs) and methionine compared to standard enteral formulas. These changes seek to address the high levels of AAAs and low levels of BCAAs found in the blood of patients with hepatic insufficiency. Theoretically, these products might be helpful for patients with hepatic encephalopathy (HE). One of the mechanisms postulated as a cause of HE is the false neurotransmitter hypothesis. According to this hypothesis, high levels of AAAs in the blood allow large quantities of these amino acids to cross the blood-brain barrier and form false neurotransmitters such as octopamine. Administration of high amounts of BCAAs could competitively inhibit some of the AAAs from crossing the blood-brain barrier, thus decreasing the formation of false neurotransmitters. The hepatic formulas are distinguished from the BCAA-enriched formulas historically used in critical illness and stress by the low AAA content of the hepatic formulas. Although there are some data supporting the use of these specialty products in the treatment of moderate to severe HE, improvement in mortality attributable to them has not been consistent.[3] Therefore, many institutions and clinicians prefer to use less expensive polymeric enteral formulas containing standard protein sources for patients with hepatic insufficiency. The specialty formulas are recommended only for patients with chronic cirrhosis who cannot ingest 1 g protein per kilogram per day without becoming encephalopathic.[3] An example of a specialized hepatic formula is Hepatic-Aid II®, a product that is supplied as a powder for reconstitution and that requires vitamin, mineral, and electrolyte supplementation. A second product is NutriHep®, which is supplied as a liquid formula containing the recommended amounts of key vitamins, minerals, and electrolytes.

MONITORING AND COMPLICATIONS

Although complications of EN generally are considered to be less serious than with PN, some complications nevertheless can be dangerous or can lead to impaired delivery of the desired nutrient load. The complications of EN can be divided into four categories: GI, technical, infectious, and metabolic. The first three of these categories of complications, along with common causes, are listed in Table 98–8. Patients on EN must be monitored for prevention of complications (Table 98–9). Note that monitoring of many of these parameters can become less frequent as the patient's condition stabilizes. Monitoring for efficacy of EN is also important.

GI Complications

❽ *GI complications are the most common complications of EN limiting the amount of feeding that patients receive.* Although diarrhea frequently is blamed on the tube feeding formula or the method of EN administration, other possible causes of diarrhea usually exist (see Table 98–8). Many of these possibilities are related to the fact that, particularly in the inpatient setting, patients receiving EN frequently are some of the sickest patients in the hospital. Along these lines, *Clostridium difficile* colitis must be considered as a possible cause of diarrhea, especially in patients who have been receiving antimicrobial therapy or proton pump inhibitors.[31,32] Antibiotic therapy is one of the major causes of diarrhea in acutely ill patients, including those receiving EN. A medication-related cause of diarrhea that was largely overlooked until the early 1990s is the sorbitol content of medications.[33] Large quantities of this substance present in many oral liquid medications (often considered the dosage form of choice for administration through a feeding tube) can cause diarrhea. Unfortunately, the sorbitol content of many medications is not listed on their labeling, and some manufacturers state that they frequently reformulate these preparations to contain varying amounts of excipients such as sorbitol. Determining the cause of the diarrhea is obviously important to know how to address the problem. Whereas *C. difficile* colitis should be treated with metronidazole, sorbitol- or other medication-induced diarrhea can be addressed by removal of the offending agent. Likewise, diarrhea secondary to malabsorption sometimes can be addressed by changing to an oligomeric EN formula. Antiperistaltic agents such as loperamide may be useful in some cases of diarrhea of noninfectious etiology.

On the other hand, constipation may occur in some patients receiving tube feedings, especially the elderly. Increased provision of fluid or fiber may be useful in attaining bowel regularity. As with diarrhea, constipation may be drug-related, in which case discontinuation or replacement of the offending drug may help to alleviate the problem.

Impaired gastric emptying is another problem seen commonly in EN patients receiving gastric feedings and may be associated with nausea and vomiting. The impaired gastric emptying may be related to a disease process (e.g., diabetic gastroparesis or sequelae to head injury) or to drug therapy, most notably narcotics used for analgesia. Gastric residual checks frequently are measured in patients receiving gastric feedings (see Table 98–9). To accomplish such a check, a syringe is attached to the feeding device, and as much liquid as possible is aspirated into the syringe. Much debate is ongoing as to what constitutes a significant gastric aspirate,

TABLE 98–8. Complications of Tube Feeding

Complication	Causes
Gastrointestinal	
Diarrhea	Drug related
	Antibiotic-induced bacterial overgrowth
	Hyperosmolar medications administered via feeding tubes
	Antacids containing magnesium
	Malabsorption
	Hypoalbuminemia/gut mucosal atrophy
	Pancreatic insufficiency
	Inadequate GIT surface area
	Rapid GIT transit
	Radiation enteritis
	Tube feeding related
	Rapid formula administration
	Formula hyperosmolalty
	Low residue (fiber) content
	Lactose intolerance
	Bacterial contamination
Nausea and vomiting	Gastric dysmotility (surgery, anticholinergic drugs, diabetic gastroparesis)
	Rapid infusion of hyperosmolar formula
Constipation	Dehydration
	Drug induced (anticholinergics)
	Inactivity
	Low residue (fiber) content
	Obstruction/fecal impaction
Abdominal distention/cramping	Too rapid formula administration
Technical	
Occluded feeding tube lumen	Insoluble complexation of enteral formula and medication(s)
	Inadequate flushing of feeding tube
	Undissolved feeding formula
Tube displacement	Self-extubation
	Vomiting or coughing
	Inadequate fixation (jejunostomy)
Aspiration	Improper patient position
	Gastroparesis/atony causing regurgitation
	Feeding tube malpositioned
	Compromised lower esophageal sphincter
	Diminished gag reflex
Peristomal excoriation	Improper skin and tube care
	GIT secretions leaking peristomally
Infectious	
Aspiration pneumonia	Same as technical—aspiration comments
	Prolonged use of large-bore polyvinylchloride tube

From DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 5th ed. New York: McGraw-Hill; 2005: Table 138–14.

with numbers between 100 and 400 mL most commonly defended.[34,35] Approaches to the patient with delayed gastric emptying might include changing to an enteral formula containing less fat because dietary fat is associated with slower gastric emptying. Metoclopramide often is given to patients receiving gastric feedings to facilitate gastric emptying. Erythromcyin is an alternative medication that may be useful in stimulating gastric motility, although it also can be associated with potentially serious drug-drug interactions. Patients with consistently high gastric aspirates are considered to be at higher risk of aspirating feedings into their lungs and should be considered for transition to postpyloric feedings. Postpyloric feedings also may help to relieve the EN-related nausea and vomiting seen in some patients and are preferred for patients without an intact gag reflex. One of the most important practices to help prevent aspiration is elevation of the head of the bed to at least 30 degrees during continuous feedings and during and for 30 to 60 minutes after intermittent and bolus feedings. The practice of adding blue food coloring to tube feeding formulas to help detect aspiration in bronchial or tracheal aspirates has been abandoned largely owing to reports of absorption of this supposedly nonabsorbable substance in patients with sepsis.[36]

TABLE 98–9. Suggested Monitoring for EN Patients to Prevent the Development of Complications

Parameter	During Initiation of EN Therapy	During Stable EN Therapy
Vital signs	Every 4–6 hours	As needed
Clinical assessment		
Weight	Daily	Weekly
Length/height (children)	Weekly–monthly	Monthly
Head circumference (less than 3 y of age)	Weekly–monthly	Monthly
Total intake/output	Daily	As needed
Tube feeding intake	Daily	Daily
Enterostomy tube site assessment	Daily	Daily
GI tolerance		
Stool frequency/volume	Daily	Daily
Abdomen assessment	Daily	Daily
Nausea or vomiting	Daily	Daily
Gastric residual volumes	Every 4–8 hours (varies)	As needed
Tube placement	Prior to starting, then ongoing	Ongoing
Laboratory		
Electrolytes, BUN/S_{cr}, glucose	Daily	As needed
Calcium, magnesium, phosphorus	3–7 times/wk	As needed
Liver function tests	Weekly	As needed
Trace elements, vitamins	Patient-specific	Patient-specific

BUN, blood urea nitrogen; S_{cr}, serum creatinine.
From DiPiro JT, Talbert RL, Yee GC, et al, (eds.) *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005: Table 138–10.

Technical Complications

Technical or mechanical complications are encountered frequently in the patient receiving EN. Tube occlusion most commonly is related to formula occlusion or medication administration through the tube. ❾ *An important practice to help prevent medication-related occlusion is adequate water flushing of the tube before, between, and after each medication is given through the tube.* If intermittent feedings are being used, water flushing after each feeding is recommended. Tube occlusion can increase the cost of EN significantly if the tube has to be removed and replaced. Clearing of the occlusion using water or pancreatic enzymes plus sodium bicarbonate can be attempted, and special devices and kits (e.g., Clog Zapper®) are also available for this purpose.[37]

Tube displacement is a potentially significant complication of EN. This may be seen secondary to an agitated patient pulling at his or her tube, or in some cases the tip of the tube migrates spontaneously. The danger of this complication arises if the tip of the tube is positioned in the tracheobronchial tree and feeding is delivered to this area, potentially leading to pneumonia, pneumothorax, and other problems. The location of the tip of the feeding tube should be confirmed initially by chest radiograph after placement and before use. For ongoing assessment of tube placement, auscultation and measurement of aspirate pH can be used; debate continues as to the best method of monitoring tube placement.

Endoscopic and surgical feeding tubes can be complicated by erosion of the exit site caused by leakage of gastric or intestinal contents onto the skin. This complication must be addressed by good wound care and repair or replacement of the access device. Similarly, NG, ND, and NJ tubes can be complicated by nasopharyngeal irritation or necrosis. This is one of the reasons why such tubes should be considered for short-term use only.

Infectious Complications

Infectious complications of EN include aspiration pneumonia and infections related to delivery of contaminated EN formula. Aspiration is a complication with GI, mechanical, and infectious implications. Although GI infections owing to contamination of enteral formulas have been reported uncommonly, there is ample opportunity for these formulas to be seeded with organisms during the processes of transferring from the can to the delivery bag with ready-to-use formulas and during the process of reconstitution with powdered formulas. The so-called closed systems of delivery, wherein the formulas come from the manufacturer premixed in a delivery bag, should help to decrease the chance of formula contamination.

Metabolic Complications

Metabolic complications of EN most commonly include disorders of fluid and electrolyte homeostasis and hyperglycemia. More severely ill patients require more frequent monitoring than those who are more stable (see Table 98–9). Both dehydration and fluid overload can occur with tube feeding. Careful monitoring of fluid inputs and outputs as well as body weight is important. Dehydration may be due either to excessive fluid

losses or inadequate fluid intake. The trend in the BUN-to-serum-creatinine ratio can be useful in helping to monitor for this complication; a ratio of greater than about 15:1 may be an indicator of dehydration. Attention should be paid to the free-water content of EN formulas; this information usually is included on the product labeling. The free-water content of EN formulas varies from about 65% to 85%, with the percentage of free water typically dropping as the caloric density of the formula rises. If a patient develops dehydration, switching to a less calorically dense formula or using more water flushes with the feeding may be appropriate. Fluid overload is reflected by increases in weight, lower extremity edema, and pulmonary rales and particularly may be a problem in patients with renal or cardiac insufficiency. Use of an EN formula that is more calorically dense (i.e., contains less free water) may be helpful, and diuretic therapy may be necessary. Fluid imbalances often are associated with abnormalities of sodium homeostasis that should be addressed in concert with the fluid imbalance.

Hypokalemia, hypomagnesemia, and hypophosphatemia are some of the most common electrolyte abnormalities in sick, hospitalized patients. These can occur in the context of the so-called refeeding syndrome. This syndrome occurs in chronically malnourished patients when aggressively started on a feeding regime. Although more classically associated with PN, refeeding syndrome can occur with aggressive EN as well. Careful monitoring of these electrolytes, coupled with a feeding regimen that is increased gradually to goal rate over a period of several days to a week, should help to protect the at-risk patient from this potentially harmful complication. Hypokalemia and hypomagnesemia also may be associated with excessive losses through the GI tract or urine and may be associated with various medication therapies, including diuretics. Repletion of these conditions may be accomplished enterally in the nonsymptomatic patient or parenterally if the patient is symptomatic or the abnormality is severe. Enteral repletion with magnesium and phosphate can be associated with diarrhea. Hyperkalemia, hypermagnesemia, and hyperphosphatemia are encountered less commonly and usually are associated with renal insufficiency and decreased excretion. Hyperkalemia also is associated with several medications, including potassium-sparing diuretics and angiotensin-converting enzymes frequently used in hospitalized patients.

Although hyperglycemia is less common with EN than with PN, it can occur nevertheless. Many of the severely ill patients (e.g., septic, highly stressed) receiving EN have a metabolic milieu promoting hyperglycemia. In addition, many of these patients have preexisting or undiagnosed diabetes mellitus. For the intensive-care-unit patient with hyperglycemia receiving continuous EN, an intravenous insulin drip may be the most effective way to achieve the tight glycemic control now generally recommended. Administration of scheduled long-acting insulin is preferred over sliding-scale insulin in patients requiring insulin after they have been stabilized on their enteral feeding regimen. Administration of a higher-fat, lower-carbohydrate EN formula also may be useful in selected patients.

Monitoring for Efficacy/Outcome Evaluation

The most useful physical measurement of efficacy of EN in the long-term patient is typically body weight. Depending on the clinical situation, the goal may be weight gain, weight maintenance, or weight loss. Whereas day-to-day fluctuations in weight generally reflect fluid changes, week-to-week variations are more useful in determining if caloric provision is appropriate.

The amount of EN actually administered is often less than the amount ordered owing to interruptions in therapy for performance of procedures and other daily activities, especially in hospitalized patients. It is imperative to monitor volume of feedings actually received and to make adjustments in rates or amounts of EN as necessary.

Biochemical markers may help the SNS practitioner interpret the adequacy of the EN therapy. Albumin frequently is measured as part of standard metabolic lab panels. However, its long half-life makes this visceral protein less useful for making decisions regarding the adequacy of the nutritional prescription over the short term. Prealbumin, a protein with a much shorter half-life that is expected to increase more rapidly in the setting of sufficient calorie and protein provision, has become the major biochemical monitoring parameter used to determine efficacy of SNS. However, in the acute phase of an illness characterized by a proinflammatory state, proteins known as *acute-phase reactants* are preferentially synthesized. One of these acute-phase reactants commonly measured clinically is C-reactive protein (CRP). Therefore, in some patients with significant illness, prealbumin levels may not rise, even though the patients are receiving the appropriate EN regimen, until the CRP level begins to fall. Collection of urine to measure nitrogen balance also can help to analyze adequacy of caloric and protein provision but must be performed with care to obtain reliable information.

In patients with wounds (e.g., decubitus ulcers), a goal of nutritional therapy is usually to help facilitate wound healing. Therefore, monitoring the status of the wound becomes part of the ongoing nutritional assessment. In debilitated patients, particularly those on long-term EN, measures of functional status such as grip strength and ability to perform activities of daily living become important parts of the assessment of nutritional adequacy.

MEDICATION ADMINISTRATION IN PATIENTS RECEIVING EN

Medication Administration Through Feeding Tubes

If a patient receiving EN is alert and can swallow oral medications, then the medications should be given by mouth. However, many patients are not able to receive their medications by this

route, and the feeding tube may be considered as a route of delivery of some medications. Although used widely, the effects of medication administration through feeding tubes on the delivery of both the drug and the EN formula nutrients have been inadequately studied, and many important questions remain to be answered.[38]

⑩ *Compatibility of medication with an EN formula and, conversely, an EN formula with administered medication is of concern when administering medications through feeding tubes.* An important technical complication of EN is tube occlusion, which is related most commonly to medication administration through the tube. Not only must compatibility of the medication and the EN formula be considered, but interactions between these components and the feeding tube itself also must be considered. Since either medication or EN formula or some combination thereof can physically stick to the tube itself, strict protocols for flushing the tube before, between, and after administration of medications are important. The best fluid for flushing feeding tubes is warm water. Although carbonated beverages and fruit juices have been used commonly in the past, these are no longer recommended and should be avoided because the sugar in these products may stick to the surface of the feeding tube. Between 10 and 30 mL of water should be used as a flush before and after any medication administration through a feeding tube. Medications should be administered one at a time sequentially rather than being mixed together for simultaneous administration down the tube; about 5 mL of water should be used as a flush between each medication. This should help to prevent interactions between drugs within the feeding tube itself that could lead to tube occlusion.

Different dosage forms each present unique challenges for administration through feeding tubes. Certain solid dosage forms should not be crushed because crushing would cause a significant alteration in the release characteristics of the drug.[39] For example, controlled-release, extended-release, and sustained-release preparations should not be crushed; crushing would allow a quicker release of more drug initially than the original dosage form was designed to deliver. Sublingual dosage forms also should not be crushed. Enteric-coated dosage forms generally are designed to protect acid-labile medications from stomach acid; when these dosage forms reach the small bowel with its higher pH, the drug then is released into an environment in which it is more stable. Alternatively, enteric-coated dosage forms protect the stomach from medications that could cause irritation. Thus, crushing of the enteric coating for delivery down a gastric feeding tube defeats the purpose of the dosage form and could lead to decreased efficacy or increased adverse events with the medication.

Medications available commercially as compressed tablets can be crushed for administration through feeding tubes. After such a tablet is crushed into a fine powder, it should be mixed with 10 to 30 mL of fluid (usually warm water) for administration through the tube. A powdered dosage form inside a hard-gelatin capsule similarly can be poured out and mixed with water for administration through feeding tubes. Soft-gelatin capsules can be dissolved in warm water for administration through a tube. Some enteric-coated and delayed-release microencapsulated products can be opened, and the individually coated particles can be administered through the tube without crushing if the tube has a large enough diameter.

If a liquid dosage form of a medication exists, it would seem rational to use this dosage form for administration through a feeding tube. Although such a decision may decrease the potential for tube clogging, it may in some instances decrease tolerability of the medication administration. Sorbitol is an excipient found in many liquid medications in amounts sufficient to cause diarrhea. If diarrhea secondary to sorbitol in a liquid medication is suspected in a patient on EN, contact with the manufacturer to ascertain sorbitol content may be necessary.

Another potential problem with administration of liquid medications through feeding tubes is the high osmolality of some of these products. Dilution of hypertonic medications with 30 to 60 mL of water (depending on the osmolality of the medication and the dosage volume of the undiluted medication) or administration of smaller dosages of the drug more frequently may help to prevent diarrhea. Although administration of intravenous medications through feeding tubes sometimes may be entertained, these dosage forms frequently are hypertonic and contain excipients that can be problematic when given via the GI tract.

It is generally not recommended to mix medications directly into the EN formula because of concerns that physical incompatibilities between the medications and the formula might lead to tube occlusion. There is some evidence that polymeric formulas are more likely to demonstrate physical incompatibility with medications compared with monomeric formulas, although most of the work in this area has used casein or caseinate-based formulas, and other proteins may act differently.[38] The limited data currently available would indicate that acidic syrups and elixirs may be the worst for causing physical incompatibility when admixed with EN formulas. It has been postulated that this incompatibility is due to changes in the protein structure after exposure to acid or alcohol.[38]

It would seem logical that medications considered to be absorbed to a greater extent in the fasted state either should be given between feedings on an intermittent feeding schedule or the feedings should be held for a period before and after medication administration. However, results of one provocative study with the antihypertensive medication hydralazine indicated that a continuous feeding into the stomach resulted in a situation mimicking fasting in terms of the rate of gastric emptying and the drug's absorption.[38] This issue deserves further study.

The location of the tip of the feeding tube is important when considering medication administration down a feeding tube. This is particularly true if the medication acts locally in the GI tract itself. For example, sucralfate and antacids act locally in the stomach. Therefore, administration of these medications through a duodenal or jejunal tube is not logical. Likewise, for medications such as itraconazole that require acid for best absorption, administration directly into the duodenum or jejunum would be expected to result in suboptimal absorption. Absorption of drugs when administered directly into the small bowel, especially the jejunum, rather than into the stomach is another area where more research would be useful.

Problem Medications

Phenytoin

Certain medications present specific challenges when administered through feeding tubes. The medication falling into this category that has been studied most thoroughly is phenytoin. Most studies have shown significant decreases in phenytoin absorption when the medication was administered enterally to patients receiving EN. Several mechanisms have been proposed for this apparent interaction, but no consensus has been reached. Many institutions have adopted a policy of holding tube feedings for 1 or 2 hours before and after administration of phenytoin to decrease the interaction, although some EN patients subjected to this routine still will require relatively high dosages of phenytoin to achieve therapeutic serum concentrations. Likewise, holding the feeding around medication administration can make meeting nutritional requirements difficult with continuous feedings, especially if the phenytoin is administered several times daily. Diligent monitoring of phenytoin serum concentrations is necessary for the patient on EN also receiving this medication.



Patient Encounter, Part 3

After a week in the intensive-care unit, the patient was transferred to a stepdown unit and was switched to a standard polymeric EN formula. He required 3 weeks of inpatient care owing to complications from his injuries, including seizures and a wound infection. He eventually was transferred to a rehabilitation facility still requiring EN.

- How should the patient be monitored for adequacy of his EN regimen?
- Outline a monitoring plan for tolerance of the EN regimen in the intensive-care unit, stepdown unit, and rehabilitation facility.
- Discuss work-up of the patient if diarrhea occurs while he is receiving tube feedings.
- If the patient requires phenytoin for his seizures, how should this medication be administered?



Patient Care and Monitoring

1. Assess the patient's condition to estimate the amount of time he or she is expected to be unable to eat adequately to meet nutritional requirements. If inadequate intake has occurred or is anticipated for 7 to 14 days, start SNS. The threshold for starting SNS is lower for previously malnourished patients than for previously well-nourished patients.
2. Assess whether the GI tract is functional. If it is not, then PN is the first SNS therapy of choice. If the GI tract is functional and no contraindication to EN exists, then EN is the SNS therapy of choice.
3. Does the patient have any condition precluding gastric feeding? If so, then postpyloric feeding should be started.
4. Choose the appropriate type of enteral access device based on the expected duration of SNS.
5. Choose an appropriate feeding formula based on patient-specific factors. This necessitates assessing the patient's nutritional requirements. Standard polymeric formulas are appropriate for the majority of patients.
6. Choose the method of feeding administration (e.g., intermittent or continuous) based on the type of feeding access (i.e., gastric versus postpyloric) and other patient factors. For example, in a patient with a gastric access, starting with or later transitioning to intermittent feedings may be preferred if it is anticipated that the patient will be discharged still receiving these feedings to a long-term care facility or to home.
7. Develop a plan to include monitoring at appropriate intervals for metabolic, gastrointestinal, technical, and infectious complications.
8. Start the tube feeding at full strength and at a low rate, and increase the rate as tolerated to the goal that will meet the patient's nutritional requirements.
9. Develop a monitoring plan for adequacy of the nutritional regimen.
10. If the patient is to be discharged to home on EN, educate the patient or caregiver on
    - Enteral access device care
    - Feeding delivery
    - Troubleshooting
    - Complications to observe for (e.g., fluid overload, dehydration)

In some cases, use of intravenous phenytoin or another anticonvulsant medication may be prudent.

Warfarin

EN formulas contain vitamin K, which can antagonize the pharmacologic activity of warfarin. The vitamin K content of EN formulas generally has been adjusted down over the past

several decades, resulting in products today that contain amounts of vitamin K unlikely to affect anticoagulation by warfarin significantly. However, inadequate warfarin anticoagulation in EN patients receiving formulas containing minimal vitamin K has been reported. There is some thought that a component of certain tube feedings, perhaps protein, may bind warfarin and result in suboptimal activity of the drug. When tube feedings are started, changed, or discontinued, the international normalized ratio (INR) should be monitored closely.

Fluoroquinolones

Absorption of antimicrobial agents such as fluoroquinolones and tetracyclines that can be bound by divalent and trivalent cations potentially could be compromised by administration with EN formulas containing these cations. The fluoroquinolones (e.g., levofloxacin and ciprofloxacin) have been best studied in this regard, and results of studies are not consistent. Mechanisms for an interaction between fluoroquinolones and EN formulas other than chelation by cations have been postulated.[40] Some institutions hold tube feedings for 30 to 60 minutes or more before and after enteral dosages of fluoroquinolones. Because ciprofloxacin absorption has been shown to be decreased with jejunal administration, this drug probably should not be given by jejunal tube.[41]

SUMMARY AND CONCLUSION

EN is an important method of feeding patients who cannot or should not eat enough to meet their nutrient requirements for a prolonged time. When the GI tract can be used safely, EN is preferred over PN. Various types of enteral access devices are available. Whereas tubes inserted through the nose often are adequate for patients who are expected to receive EN for a short time, more permanent devices (endoscopically or surgically placed) are preferred for longer-term patients. The choice of whether to feed into the stomach or postpylorically is patient-specific. Although numerous EN formulas are available commercially, many of the products are very similar, making a limited formulary feasible. Data supporting many of the specialized types of EN formulas are limited. Although complications of EN tend to be less serious than with PN, the adverse effects encountered can be significant, and diligent ongoing monitoring for them is necessary. Although medications can be administered through feeding tubes, various factors must be taken into account in each individual patient to ensure that this practice is prudent.

ABBREVIATIONS

AAA: aromatic amino acids
BCAA: branched-chain amino acids
DHA: docosahexenoic acid
EAAs: essential amino acids
EFAs: essential fatty acids
EN: enteral nutrition
EPA: eicosapentenoic acid
FOSs: fructooligosaccharides
GALT: gut-associated lymphoid tissue
GI: gastrointestinal
GLA: γ-linolenic acid
HE: hepatic encephalopathy
LCTs: long-chain triglycerides
MCTs: medium-chain triglycerides
NO: nitric oxide
PN: parenteral nutrition
PUFAs: polyunsaturated fatty acids
SCFAs: short-chain fatty acids
SNS: specialized nutrition support

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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99 Overweight and Obesity

Maqual R. Graham and Cameron C. Lindsey



Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Explain the underlying causes of overweight and obesity.
2. Identify parameters used to diagnose obesity and other objective information that indicates the severity of disease.
3. Identify desired therapeutic goals for patients who are overweight or obese.
4. Recommend appropriate nonpharmacologic and pharmacologic therapeutic interventions for overweight or obese patients.
5. Implement a monitoring plan that will assess both the efficacy and safety of therapy initiated.
6. Educate patients about the disease state and associated risks, appropriate lifestyle modifications, drug therapy, and surgical options necessary for effective treatment.

Key Concepts

❶ Body mass index (BMI), waist circumference, comorbidities, and readiness to lose weight are used in the assessment of the overweight or obese patient.

❷ Presence of comorbidities [coronary heart disease (CHD), atherosclerosis, type 2 diabetes mellitus, and sleep apnea] and cardiovascular risk factors (cigarette smoking, hypertension, elevated low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, impaired fasting glucose, family history of premature CHD, and age) requires identification and aggressive management for overall effective treatment of the overweight or obese patient.

❸ Management is directed at preventing weight gain in patients with a BMI greater than or equal to 25 kg/m^2. Weight loss is indicated for patients with a BMI of 25 to 29.9 kg/m^2 or an elevated waist circumference with two or more comorbidities or for any patient with a BMI of 30 kg/m^2 or greater.

❹ The treatment goals for overweight and obesity are to prevent additional weight gain, reduce and maintain a lower body weight, and control related risks.

❺ Weight maintenance occurs following successful achievement of weight loss.

❻ Treatment of obesity includes lifestyle changes (e.g., dietary modification, enhanced physical activity, and behavioral therapy), pharmacologic treatment, surgical intervention, or a combination of modalities.

❼ Pharmacotherapy, in addition to lifestyle modifications, is reserved for patients with a BMI of 30 kg/m^2 or greater or a BMI of 27 kg/m^2 or greater with other obesity-related risk factors.

❽ Weight likely will be regained if lifestyle changes are not continued indefinitely.

❾ Surgery is warranted when other treatment attempts have failed in severely obese patients (BMI of 40 kg/m^2 or greater or 35 kg/m^2 or greater with other obesity-related risk factors).

Overweight is defined as an excess body weight relative to height. Conversely, *obesity* relates to a condition of excess body fat as assessed by various modalities.[1] ❶ *Body mass index (BMI), waist circumference, comorbidities, and readiness to lose weight are used in the assessment of the overweight or obese patient.* The primary modality in defining overweight and obesity is the **body mass index** (BMI)—a measure of body fat based on height and weight that applies to both adult men and women. The BMI accurately measures body fat when compared with body weight alone.[2] Several surveys were conducted to establish categories of BMI.[3] BMI does not reflect distribution of body fat; therefore, the measurement of **waist circumference** is a more practical method to evaluate abdominal fat before and during weight-loss treatment. Abdominal fat poses a greater

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health risk over peripheral fat and may be an independent risk predictor when BMI is not elevated significantly.[4,5] Both BMI and waist circumference should be used in the diagnosis and management of weight loss. Evaluation of the patient's risk status involves not only calculation of the BMI and measurement of waist circumference but also determination of comorbidities or the presence of cardiovascular disease (CVD) risk factors.

❷ *Presence of comorbidities [coronary heart disease (CHD), atherosclerosis, type 2 diabetes mellitus, and sleep apnea] and cardiovascular risk factors (cigarette smoking, hypertension, elevated low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, impaired fasting glucose, family history of premature CHD, and age) requires identification and aggressive management for overall effective treatment of the overweight or obese patient.* Obese patients may be at very high risk for mortality if concomitant risk factors exist; therefore, high-risk patients require aggressive modification of risk factors in addition to obesity treatment.[6]

ETIOLOGY AND EPIDEMIOLOGY

Obesity is a multifactorial, complex disease that occurs following an interaction between genotype and the environment. While the etiology is not known completely, it involves overlapping silos of social, behavioral, and cultural influence; pathophysiology; metabolism; and genetic composition.[7] The majority of overweight or obese individuals are adults, but these diseases are also prevalent in children between 2 and 20 years of age. Over 105 million Americans are overweight or obese, including 9 million children over 6 years of age.[8,9] Overweight children typically mature to overweight adults, but most obese adults were not overweight as children.[10] Overweight and obesity, when present in young adults, therefore may be a better predictor of prevalence.[10] Additionally, adulthood overweight and obesity contribute to an increased risk of death in the presence of hypertension, hyperlipidemia, diabetes mellitus, coronary artery disease (CAD), stroke, sleep apnea, gallbladder disease, osteoarthritis, and certain cancers.[6] Psychosocial functioning also may be hindered because obese patients may be at risk for discrimination if negatively stereotyped.[6] Pediatric obesity is also associated with significant health-related problems and thus is a risk factor for much of the adult morbidity and mortality discussed previously.[11,12] Cardiovascular (e.g., dyslipidemia, hypercholesterolemia, and hypertension), endocrine (e.g., hyperinsulinemia, impaired glucose tolerance, type 2 diabetes mellitus, and menstrual irregularities), and mental (e.g., low self-esteem and depression) health problems exist for obese children and adolescents.[13]

The prevalence of overweight and obesity continues to increase, keeping this disease a major public health concern. Results from the most recent National Health and Nutrition Examination Survey (NHANES) reflect an increased combined prevalence for overweight and obesity among adults from 56% (1988–1994) to 65% (1999–2002).[14] Obesity alone has escalated 7%. Likewise, the number of overweight children and adolescents 6 to 19 years of age has increased by 5% during the same time frame.[14]

PATHOPHYSIOLOGY

While a correlation between body weight in parents and children exists, the specific gene or genes contributing to obesity are unknown.[15] Syndromes where obesity is a major component collectively contribute very little to the incidence of obesity.[16] The key factor in the development of overweight and obesity is the imbalance that occurs between energy intake and energy expenditure. The extent of obesity is determined by the length of time this imbalance has been present. Energy intake is affected by environmental influences, including social, behavioral, and cultural factors, whereas genetic composition and metabolism affect energy expenditure.[17]

Energy Intake

Food intake is regulated by various receptor systems. Direct stimulation of 5-HT_{1A} and noradrenergic α_2-receptors will increase food intake, whereas 5-HT_{2C} and noradrenergic α_1- or β_2-receptor activation decreases food intake. Stimulation of histamine receptor subtypes 1 and 3 and dopamine receptors 1 and 2 result in lower food consumption. Recently, the cannabinoid receptor (CB1), which is a G-protein-coupled receptor in the endocannabinoid system, has been identified and associated with food intake and regulation of energy homeostasis.[18–20] Inhibition of CB1 is shown to decrease the craving for food, resulting in weight loss when coupled with dietary and lifestyle modifications.[21] In addition to receptor-modulated food consumption, higher levels of the protein leptin are associated with decreased food intake.[22] In contrast, elevated levels of neuropeptide Y increase food intake.[22]

It is debatable whether obesity is related to total calorie intake or composition of macronutrients. Of the three macronutrients (i.e., carbohydrate, protein, and fat), fat has received the most attention given its desirable texture and its ability to augment the flavor of other foods. Food high in fat promotes weight gain in comparison with the other macronutrients because fat is more energy-dense. When compared with carbohydrate and protein, more than twice as many calories per gram are contained in fat. In addition, fat is stored more easily by the body compared with protein and carbohydrate.[23]

Energy Expenditure

A person's metabolic rate is the primary determinant of energy expenditure. Metabolic rate is enhanced following food consumption and directly related to the amount and type.[16] Physical inactivity may predispose an individual to overweight

TABLE 99–1. BMI Classification[6]

Underweight	Less than 18.5 kg/m^2
Normal weight	18.5 to 24.9 kg/m^2
Overweight	25 to 29.9 kg/m^2
Obesity (class 1)	30 to 34.9 kg/m^2
Obesity (class 2)	35 to 39.9 kg/m^2
Extreme obesity (class 3)	Greater than or equal to 40 kg/m^2

and obesity. In addition, endocrine-related disorders (e.g., hypothyroidism and Cushing's syndrome) may lower the metabolic rate, further contributing to the development of overweight and obesity.

CLINICAL PRESENTATION AND DIAGNOSIS

Any interaction between a patient and a health care provider presents an opportunity to evaluate the patient's height and weight. From these parameters, the BMI should be determined, as well as waist circumference and the presence of comorbidities or associated risks. ❶ *Body mass index (BMI), waist circumference, comorbidities, and readiness to lose weight are used in the assessment of the overweight or obese patient.* The BMI is calculated using the measured weight in kilograms divided by the height in meters squared (kg/m^2) for all patients regardless of gender. BMI then should be classified according to Table 99–1. When determining waist circumference, place a measuring tape at the top of the right iliac crest and proceed around the abdomen, ensuring that the tape is tight but not constricting the skin. The value is measured following normal expiration.[6] Table 99–2 defines high-risk waist circumference.[6] After obtaining measurable parameters, further assess the patient for the presence of comorbidities and cardiovascular risk factors. ❷ *Presence of comorbidities [coronary heart disease (CHD), atherosclerosis, type 2 diabetes mellitus, and sleep apnea] and cardiovascular risk factors (cigarette smoking, hypertension, elevated low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, impaired fasting glucose, family history of premature CHD, and age) requires identification and aggressive management for overall effective treatment of the overweight or obese patient.* A patient is at very high absolute risk if diagnosed with CHD or other atherosclerotic diseases, type 2 diabetes mellitus, or sleep apnea or if three or more of the risk factors listed in Table 99–3 are present.[6] Aggressive disease management should be initiated and not limited to weight loss.

TABLE 99–2. High-Risk Waist Circumference[6]

Men	Greater than 40 in (102 cm)
Women	Greater than 35 in (89 cm)

TABLE 99–3. Risk Factors[6,24]

Cigarette smoking
Hypertension (systolic blood pressure greater than or equal to 140 mm Hg or diastolic blood pressure greater than or equal to 90 mm Hg) or current use of blood-pressure-lowering medication(s)
Low-density lipoprotein cholesterol greater than or equal to 160 mg/dL (4.14 mmol/L)
Low-density lipoprotein cholesterol greater than or equal to 130 to 159 mg/dL (3.37 to 4.12 mmol/L) plus two additional risk factors
High-density lipoprotein cholesterol less than 35 mg/dL (0.91 mmol/L)
Impaired fasting glucose [fasting blood glucose 100–125 mg/dL (5.6 to 6.9 mmol/L)]
Family history of premature coronary heart disease (first-degree male relative less than 55 years of age or first-degree female relative less than 65 years of age)
Males greater than or equal to 45
Females greater than or equal to 55

TREATMENT

Desired Outcome

General management of obesity is directed at weight reduction, maintenance of weight loss, and prevention of weight regain. ❹ *The treatment goals for overweight and obesity are to prevent additional weight gain, reduce and maintain a lower body weight, and control related risks.* A 10% weight loss as derived from the patient's current weight is the initial goal of obesity management because favorable outcomes on the negative effects of obesity have been documented.[6,25] Weight loss should occur at a rate of 1 to 2 lb per week, meeting the initial goal within the first 6 months of therapy. Weight then should be maintained [minimal regain of less than 3 kg (6.6 lb) and continued reduction in waist circumference of 1.6 in (4 cm)].



Patient Encounter, Part 1

A 35-year-old woman with a history of hypertension presents to your clinic complaining of low energy and irritability. She reports not following any specific diet because they have all failed in the past. She does admit to eating out frequently. This patient does not exercise because her job and her kids are too demanding. Patient does smoke a half pack of cigarettes per day and consumes low-calorie, caffeinated and alcoholic drinks most days. Her BMI is 32 kg/m^2, and her waist circumference is 38 in (97 cm).

- What classification of overweight and obesity is appropriate for this patient?
- Does she have other risk factors that may contribute to morbidity and/or mortality?
- What additional information do you need to know before creating a treatment plan for this patient?

If weight loss has been achieved and/or maintained for 6 months, further therapy promoting weight loss may be considered. Once maximal weight loss has been attained, any therapy used to promote the weight loss must be sustained in order to prevent weight regain.[6] ❺ *Weight maintenance occurs following successful achievement of weight loss.*

General Approach to Treatment

Since the goals for obesity management are multifactorial, it should be considered a chronic illness where treatment is maintained for life. Any implemented therapy promoting weight loss should focus on behavior modification directed toward both dietary restriction and increased activity in conjunction with the selective use of pharmacologic or surgical intervention. Before initiating therapy, secondary causes of obesity (e.g., hypothyroidism and Cushing's syndrome) must be considered. If no secondary cause exists, the presence of other cardiovascular risk factors and comorbidities must be determined to guide clinical decisions. ❷ *Presence of comorbidities [coronary heart disease (CHD), atherosclerosis, type 2 diabetes mellitus, and sleep apnea) and cardiovascular risk factors (cigarette smoking, hypertension, elevated low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, impaired fasting glucose, family history of premature CHD, and age] requires identification and aggressive management for overall effective treatment of the overweight or obese patient.* Therapy implemented to minimize associated risk(s) may not enhance weight loss, but weight loss will positively address risk factors. Weight loss should not be initiated in pregnant or lactating patients, decompensated psychiatric patients, or patients in whom reduced caloric intake can exacerbate an acute, serious illness.[6] ❻ *Treatment of obesity includes lifestyle changes (dietary modification, enhanced physical activity, and behavioral therapy), pharmacologic treatment, surgical intervention, or a combination of modalities.*

Nonpharmacologic Therapy

Dietary

A low-calorie diet is essential for weight-loss management in overweight and obese patients. The Step 1 Diet (Table 99–4) is a low-calorie diet (LCD) recommended as part of an obesity education initiative from the National Heart, Lung, and Blood Institute.[6] In general, the Step 1 Diet restricts daily calories to a range of 1000 to 1200 kcal (4184 to 5021 kJ)/day for women weighing less than 165 lb (75 kg) and 1400 to 1600 kcal (5858 to 6694 kJ)/day for all others. However, this daily limit should be considered after assessing a patient's normal daily caloric intake and ensuring that the initial caloric restriction does not exceed 500 to 1000 kcal (2092–4184 kJ)/day. For example, a male patient who consumes 3000 kcal (12.552 kJ)/day should not reduce his daily caloric intake to less than 2000 kcal (8368 kJ)/day when initially implementing a dietary program. Further reduction to the target of 1600 kcal (6694 kJ)/day can be attempted once the patient has reduced calories successfully as initially recommended for a period agreeable by the provider and the patient.[6] Diets too restrictive in calorie reduction are successful initially but fail long term because compliance is difficult to sustain.[26] Therefore, this less aggressive approach promotes gradual weight loss and weight maintenance.

Dietary consumption should be balanced in carbohydrates, protein, and fat. Several diet plans exist that promote weight loss through strict limitation or overabundance of only one macronutrient (e.g., low-fat, low-carbohydrate, or high-protein diets); however, overall energy consumption and expenditure will determine the amount of weight alteration. Consultation with a dietician is recommended when

TABLE 99–4. Low-Calorie Step I Diet[6]

Nutrient	Recommended Intake
Calories[a]	Approximately 500 to 1000 kcal/day (2092 to 4184 kJ/day) reduction from usual intake
Total fat[b]	30% or less of total calories
Saturated fatty acids[c]	8–10% of total calories
Monounsaturated fatty acids	Up to 15% of total calories
Polyunsaturated fatty acids	Up to 10% of total calories
Cholesterol[c]	Less than 300 mg/day
Protein[d]	Approximately 15% of total calories
Carbohydrate[e]	55% or more of total calories
Sodium chloride	No more than 100 mmol/day (approximately 2.4 g of sodium or approximately 6 g of sodium chloride)
Calcium[f]	1000 to 1500 mg/day
Fiber[e]	20 to 30 g/day

[a]A reduction in calories of 500 to 1000 kcal/day (2092 to 4184 kJ/day) will help achieve a weight loss of 1 to 2 lb/week (0.45 to 0.9 kg/week). Alcohol provides unneeded calories and displaces more nutritious foods. Alcohol consumption not only increases the number of calories in a diet but has been associated with obesity in epidemiologic studies as well as in experimental studies. The impact of alcohol calories on a person's overall caloric intake needs to be assessed and appropriately controlled.

[b]Fat-modified foods may provide a helpful strategy for lowering total fat intake but will only be effective if they are also low in calories and if there is no compensation by calories from other foods.

[c]Patients with high blood cholesterol levels may need to use the Step II diet to achieve further reductions in LDL-cholesterol levels; in the Step II diet, saturated fats are reduced to less than 7% of total calories, and cholesterol levels to less than 200 mg/day. All of the other nutrients are the same as in Step I.

[d]Proteins should be derived from plant sources and lean sources of animal protein.

[e]Complex carbohydrates from different vegetables, fruits, and whole grains are good sources of vitamins, minerals, and fiber. A diet rich in soluble fiber, including oat bran, legumes, barley, and most fruits and vegetables, may be effective in reducing blood cholesterol levels. A diet high in all types of fiber may also aid in weight management by promoting satiety at lower levels of calorie and fat intake. Some authorities recommend 20 to 30g of fiber daily, with an upper limit of 35g.

[f]During weight loss, attention should be given to maintaining an adequate intake of vitamins and minerals. Maintenance of the recommended calcium intake of 1000 to 1500 mg/day is especially important for women who may be at risk of osteoporosis.

TABLE 99–5. Examples of Moderate Physical Activity[6]

Common Chores[a,b]	Sporting Activities[a,b]
Washing and waxing a car for 45–60 minutes	Playing volleyball for 45–60 minutes
Washing windows or floors for 45–60 minutes	Playing touch football for 45 minutes
Gardening for 30–45 minutes	Walking 1¾ miles in 35 minutes (20 minute/mile)
Wheeling self in wheelchair for 30–40 minutes	Basketball (shooting baskets) for 30 minutes
Pushing a stroller 1½ miles in 30 minutes	Bicycling 5 miles in 30 minutes
Raking leaves for 30 minutes	Dancing fast (social) for 30 minutes
Walking 2 miles in 30 minutes (15 minute/mile)	Water aerobics for 30 minutes
Shoveling snow for 15 minutes	Swimming laps for 20 minutes
Stairwalking for 15 minutes	Basketball (playing a game) for 15–20 minutes
	Jumping rope for 15 minutes
	Running 1½ miles in 15 minutes (15 minute/mile)

[a]A moderate amount of physical activity is roughly equivalent to physical activity that uses approximately 150 calories of energy per day, or 1000 calories per week.
[b]Some activities can be performed at various intensities; the suggested duration correspond to expected intensity of effort.

implementing a healthy meal plan tailored to the individual's nutritional needs.

Exercise

While diet and exercise contribute to weight loss, combining a low-calorie diet with physical activity results in greater weight loss compared with either therapy alone.[25] Additionally, physical activity can help to prevent weight regain and reduce related cardiovascular risks.[6] Slow titration of both the amount and intensity of physical activity is recommended for most overweight and obese patients.[6] A program that incorporates daily walking is a viable option for most patients (Table 99–5). Consider 10 minutes per day 3 days per week with a target of 30 to 45 minutes most days, if not every day.[6,27] This type and amount of activity equate to a 100 to 200 kcal (418–836 kJ)/day caloric expenditure.[6]

Behavioral

Non-adherence with recommended lifestyle changes may result in unsuccessful weight loss.[6,25] Therefore, eliminating these barriers through behavior modification is necessary to gain maximal benefit from both dietary modification and exercise. Components to successful behavioral modification include, but are not limited to, the following steps:

- Determine the patient's readiness to lose weight and willingness to implement a weight-loss plan.
- Build and nurture the patient-provider partnership.
- Restructure cognitive abilities.
- Set achievable goals.
- Contact the patient frequently.
- Instruct the patient on the importance and technique of self-monitoring.
- Control stimuli that negatively affect weight loss or weight maintenance.
- Reward the patient for any amount of weight loss or avoidance of weight regain.

Pharmacologic Therapy

Pharmacotherapy is not recommended for individuals with a BMI of less than 27 kg/m^2. However, drug therapy, in addition to a healthy lifestyle, is warranted for overweight individuals with other related risks and for obese patients. ❼ *Pharmacotherapy, in addition to lifestyle modification, is reserved for patients with a BMI of 30 kg/m^2 or greater or a BMI of 27 kg/m^2 or greater with other obesity-related risk factors.* Currently available pharmacologic products are classified according to their mechanism of action, which includes the suppression of appetite and the suppression of fat absorption (Table 99–6). Therapy was indicated previously for short-term use; however, as obesity-related risks resurface with weight regain, long-term treatment is recommended to minimize these sequelae. ❽ *Weight likely will be regained if lifestyle changes are not continued indefinitely.* Prolonged use of both fenfluramine and dexfenfluramine monotherapy and fenfluramine and phentermine in combination (Fen-Phen) resulted in cardiac valvular disease.[28] Therefore, only two drugs are currently approved for long-term use in promoting weight loss and preventing weight regain. Sibutramine (Meridia®, Abbott Laboratories) was approved by the Food and Drug Administration (FDA) in 1997, and orlistat (Xenical®, Roche Pharmaceuticals) received FDA approval in 1999. Rimonabant is a new medication entity currently under study in phase III clinical trials.

Sibutramine

Sibutramine and its two active metabolites (M_1 and M_2) exert their effect by inhibiting the reuptake of serotonin, norepinephrine, and dopamine.[29] Appetite becomes suppressed because patients feel a sense of satiety.

The effect of prolonged sibutramine use on morbidity and mortality is unknown. Most studies vary in dose and length, from 1 to 30 mg/day and 3 to 12 months of use, respectively.[29] Weight loss appears proportional to the dose of sibutramine used, with greater weight loss observed using higher doses of sibutramine.[29] In one trial, subjects randomized to placebo lost an average of 1.4 kg compared with an average loss of 2.9 and 5 kg using a 5 and 20 mg/day dose of sibutramine, respectively.[30] Two longer-term studies have documented maximal weight loss following 6 months of sibutramine therapy and sustained weight loss over 12 months of use.[29] Three trials with a study duration of greater than 6 months suggest that

TABLE 99–6. Summary of Approved Pharmacologic Weight-Loss Agents

Drug	Class	Daily Dose	Duration of Therapy
Sibutramine	Noradrenergic/serotonergic agent	5–15 mg	Greater than 3 months[a]
Orlistat	Lipase inhibitor	360 mg	Greater than 3 months[b]
Phentermine	Noradrenergic agent	15–37.5 mg	Up to 6 months
Diethylpropion	Noradrenergic agent	75 mg	Up to 12 months

[a]Efficacy and safety have not been determined beyond 2 years of use.
[b]Efficacy and safety have not been determined beyond 4 years of use.

subjects losing 4 lb within 4 weeks of sibutramine initiation are more likely to achieve long-term weight loss.[29] Conversely, sibutramine may not be effective for patients who do not achieve a weight loss of 4 lb within the initial 4 weeks.

Pediatric use has not been established in patients younger than 16 years of age and thus is not recommended.[29]

Since an increased waist circumference is associated with increased risk for type 2 diabetes mellitus, hyperlipidemia, hypertension, and CVD, a decrease then should reduce risk. A significant dose-related reduction in waist circumference has been reported in 6- and 12-month sibutramine trials.[29] Blood glucose and lipid parameters are not adversely affected, but a small rise in blood pressure and pulse has been observed in clinical trials. On average, the blood pressure increased by 1 to 3 mm Hg, and the heart rate increased by 4 to 5 beats per minute. Larger increases have been observed for both blood pressure and heart rate when higher doses of sibutramine were studied. Sibutramine should be used cautiously in patients with hypertension or other disease states resulting in elevated blood pressure and/or pulse. Sibutramine is not recommended for patients with a history of congestive heart failure, CVD, arrhythmias, or stroke. Blood pressure and heart rate should be measured prior to initiating sibutramine and reassessed at regular intervals. A dose reduction or discontinuation of sibutramine should be considered for patients experiencing a sustained elevation in either blood pressure or heart rate. More common adverse reactions include dry mouth, anorexia, insomnia, constipation, and headache.

Although not evaluated systematically, drugs that exhibit their effect on the central nervous system may interact with sibutramine. Since sibutramine inhibits the reuptake of serotonin, use of this drug in combination with a monoamine oxidase inhibitor (MAOI) can elevate blood levels of serotonin, resulting in a serious, potentially fatal reaction known as the *serotonin syndrome.* This syndrome consists of a collection of symptoms that includes one or more of the following: excitement, hypomania, restlessness, loss of consciousness, confusion, disorientation, anxiety, agitation, motor weakness, **myoclonus,** tremor, **hemiballismus,** hypereflexia, ataxia, dysarthria, incoordination, hyperthermia, shivering, pupillary dilation, diaphoresis, emesis, and tachycardia. Two weeks should elapse between discontinuation of the MAOI (or sibutramine) and initiation of sibutramine (or MAOI) to avoid this potentially serious interaction. Concomitant administration of other serotonergic drugs (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, and venlafaxine) and sibutramine also should be avoided to eliminate the risk of serotonin syndrome.[29] Co-administration of a decongestant and sibutramine may increase blood pressure or heart rate. Cytochrome P-450 inhibitors, including ketoconazole, erythromycin, and cimetidine, in combination with sibutramine have resulted in increased blood levels of sibutramine; however, the clinical relevance of this is unknown.[29] Highly protein-bound drugs such as warfarin or phenytoin have the potential to interact with sibutramine because it too is highly protein-bound. No data exist to evaluate the extent of this interaction.[29]

Since no human data exist to determine its safe use in pregnant women, sibutramine is not recommended; therefore, women of childbearing potential should use effective methods of contraception while taking sibutramine. Further, sibutramine is not recommended for lactating mothers because its excretion in breast milk is likewise unknown.[29]

Initiate sibutramine at a dose of 10 mg once daily, preferably in the morning without regard to meals. The dose may be increased after 4 weeks to 15 mg once daily if weight-loss goals are not attained. Doses exceeding 15 mg/day are not recommended. For patients intolerant of the 10 mg/day, a dose of 5 mg once a day may be used.[29]

Orlistat

Orlistat promotes and maintains weight loss by acting locally in the gastrointestinal (GI) tract. Orlistat is a chemically synthesized derivative of lipstatin, a natural product of *Streptomyces toxitricini* that inhibits pancreatic and gastric lipases, as well as triglyceride hydrolysis. As a result, undigested triglycerides are not absorbed, causing a caloric deficit and weight loss.[31]

Several studies have reported significant weight loss for patients receiving orlistat 120 mg three times a day compared with placebo.[32,33] Weight maintenance or prevention of weight regain also has been documented with continued orlistat use.[32,34] After 1 year of treatment, 57% of orlistat-treated patients lost at least 5% of their baseline weight.[31] The long-term weight-loss effect on one obesity-related comorbidity was assessed in a large placebo-controlled study. In 3000 obese patients, 21% had impaired glucose tolerance at enrollment.

After 4 years, weight loss was greater and the incidence of new diabetes was lower in patients receiving orlistat.[35]

The effect of orlistat in adolescent patients has been evaluated recently. In a group of 12- to 16-year-old individuals, orlistat (120 mg three times daily) in combination with diet, exercise, and behavior modification exhibited minimal weight increase after 1 year (0.53 kg) compared with placebo-treated patients (3.14 kg). Common adverse reactions observed were fatty or oily stools, oily spotting, oily evacuation, or abdominal pain and/or flatulence with bowel movements. Soft stools, nausea, increased defecation, and fecal incontinence also were noted. Orlistat may be better suited for prevention of weight gain in tolerant adolescents, but more studies are warranted before providing a solid recommendation.[36]

The safety and efficacy of orlistat have not been determined beyond 4 years of use. Minimal systemic effects exist because orlistat acts locally in the GI tract. Thus, common side effects reported include oily spotting, flatus with discharge, fecal urgency, fatty/oily stools, oily evacuation, increased defecation, and fecal incontinence.[31] Other adverse events include bloating, abdominal pain, dyspepsia, nausea, vomiting, diarrhea, and headache.[37]

Orlistat reduces the absorption of fat-soluble vitamins. Daily intake of a multivitamin containing vitamins A, D, E, and K, as well as β-carotene, is recommended. Patients should take the multivitamin 2 hours prior to or after the dose of orlistat.[31] Since availability of vitamin K may decline in patients receiving orlistat therapy, close monitoring of coagulation status should occur with concomitant administration of warfarin.[31] Administration of orlistat in conjunction with cyclosporine can result in decreased cyclosporine plasma levels. To avoid this interaction, cyclosporine should be taken 2 hours preceding or following the dose of orlistat. Additionally, cyclosporine levels should be monitored more frequently.[31]

Pregnant or lactating women should not take orlistat because no data exist to establish safety. Orlistat is contraindicated in patients with chronic malabsorption syndrome or cholestasis.[31]

Initiate orlistat 120 mg three times a day with a well-balanced but reduced-caloric meal containing no more than 30% of calories from fat. Orlistat may be taken during or up to 1 hour after the meal. If a meal is missed or contains little fat, the dose of orlistat may be omitted. Doses above 360 mg/day provide no greater benefit and thus are not recommended.

Rimonabant

Rimonabant is a selective CB1 receptor antagonist that is currently under investigation in phase III trials. CB1 receptors are found in the brain, adipose tissue, the GI tract, pituitary and adrenal glands, sympathetic ganglia, heart, lungs, liver, and bladder.[17,18] Food cravings are diminished following inhibition of this receptor.[19]

A 2-year study is currently being conducted. Results from the first year of this 24-month study have been evaluated. Individuals enrolled are 18 years of age and older with a BMI of greater than 30 kg/m^2 or a BMI greater than 27 kg/m^2 with hypertension or dyslipidemia. Patients are randomized to receive rimonabant 5 mg, rimonabant 20 mg, or placebo. All patients are prescribed a hypocaloric diet. After 1 year, rimonbant showed significant absolute weight reduction compared with placebo (5 mg versus placebo, $p = 0.002$, and 20 mg versus placebo, p less than 0.001). Weight was reduced by 4.8 and 8.6 kg in the 5- and 20-mg rimonabant groups, respectively. Waist circumference decreased by 5.3 and 8.5 cm, respectively, for the two treatment groups. Improvement in blood pressure, lipid concentrations, and insulin resistance has been observed for rimonabant. Adverse events commonly reported include nausea, vomiting, dizziness, arthralgia, headache, anxiety, and diarrhea. Adverse events were more prevalent in the patients taking rimonabant 20 mg compared with those taking rimonabant 5 mg or placebo.[19]

Drug-drug and drug-disease interactions have not been evaluated extensively. One precaution to consider when using rimonabant includes increased GI motility.[19] Increased monitoring of patients with diabetes or hyperlipidemia may be necessary given that decreased insulin resistance, increased glucose tolerance, decreased triglycerides, and increased high-density lipoprotein are observed when CB1 receptors are blocked in adipose tissue.[19]

Phentermine

Phentermine decreases food intake, and hence weight, by increasing norepinephrine and dopamine release in the central nervous system. This drug is indicated for short-term use—no more than a few weeks—in addition to lifestyle modifications in obese patients with a BMI of 30 kg/m^2 or greater or a BMI of 27 kg/m^{2-} or greater in the presence of other risk factors.[38]

A recent meta-analysis evaluated patients at doses of 15 and 30 mg daily. Patients were analyzed for periods of 2 to 24 weeks. The majority of patients enrolled were female, and more than 80% of the patients evaluated received adjunctive modification in lifestyle. An average weight loss of 3.6 kg (7.9 lbs) was demonstrated for patients treated with phentermine compared with placebo. Although modest in amount, this value was statistically significant.[37]

Safety and efficacy have not been determined in pediatric patients.[38]

Common adverse reactions seen with phentermine use include heart palpitations, tachycardia, elevated blood pressure, stimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, dry mouth, constipation, and diarrhea. Phentermine should be avoided in patients with unstable cardiac status, hypertension, hyperthyroidism, agitated states, or glaucoma. In combination with fenfluramine or dexfenfluramine, pulmonary hypertension and valvular heart disease have been reported. The risk of developing either serious adverse effect cannot be ruled out with use of phentermine alone. Since phentermine is related to the amphetamines, the

potential for abuse is high; thus, this should be kept in mind when selecting this agent as an aid for weight loss.[38]

Phentermine use should be avoided in patients concomitantly receiving or having received an MAOI within the preceding 14 days. Combination therapy with any stimulant or MAOI has the potential for causing hypertensive crisis. Alcohol is not recommended for patients prescribed phentermine.[38]

Since no studies have been conducted in pregnant women, phentermine should be administered only when clearly indicated. Owing to the potential for severe adverse effects in nursing infants, a decision to stop the drug or discontinue nursing must be made.[38]

Phentermine is available as an immediate-release and a sustained-release product. In conjunction with a healthy lifestyle, 30 to 37.5 mg of phentermine is administered once daily, typically before breakfast or 1 to 2 hours following the morning meal. The dosage should be individualized; some patients may be managed adequately at 15 to 18.75 mg daily, whereas a dose of 18.75 mg twice daily may be used to minimize side effects, excluding insomnia. To lessen the risk of insomnia, dosing phentermine in the evening should be avoided. Timed-release preparations of phentermine are not recommended because phentermine's half-life is approximately 20 hours.[39]

Diethylpropion

This sympathomimetic amine exudes similar pharmacologic activity as the amphetamines, resulting in central nervous system stimulation and appetite suppression. This drug is indicated for short-term use in conjunction with a reduced-calorie diet and exercise in obese patients with a BMI of 30 kg/m^2 or greater following failed attempts of diet and exercise alone.[40]

One meta-analysis reviewed patients receiving doses of 75 mg daily during periods of 6 to 52 weeks. Similar to study characteristics for phentermine, the majority of patients enrolled were female, and all patients implemented adjunctive lifestyle modifications. The average additional weight loss observed was 3 kg (6.6 lbs) compared with diet and exercise alone, resulting in a borderline statistically significant difference.[37]

Safety and effectiveness of diethylpropion have not been established in patients under the age of 16; therefore, its use is not recommended.[40]

Use of diethylpropion for a period longer than 3 months is associated with an increased risk for development of pulmonary hypertension. When used as directed, reported common central nervous system adverse effects included overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, jitteriness, anxiety, nervousness, depression, drowsiness, malaise, **mydriasis,** and blurred vision. In addition, diethylpropion can decrease seizure threshold, subsequently increasing a patient's risk for an epileptic event. Other organ systems also can adversely be affected, resulting in tachycardia, elevated blood pressure, palpitations, dry mouth, abdominal discomfort, constipation, diarrhea, nausea, vomiting, impotence or change in libido, gynecomastia, bone marrow suppression, agranulocytosis, and leukopenia. Diethylpropion is contraindicated in patients with pulmonary hypertension, advanced arteriosclerosis, severe hypertension, hyperthyroidism, agitated states, or glaucoma. Since diethylpropion is related to the amphetamines, the potential for abuse is high, and therefore, its use is contraindicated in patients with a history of substance abuse.[40]

As with phentermine, use of diethypropion should be avoided in patients concomitantly receiving or having received an MAOI within the preceding 14 days to prevent hypertensive crisis. Combination with other anorectic agents should be avoided.[40]



Patient Encounter, Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH
- Hypertension for 3 years, currently at goal
- Depression

FH
Father alive at 58 years of age. Mother also alive with a history of obesity and depression.

SH
Registered nurse. Drinks one beer nightly after work. Smokes a half pack of cigarettes per day.

Current Meds
- Irbesartan 150 mg once daily
- Hydrochlorothiazide 25 mg once daily
- Fluoxetine 20 mg once daily

ROS
(+) heartburn, regurgitation; (–) chest pain, nausea, vomiting, diarrhea, change in appetite, SOB, or cough

PE
- **VS:** Blood pressure 120/82, heart rate 82, respiratory rate 16, temperature 37°C (98.6°F)
- **Weight:** 240 lb (109 kg)
- **Height:** 64 in (163 cm)
- **Waist circumference:** 38 in (97 cm)
- **Cardiovascular:** Regular rate and rhythm; no murmurs, rubs, or gallops
- **Abd:** Obese, soft, non-tender, non-distended; (+) bowel sounds
- **Exts:** (–) edema
- **Laboratory:** All values are within normal limits.
- **Electrocardiogram:** No evidence of past ischemia.

- Given this additional information, what is your assessment of this patient?
- Identify your treatment goals for the patient.
- What nonpharmacologic and pharmacologic alternatives are available for this patient?

No adequate studies have been conducted using diethylpropion in pregnant women; therefore, the drug should be used only if the benefit outweighs potential fetal risk. Use with caution in nursing mothers because the drug is excreted in breast milk.[40]

Diethylpropion is available as both an immediate-release and a controlled-release product. In conjunction with a reduced-calorie diet and/or exercise, dose diethylpropion (immediate-release) 25 mg three times a day before meals or 75 mg (controlled-release) once a day, usually midmorning.[40]

Other noradrenergic agents not approved by the Food and Drug Administration (FDA) and subsequently not recommended for weight loss include amphetamine salts (e.g., ephedrine and phenylpropanolamine), methamphetamine, and benzophetamine. Although the selective serotonin reuptake inhibitors (e.g., fluoxetine and sertraline) appear to promote weight loss, further study is warranted given the inconsistent results available to date. Dietary supplements containing ephedra or ephedrine alkaloids are banned from sale following the FDA's final ruling.[41] However, ephedrine is available in over-the-counter and prescription formulations for the treatment of bronchospasm, nasal congestion, hypotension/shock, and cardiac arrhythmias. Herbal products lack consistency in labeling, vary in effect, and present potentially dangerous health risks. Herbal products are not recommended.

Surgical Intervention

Weight-reduction (bariatric) surgery is an option for patients whose BMIs are 40 kg/m^2 or greater or 35 kg/m^2 or greater in the presence of other comorbid conditions and who have failed more conventional approaches to weight loss.[6,42] ❾ *Surgery is warranted when other treatment attempts have failed in severely obese patients (BMI of 40 kg/m^2 or greater or35 kg/m^2 or greater with obesity-related risk factors).* There are two basic surgical techniques: (1) gastric bypass—the full partitioning of the proximal gastric segment into a jejunal loop of the intestine—whereby weight loss is induced through both malabsorption of food and limited gastric capacity, and (2) gastroplasty—incomplete partitioning at the proximal gastric segment with the placement of a gastric outlet stoma of set diameter—which promotes weight loss by limiting gastric capacity.[6,42]

A recent meta-analysis of surgical options for obesity reported that surgical treatment produces a weight loss of 20 to 30 kg (44–66 lbs) that is maintained for 5 to 10 years. Additionally, favorable outcomes for comorbid conditions are observed following surgery. When evaluating the various types of surgery available, pooled data concluded that gastric bypass produces a 10 kg (22 lbs) greater weight loss at 12 and 36 months than gastroplasty procedures. Complications are inherent to any surgical procedure. The more common bariatric surgery complications are respiratory problems, wound formation, wound infections, hernia development, deep venous thrombosis, and pulmonary embolism. No differences were observed in mortality rates among various surgical procedures. Postoperative weight loss is much greater when compared with pharmacologic therapies, but no comparative trials exist.[43]

Candidates for bariatric surgery should be part of an integrated program of health education, diet, exercise, and behavioral modification before and following surgery.[6] Patients must understand and commit to a substantial change in eating patterns to maintain long-term weight reduction.[43]

SPECIAL POPULATION CONSIDERATIONS

Childhood/Adolescent Patients with Obesity

Although the prevalence of overweight and obesity is increasing among children and adolescents, current guidelines do not incorporate treatment recommendations because long-term outcome data are limited. As such, prevention of childhood obesity is a national priority for the National Academies' Institute of Medicine (IOM) and cannot succeed without the engagement of those entities (e.g., family, school, and community) that affect the environment and behavior of American youths. The IOM report establishes steps to confront this epidemic and includes the involvement of the federal, state, and local governments; industry and media; health care professionals; community organizations; state and local schools; and parents and families.[44]

The BMI should be calculated for all children and adolescents yearly to identify excessive weight gain relative to linear growth. Education and encouragement should be provided to parents or caregivers to promote healthy eating patterns and self-regulation of food intake. Examples include support for healthy snack selections and parent (caregiver) modeling of nutritious food consumption. Routine physical activity should be advocated, as well as limiting television viewing and video time to 2 hours daily. If children or adolescent patients are overweight or obese, assessment of obesity-related risk factors also should occur.[13]

Elderly Patients with Obesity

The prevalence of obesity in older adults is increasing; therefore, it should not be surprising that more cardiovascular risk factors are present in this group of individuals. Additionally, obesity is a major predictor of functional limitation and mobility problems in older persons. Age alone should not prejudice the clinician from treating geriatric patients, whereas the benefits of cardiovascular health and functionality should be considered. Treatments should be initiated that minimize adverse effects on bone health and nutritional status and should include dietary and activity modifications.[6]



Patient Encounter, Part 3: Creating a Care Plan

Based on the information presented, create a care plan for this patient's obesity. Your plan should include (1) a statement of the drug-related problems, (2) the goals of therapy, (3) a detailed patient-specific therapeutic plan, and (4) a monitoring plan that would determine if goals are achieved and adverse effects avoided.

OUTCOME EVALUATION

Successful management of overweight and obesity is determined by the ability the treatment plan has to (1) prevent weight gain, (2) reduce and maintain a lower body weight, and (3) decrease the risk of obesity-related comorbidities. Since weight is necessary to calculate the BMI, it, as well as waist circumference, should be determined. Obesity management may encompass more than weight loss or maintenance in the presence of other conditions; other pertinent parameters should be assessed at baseline. The presence of hypertension, type 2 diabetes, hyperlipidemia, CAD, sleep apnea, hypothyroidism, osteoarthritis, gallbladder disease, gout, or cancer should be determined. Blood pressure and heart rate should be measured prior to implementation of any therapy. Certain laboratory parameters also should be assessed. A basic metabolic panel, liver function tests, complete blood count, fasting lipid profile, full thyroid function tests, and other laboratory studies as deemed necessary should be obtained. An electrocardiogram should be performed if recent results are unknown.

The patient should be assessed in 2 to 4 weeks following the implementation of therapy to determine effectiveness of and intolerance to treatment. Monthly visits are encouraged during the first 3 months. More frequent follow-up may be necessary in the presence of other medical conditions. Less frequent follow-up occurs after 6 months of effective weight-loss therapy.

At each follow-up visit, compliance with a healthy lifestyle should be determined, as well as measurement of physical parameters, including weight, blood pressure, and heart rate. Waist circumference should be measured intermittently. A complete assessment also would include identification of adverse drug reactions or drug interactions if weight-loss medications have been initiated.

Once the patient has achieved the recommended weight loss, he or she then enters the weight-maintenance phase, which includes continued contact for education, guidance, and risk-factor assessment. If weight loss is not attained, further assessment is required to determine why the goals of therapy have not been met. The interaction should be directed toward determining the motivation to lose weight, balance between caloric intake and physical activity, adherence to behavioral therapy, and determination of psychological stressors present.



Patient Care and Monitoring

1. Determine if history of BMI greater than 25 kg/m^2. If unavailable or BMI unknown, obtain weight, height, and waist circumference. Calculate the BMI. Assess the patient's willingness to lose weight.
2. If the BMI is greater than 25 kg/m^2 or waist circumference is greater than 35 in (89 cm) for females or 40 in (102 cm) for male patients, determine the presence of risk factors.
3. Prevention of weight gain is recommended in all patients with a BMI of 25 kg/m^2 or greater. Weight loss is indicated for patients with a BMI of 25 to 29.9 kg/m^2 or an elevated waist circumference with two or more risk factors or for any patient with a BMI of 30 kg/m^2 or greater.
4. Educate the patient regarding a healthy lifestyle, one that includes a balance between caloric intake and energy expenditure, as well as suggest methods to modify behavior.
5. If the patient presents with a desire to lose weight, develop treatment goals and weight-loss strategies (e.g., nonpharmacologic, drug therapy, or surgical intervention), including control of associated risks.
6. Close monitoring should follow to assess weight, BMI, waist circumference, and presence of complications related to the treatment plan. If weight-loss goals are not attained, determine reasons for failure.

ABBREVIATIONS

BMI:	body mass index
CAD:	coronary artery disease
CB1:	cannabinoid receptor
CHD:	coronary heart disease
CVD:	cardiovascular disease
FDA:	Food and Drug Administration
GERD:	gastroesophageal reflux disease
IOM:	Institute of Medicine
kcal:	kilocalories (= calorie = 1000 calories)
kJ:	kilojoules
LCD:	low-calorie diet
MAOI:	monoamine oxidase inhibitor
NHANES:	National Health and Nutrition Examination Survey
NHLBI:	National Heart, Lung and Blood Institute
5-HT$_{1A}$:	serotonin 1A sub-type
5-HT$_{2C}$:	serotonin 2C sub-type

Reference lists and self-assessment questions and answers are available at www.ChisholmPharmacotherapy.com.

Log into the website: www.pharmacotherapyprinciples.com for information on obtaining continuing education credit for this chapter.

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APPENDIX A CONVERSION FACTORS AND ANTHROPOMETRICS*

CONVERSION FACTORS

SI Units

SI (*le Systéme International d'Unités*) units are used in *many* countries to express clinical laboratory and serum drug concentration data. Instead of employing units of mass (such as micrograms), the SI system uses moles (mol) to represent the amount of a substance. A molar solution contains 1 mol (the molecular weight of the substance in grams) of the solute in 1 L of solution. The following formula is used to convert units of mass to moles (mcg/mL to μmol/L or, by substitution of terms, mg/mL to mmol/L or ng/mL to nmol/L).

Micromoles per Liter (μmol/L)

$$\mu\text{mol/L} = \frac{\text{drug concentration (mcg/mL)} \times 1000}{\text{molecular weight of drug (g/mol)}}$$

Milliequivalents

An equivalent weight of a substance is that weight which will combine with or replace 1 g of hydrogen; a milliequivalent is 1/1000 of an equivalent weight.

Milliequivalents per Liter (mEq/L)

$$\text{mEq/L} = \frac{\text{weight of salt (g)} \times \text{valence of ion} \times 1000}{\text{molecular weight of salt}}$$

$$\text{Weight of salt (g)} = \frac{\text{mEq/L} \times \text{molecular weight of salt}}{\text{valence of ion} \times 1000}$$

Approximate Milliequivalents

Weights of Selected Ions

Salt	mEq/g Salt	mg Salt/mEq
Calcium carbonate ($CaCO_3$)	20.0	50.0
Calcium chloride ($CaCl_2 \cdot 2H_2O$)	13.6	73.5
Calcium gluceptate ($Ca[C_7H_{13}O_8]_2$)	4.1	245.2
Calcium gluconate ($Ca[C_6H_{11}O_7]_2 \cdot H_2O$)	4.5	224.1
Calcium lactate ($Ca[C_3H_5O_3]_2 \cdot 5H_2O$)	6.5	154.1
Magnesium gluconate ($Mg[C_6H_{11}O_7]_2 \cdot H_2O$)	4.6	216.3
Magnesium oxide (MgO)	49.6	20.2
Magnesium sulfate ($MgSO_4$)	16.6	60.2
Magnesium sulfate ($MgSO_4 \cdot 7H_2O$)	8.1	123.2
Potassium acetate ($K[C_2H_3O_2]$)	10.2	98.1
Potassium chloride (KCl)	13.4	74.6
Potassium citrate ($K_3[C_6H_5O_7] \cdot H_2O$)	9.2	108.1
Potassium iodide (KI)	6.0	166.0
Sodium acetate ($Na[C_2H_3O_2]$)	12.2	82.0
Sodium acetate ($Na[C_2H_3O_2] \cdot 3H_2O$)	7.3	136.1
Sodium bicarbonate ($NaHCO_3$)	11.9	84.0
Sodium chloride ($NaCl$)	17.1	58.4
Sodium citrate ($Na_3[C_6H_5O_7] \cdot 2H_2O$)	10.2	98.0
Sodium iodide (NaI)	6.7	149.9
Sodium lactate ($Na[C_3H_5O_3]$)	8.9	112.1
Zinc sulfate ($ZnSO_4 \cdot 7H_2O$)	7.0	143.8

Valences and Atomic Weights of Selected Ions

Substance	Electrolyte	Valence	Molecular Weight
Calcium	Ca^{2+}	2	40.1
Chloride	Cl^-	1	35.5
Magnesium	Mg^{2+}	2	24.3
Phosphate (pH = 7.4)	HPO_4^- (80%) $H_2PO_4^-$ (20%)	1.8	96.0[a]
Potassium	K^+	1	39.1
Sodium	Na^+	1	23.0
Sulfate	SO_4^-	2	96.0[a]

[a]The molecular weight of phosphorus only is 31; that of sulfur only is 32.1.

*This appendix contains information from Appendices 1 and 2 of Anderson PO, Knoben JE, Troutman WG, et al (eds). *Handbook of Clinical Drug Data,* 10th ed. New York: McGraw-Hill, 2002:1053–1058, with permission.

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Anion Gap

The anion gap is the concentration of plasma anions not routinely measured by laboratory screening. It is useful in the evaluation of acid-base disorders. The anion gap is greater with increased plasma concentrations of endogenous species (e.g., phosphate, sulfate, lactate, and ketoacids) or exogenous species (e.g., salicylate, penicillin, ethylene glycol, ethanol, and methanol). The formulas for calculating the anion gap are as follows:

$$\text{Anion gap} = (Na^+ + K^+) - (Cl^- + HCO_3^-)$$

or

$$\text{Anion gap} = Na^+ - (Cl^- + HCO_3^-)$$

where the expected normal value for the first equation is 11 to 20 mmol/L, and the expected normal value for the second equation is 7 to 16 mmol/L. Note that there is a variation in the upper and lower limits of the normal range.

Temperature

Fahrenheit to Centigrade: (°F – 32) × 5/9 = °C
Centigrade to Fahrenheit: (°C × 9/5) + 32 = °F
Centigrade to Kelvin: °C + 273 = °K

Calories

1 Calorie = 1 kilocalorie = 1000 calories = 4.184 kilojoules (kJ)
1 kilojoule = 0.239 calories = 0.239 kilocalories = 239 calories

Weights and Measures

Metric Weight Equivalents

1 kilogram (kg) = 1000 grams
1 gram (g) = 1000 milligrams
1 milligram (mg) = 0.001 gram
1 microgram (mcg, µg) = 0.001 milligram
1 nanogram (ng) = 0.001 microgram
1 picogram (pg) = 0.001 nanogram
1 femtogram (fg) = 0.001 picogram

Metric Volume Equivalents

1 liter (L) = 1000 milliliters
1 deciliter (dL) = 100 milliliters
1 milliliter (mL) = 0.001 liter
1 microliter (µL) = 0.001 milliliter
1 nanoliter (nL) = 0.001 microliter
1 picoliter (pL) = 0.001 nanoliter
1 femtoliter (fL) = 0.001 picoliter

Apothecary Weight Equivalents

1 scruple (℈) = 20 grains (gr)
60 grains (gr) = 1 dram (ʒ)
8 drams (ʒ) = 1 ounce (fl ℥)
1 ounce (℥) = 480 grains
12 ounces (℥) = 1 pound (lb)

Apothecary Volume Equivalents

60 minims (♏) = 1 fluidram (fl ʒ)

8 fluidrams (fl ʒ) = 1 fluid ounce (fl ℥)

1 fluid ounce (ft ℥) = 480 minims

16 fluid ounces (fl ℥) = 1 pint (pt)

Avoirdupois Equivalents

1 ounce (oz) = 437.5 grains
16 ounces (oz) = 1 pound (lb)

Weight/Volume Equivalents

1 mg/dL = 10 mcg/mL
1 mg/dL = 1 mg%
1 ppm = 1 mg/L

Conversion Equivalents

1 gram (g) = 15.43 grains
1 grain (gr) = 64.8 milligrams
1 ounce (℥) = 31.1 grams
1 ounce (oz) = 28.35 grams
1 pound (lb) = 453.6 grams
1 kilogram (kg) = 2.2 pounds
1 milliliter (mL) = 16.23 minims
1 minim (♏) = 0.06 milliliter
1 fluid ounce (fl oz) = 29.57 milliliter
1 pint (pt) = 473.2 milliliter
0.1 milligram = 1/600 grain
0.12 milligram = 1/500 grain
0.15 milligram = 1/400 grain
0.2 milligram = 1/300 grain
0.3 milligram = 1/200 grain
0.4 milligram = 1/150 grain
0.5 milligram = 1/120 grain
0.6 milligram = 1/100 grain
0.8 milligram = 1/80 grain
1 milligram = 1/65 grain

Metric Length Equivalents

2.54 cm = 1 inch
30.48 cm = 1 foot
1.6 km = 1 mile

ANTHROPOMETRICS

Creatinine Clearance Formulas

Formulas for Estimating Creatinine Clearance in Patients with Stable Renal Function

Cockroft-Gault Formula

Adults (age 18 years and older)[1]:

$$\text{CrCl (males)} = \frac{(140 - \text{age}) \times \text{weight}}{Cr_s \times 72}$$

$$\text{CrCl (females)} = 0.85 \times \text{above value}^*$$

*Some studies suggest that the predictive accuracy of this formula for women is better *without* the correction factor of 0.85.

where CrCl is creatinine clearance (in mL/minute), Cr_s is serum creatinine (in mg/dL), age is in years, and weight is in kilograms.

Children (age 1 to 18 years)[2]:

$$\text{CrCl} = \frac{0.48 \times \text{height} \times \text{BSA}}{Cr_s \times 1.73}$$

where BSA is body surface area (in m^2), CrCl is creatinine clearance (in mL/minute), Cr_s is serum creatinine (in mg/dL), and height is in centimeters.

Formula for Estimating Creatinine Clearance from a Measured Urine Collection

$$\text{CrCl (mL/minute)} = \frac{U \times V^*}{P \times T}$$

where U is the concentration of creatinine in a urine specimen (in same units as P), V is the volume of urine (in mL), P is the concentration of creatinine in serum at the midpoint of the urine collection period (in same units as U), and T is the time of the urine collection period in minutes (e.g., 6 hours = 360 minutes; 24 hours = 1440 minutes).

*The product of $U \times V$ equals the production of creatinine during the collection period and, at steady state, should equal 20 to 25 mg/kg per day for ideal body weight (IBW) in males and 15 to 20 mg/kg per day for IBW in females. If it is less than this, inadequate urine collection may have occurred, and CrCl will be underestimated.

MDRD Formula for Estimating Glomerular Filtration Rate (from the Modification of Diet in Renal Disease Study)[3]

Conventional calibration MDRD equation [used only with those creatinine methods that have *not* been recalibrated to be traceable to isotope dilution mass spectrometry (IDMS)]

For creatinine in mg/dL:

$$X = 186\ \text{creatinine}^{-1.154} \times \text{age}^{-0.203} \times \text{constant}$$

For creatinine in µmol/L:

$$X = 32788 \times \text{creatinine}^{-1.154} \times \text{age}^{-0.203} \times \text{constant}$$

where X is the glomerular filtration rate (GFR), constant for white males is 1 and for females is 0.742, and constant for African Americans is 1.21. Creatinine levels in µmol/L can be converted to mg/dL by dividing by 88.4.

IDMS-Traceable MDRD Equation (Used Only with Creatinine Methods that Have Been Recalibrated to Be Traceable to IDMS)

For creatinine in mg/dL:

$$X = 175 \times \text{creatinine}^{-1.154} \times \text{age}^{-0.203} \times \text{constant}$$

For creatinine in µmol/L:

$$X = 175 \times (\text{creatinine}/88.4)^{-1.154} \times \text{age}^{-0.203} \times \text{constant}$$

where X is the glomerular filtration rate (GFR), constant for white males is 1 and for females is 0.742, and constant for African Americans is 1.21.

Ideal Body Weight (IBW)

IBW is the weight expected for a nonobese person of a given height. The IBW formulas below and various life insurance tables can be used to estimate IBW. Dosing methods described in the literature may use IBW as a method in dosing obese patients.

Adults (age 18 years and older)[4]:

IBW (males) = 50 + (2.3 × height in inches over 5 ft)
IBW (females) = 45.5 + (2.3 × height in inches over 5 ft)

where IBW is in kilograms.

Children (age 1 to 18 years)[2]:
Under 5 feet tall:

$$\text{IBW} = \frac{\text{height}^2 \times 1.65}{1000}$$

where IBW is in kilograms and height is in centimeters.

Five feet or taller:

IBW (males) = 39 + (2.27 × height in inches over 5 ft)
IBW (females) = 42.2 + (2.27 × height in inches over 5 ft)

where IBW is in kilograms.

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APPENDIX B COMMON LABORATORY TESTS

The following table is an alphabetical listing of some common laboratory tests and their reference ranges for adults as measured in plasma or serum (unless otherwise indicated). Reference values differ among laboratories, so readers should refer to the published reference ranges used in each institution. For some tests, both SI units and conventional units are reported.

Laboratory	Conventional Units	Conversion Factor	SI Units
Acid phosphatase			
Male	2–12 units/L	16.7	33–200 nkat/L
Female	0.3–9.2 units/L	16.7	5–154 nkat/L
Activated partial thromboplatin time (aPTT)	25–40 s		
Adrenocorticotropic hormone (ACTH)	15–80 pg/mL or ng/L	0.2202	3.3–17.6 pmol/L
Alanine aminotransferase (ALT, SGPT)	7–53 IU/L	0.01667	0.12–0.88 µkat/L
Albumin	3.5–5.0 g/dL	10	35–50 g/L
Albumin:creatinine ratio (urine)			
Normal	Less than 30 mg/g creatinine		
Microalbuminuria	30–300 mg/g creatinine		
Proteinuria	Greater than 300 mg/g creatinine		
or	or		
Normal			
Male	Less than 2.0 mg/mmol creatinine		
Female	Less than 2.8 mg/mmol creatinine		
Microalbuminuria			
Male	2.0–20 mg/mmol creatinine		
Female	2.8–28 mg/mmol creatinine		
Proteinuria			
Male	Greater than 20 mg/mmol creatinine		
Female	Greater than 28 mg/mmol creatinine		
Aldosterone			
Supine	Less than 16 ng/dL	27.7	Less than 444 pmol/L
Upright	Less than 31 ng/dL	27.7	Less than 860 pmol/L
Alkaline phosphatase			
10–15 years	130–550 IU/L	0.01667	2.17–9.17 µkat/L
16–20 years	70–260 IU/L	0.01667	1.17–4.33 µkat/L
Greater than 20 years	38–126 IU/L	0.01667	0.13–2.10 µkat/L
Alpha-fetoprotein (AFP)	Less than 15 ng/mL	1	Less than 15 mcg/L
$Alpha_1$-antitrypsin	80–200 mg/dL	0.01	0.8–2.0 g/L
Amikacin, therapeutic	15–30 mg/L peak	1.71	25.6–51.3 µmol/L peak
	Less than or equal to 8 mg/L trough		Less than or equal to 13.7 µmol/L trough
Amitriptyline	80–200 ng/ml or mcg/L	3.4	272–680 nmol/L
Ammonia (plasma)	15.33–56.20 mcg NH_3/dL	0.5872	9–33 µmol NH_3/L
Amylase	25–115 IU/L	0.01667	0.42–1.92 µkat/L
Androstenedione	50–250 ng/dL	0.0349	1.7–8.7 nmol/L
Angiotensin-converting enzyme	15–70 units/L	16.67	250–1167 nkat/L
Anion gap	7–16 mEq/L	1	7–16 mmol/L
Anti–double-stranded DNA (anti-ds DNA)	Negative		
Anti-HAV	Negative		
Anti-HBc	Negative		
Anti-HBs	Negative		
Anti-HCV	Negative		
Anti–Sm antibody	Negative		
Antinuclear antibody (ANA)	Negative		

(Continued)

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Laboratory	Conventional Units	Conversion Factor	SI Units
Apolipoprotein A-1			
Male	95–175 mg/dL	0.01	0.95–1.75 g/L
Female	100–200 mg/dL	0.01	1.0–2.0 g/L
Apolipoprotein B			
Male	50–110 mg/dL	0.01	0.5–1.10 g/L
Female	50–105 mg/dL	0.01	0.5–1.05 g/L
Aspartate aminotransferase (AST, SGOT)	11–47 IU/L	0.01667	0.18–0.78 µkat/L
$Beta_2$-microglobulin	Less than 0.2 mg/dL	10	2 mg/L
Bicarbonate	22–26 mEq/L	1	22–26 mmol/L
Bilirubin			
Total	0.3–1.1 mg/dL	17.1	5.13–18.80 µmol/L
Direct	0–0.3 mg/dL	17.1	0–5.1 µmol/L
Indirect	0.1–1.0 mg/dL	17.1	1.71–17.1 µmol/L
Bleeding time	3–7 minutes		
Blood gases (arterial)			
pH	7.35–7.45	1	7.35–7.45
P_{O_2}	80–105 mm Hg	0.133	10.6–14.0 kPa
P_{CO_2}	35–45 mm Hg	0.133	4.7–6.0 kPa
HCO_3	22–26 mEq/L	1	22–26 mmol/L
O_2 saturation	Greater than or equal to 95%	0.01	0.95
Blood urea nitrogen	8–25 mg/dL	0.357	2.9–8.9 mmol/L
B-type natriuretic peptide (BNP)	0–99 pg/mL	1	0–99 ng/L
BUN-to-creatinine ratio	10:1 to 20:1		
C-peptide	0.51–2.70 ng/mL	330 0.33	170–900 pmol/L or 0.172–0.900 nmol/L
C-reactive protein	Less than 0.8 mg/dL	10	Less than 8 mg/L
CA-125	Less than 35 units/mL	1	Less than 35 kilounits/L
CA 15-3	Less than 30 units/mL	1	Less than 30 kilounits/L
CA 19-9	Less than 37 units/mL	1	Less than 37 kilounits/L
CA 27-29	Less than 38 units/mL	1	Less than 38 kilounits/L
Calcium			
Total	8.6–10.3 mg/dL	0.25	2.15–2.58 mmol/L
	4.3–5.16 mEq/L	0.50	2.15–2.58 mmol/L
Ionized	4.5–5.1 mg/dL	0.25	1.13–1.28 mmol/L
	2.26–2.56 mEq/L	0.50	1.13–1.28 mmol/L
Carbamazepine, therapeutic	4–12 mg/L	4.23	17–51 µmol/L
Carboxyhemoglobin (nonsmoker)	Less than 2%	0.01	Less than 0.02
Carcinoembryonic antigen (CEA)			
Nonsmoker	Less than 2.5 ng/mL	1	Less than 2.5 mcg/L
Smoker	Less than 5 ng/mL		Less than 5 mcg/L
Cardiac troponin I (see troponin I)	Variable ng/mL	1	Variable mcg/L
CD4 lymphocyte count	31–61% of total lymphocytes		
CD8 lymphocyte count	18–39% of total lymphocytes		
Cerebrospinal fluid (CSF)			
Pressure	75–175 mm H_2O		
Glucose	40–70 mg/dL	0.0555	2.2–3.9 mmol/L
Protein	15–45 mg/dL	0.01	0.15–0.45 g/L
WBC	Less than 10/mm^3		
Ceruloplasmin	18–45 mg/dL	10 0.063	180–450 mg/L 1.1–2.8 µmol/L
Chloride	97–110 mEq/L	1	97–110 mmol/L
Cholesterol			
Desirable	Less than 200 mg/dL	0.0259	Less than 5.18 mmol/L
Borderline high	200–239 mg/dL	0.0259	5.18–6.19 mmol/L
High	Greater than or equal to 240 mg/dL	0.0259	Greater than or equal to 6.2 mmol/L
Chorionic gonadotropin (β-hCG)	Less than 5 milliunits/mL	1	Less than 5 units/L
Clozapine	Minimum trough 300–350 ng/mL or mcg/L	3.06	918–1071 nmol/L
CO_2 content	22–30 mEq/L	1	22–30 mmol/L
Complement component 3 (C3)	70–160 mg/dL	0.01	0.7–1.6 g/L
Complement component 4 (C4)	20–40 mg/dL	0.01	0.2–0.4 g/L

(Continued)

Laboratory	Conventional Units	Conversion Factor	SI Units
Copper	70–150 mcg/dL	0.157	11–24 µmol/L
Cortisol (fasting, morning)	5–25 mcg/dL	27.6	138–690 nmol/L
Cortisol (free, urinary)	10–100 mcg/day	2.76	28–276 nmol/day
Creatine kinase			
Male	30–200 IU/L	0.01667	0.50–3.33 µkat/L
Female	20–170 IU/L	0.01667	0.33–2.83 µkat/L
MB fraction	0–7 IU/L	0.01667	0.0–0.12 µkat/L
Creatinine clearance (CrCl) (urine)	85–135 mL/minute/1.73 m^2	0.00963	0.82–1.3 mL/s/m^2
Creatinine			
Male 4–20 years	0.2–1.0 mg/dL	88.4	18–88 µmol/L
Female 4–20 years	0.2–1.0 mg/dL	88.4	18–88 µmol/L
Male (adults)	0.7–1.3 mg/dL	88.4	62–115 µmol/L
Female (adults)	0.6–1.1 mg/dL	88.4	53–97 µmol/L
Cyclosporin			
Renal transplant	100–300 ng/mL or mcg/L	0.832	83–250 nmol/L
Cardiac, liver, or pancreatic transplant	200–350 ng/mL or mcg/L	0.832	166–291 nmol/L
Cryptococcal antigen	Negative		
D-dimers	Less than 250 ng/mL	1	Less than 250 mcg/L
Desipramine	75–300 ng/mL or mcg/L	3.75	281–1125 mmol/L
Dexamethasone suppression test (DST) (overnight)	8:00 am cortisol less than 5 mcg/dL	0.0276	Less than 0.14 µmol/L
DHEAS			
Male	170–670 mcg/dL	0.0271	4.6–18.2 µmol/L
Female			
Premenopausal	50–540 mcg/dL	0.0271	1.4–14.7 µmol/L
Postmenopausal	30–260 mcg/dL	0.0271	0.8–7.1 µmol/L
Digoxin, therapeutic	0.5–1.0 ng/mL or mcg/L	1.28	0.6–1.3 nmol/L
Erythrocyte count (blood) See under red blood cell count			
Erythrocyte sedimentation rate (ESR)			
Westergren			
Male	0–20 mm/hour		
Female	0–30 mm/hour		
Wintrobe			
Male	0–9 mm/hour		
Female	0–15 mm/hour		
Erythropoietin	2–25 mIU/mL	1	2–25 IU/L
Estradiol			
Male	10–36 pg/mL	3.67	37–132 pmol/L
Female	34–170 pg/mL	3.67	125–624 pmol/L
Ethanol, legal intoxication	Greater than or equal to 50–100 mg/dL	0.217	10.9–21.7 mmol/L
	Greater than or equal to 0.05–0.1%	217	
Ethosuccimide, therapeutic	40–100 mg/L or mcg/mL	7.08	283–708 µmol/L
Factor VIII or factor IX			
Severe hemophilia	Less than 1 IU/dL	0.01	Less than 0.01 units/mL
Moderate hemophilia	1–5 IU/dL	0.01	0.01–0.05 units/mL
Mild hemophilia	Greater than 5 IU/dL	0.01	Greater than 0.05 units/mL
Usual adult levels	60–140 IU/dL	0.01	0.60–1.40 units/mL
Ferritin			
Male	20–250 ng/mL	1	20–250 mcg/L
Female	10–150 ng/mL	1	10–150 mcg/L
Fibrin degradation products (FDP)	2–10 mg/L		
Fibrinogen	200–400 mg/dL	0.01	2.0–4.0 g/L
Folate (plasma)	3.1–12.4 ng/mL	2.266	7.0–28.1 nmol/L
Folic acid (RBC)	125–600 ng/mL	2.266	283–1360 nmol/L
Follicle-stimulating hormone (FSH)			
Male	1–7 mIU/mL	1	1–7 IU/L
Female			
Follicular phase	1–9 mIU/mL	1	1–9 IU/L
Midcycle	6–26 mIU/mL	1	6–26 IU/L
Luteal phase	1–9 mIU/mL	1	1–9 IU/L
Postmenopausal	30–118 mIU/mL	1	30–118 IU/L

(Continued)

Laboratory	Conventional Units	Conversion Factor	SI Units
Free thyroxine index (FT_4I)	6.5–12.5		
Gamma glutamyl transferase (GGT)	0–30 IU/L	0.01667	0–0.5 µkat/L
Gastrin (fasting)	0–130 pg/mL	1	0–130 ng/L
Gentamicin, therapeutic	4–10 mg/L peak Less than or equal to 2 mg/L trough	2.09	8.4–21 µmol/L peak Less than or equal to 4.2 µmol/L trough
Globulin	2.3–3.5 g/dL	10	23–35 g/L
Glucose (fasting, plasma)	65–109 mg/dL	0.0555	3.6–6.00 mmol/L
Glucose, two hour postprandial blood (PPBG)	Less than 140 mg/dL	0.0555	Less than 7.8 mmol/L
Granulocyte count	$1.8–6.6 \times 10^3/\mu L$	10^6	$1.8–6.6 \times 10^9/L$
Growth hormone (fasting)			
Male	Less than 5 ng/mL	1	Less than 5 mcg/L
Female	Less than 10 ng/mL	1	Less than 10 mcg/L
Haptoglobin	60–270 mg/dL	0.01	0.6–2.7 g/L
HBeAg	Negative		
HbsAg	Negative		
HBV DNA	Negative		
Hematocrit			
Male	40.7–50.3%	0.01	0.407–0.503
Female	36.1–44.3%	0.01	0.361–0.443
Hemoglobin (blood)			
Male	13.8–17.2 g/dL	10 Alternate SI: 0.62	138–172 g/L 8.56–10.67 mmol/L
Female	12.1–15.1 g/dL	10 Alternate SI: 0.62	121–151 g/L 7.5–9.36 mmol/L
Hemoglobin A1c	4.0–6.0%	0.01	0.04–0.06
Heparin			
Via protamine titration method	0.2–0.4 mcg/mL		
Via anti-factor Xa assay	0.3–0.7 mcg/mL		
High-density lipoprotein (HDL) cholesterol	Greater than 35 mg/dL	0.0259	Greater than 0.91 mmol/L
Homocysteine	3.3–10.4 µmol/L		
Ibuprofen			
Therapeutic	10–50 mcg/mL	4.85	49–243 µmol/L
Toxic	100–700 mcg/mL or more	4.85	485–3395 µmol/L or more
Imipramine, therapeutic	100–300 ng/mL or mcg/L	3.57	357–1071 nmol/L
Immunoglobulin A (IgA)	85–385 mg/dL	0.01	0.85–3.85 g/L
Immunoglobulin G (IgG)	565–1765 mg/dL	0.01	5.65–17.65 g/L
Immunoglobulin M (IgM)	53–375 mg/dL	0.01	0.53–3.75 g/L
Insulin (fasting)	2–20 microunits/mL or milliunits/L	7.175	14.35–143.5 pmol/L
International normalized ratio (INR), therapeutic	2.0–3.0 (2.5–3.5 for some indications)		
Iron			
Male	45–160 mcg/dL	0.179	8.1–31.3 µmol/L
Female	30–160 mcg/dL	0.179	5.4–31.3 µmol/L
Iron binding capacity (total)	220–420 mcg/dL	0.179	39.4–75.2 µmol/L
Iron saturation	15–50%	0.01	0.15–0.50
Lactate (plasma)	0.7–2.1 mEq/L 6.3–18.9 mg/dL	1 0.111	0.7–2.1 mmol/L
Lactate dehydrogenase	100–250 IU/L	0.01667	1.67–4.17 µkat/L
Lead	Less than 25 mcg/dL	0.0483	Less than 1.21 µmol/L
Leukocyte count	$3.8–9.8 \times 10^3/\mu L$	10^6	$3.8–9.8 \times 10^9/L$
Lidocaine, therapeutic	1.5–6.0 mcg/mL or mg/L	4.27	6.4–25.6 µmol/L
Lipase	Less than 100 IU/L	0.01667	1.7 µkat/L
Lithium, therapeutic	0.5–1.25 mEq/L	1	0.5–1.25 mmol/L
Low-density lipoprotein (LDL) cholesterol			
Desirable	Less than 130 mg/dL	0.0259	Less than 3.36 mmol/L
Borderline high risk	130–159 mg/dL	0.0259	3.36–4.11 mmol/L
High risk	Greater than or equal to 160 mg/dL	0.0259	Greater than or equal to 4.13 mmol/L

(Continued)

Laboratory	Conventional Units	Conversion Factor	SI Units
Luteinizing hormone (LH)			
Male	1–8 milliunits/mL	1	1–8 units/L
Female			
Follicular phase	1–12 milliunits/mL	1	1–12 units/L
Midcycle	16–104 milliunits/mL	1	16–104 units/L
Luteal phase	1–12 milliunits/mL	1	1–12 units/L
Postmenopausal	16–66 milliunits/mL	1	16–66 units/L
Lymphocyte count	1.2–3.3 × 10^3/μL	10^6	1.2–3.3 × 10^9/L
Magnesium	1.3–2.2 mEq/L	0.5	0.65–1.10 mmol/L
	1.58–2.68 mg/dL	0.411	0.65–1.10 mmol/L
Mean corpuscular volume	80.0–97.6 μm^3	1	80.0–97.6 fL
Mononuclear cell count	0.2–0.7 × 10^3/μL	10^6	0.2–0.7 × 10^9/L
Nortriptyline, therapeutic	50–150 ng/mL or mcg/L	3.8	190–570 nmol/L
NT-ProBNP (see Pro-BNP)			
Osmolality (serum)	275–300 mOsm/kg	1	275–300 mmol/kg
Osmolality (urine)	250–900 mOsm/kg	1	250–900 mmol/kg
Parathyroid hormone (PTH), intact	10–60 pg/mL or ng/L	0.107	1.1–6.4 pmol/L
Parathyroid hormone (PTH), N-terminal	8–24 pg/mL or ng/L		
Parathyroid hormone (PTH), C-terminal	50–330 pg/mL or ng/L		
Phenobarbital, therapeutic	15–40 mcg/mL or mg/L	4.31	65–172 μmol/L
Phenytoin, therapeutic	10–20 mcg/mL or mg/L	3.96	40–79 μmol/L
Phosphate	2.5–4.5 mg/dL	0.323	0.81–1.45 mmol/L
Platelet count	140–440 × 10^3/μL	10^6	140–440 × 10^9/L
Potassium (plasma)	3.3–4.9 mEq/L	1	3.3–4.9 mmol/L
Prealbumin (adult)	19.5–35.8 mg/dL	10	195–358 mg/L
Primidone, therapeutic	5–12 mcg/mL or mg/L	4.58	23–55 μmol/L
ProBNP	Less than 125 pg/mL or ng/L	0.118	Less than 14.75 pmol/L
Procainamide, therapeutic	4–10 mcg/mL or mg/L	4.23	17–42 μmol/L
Progesterone			
Male	13–97 ng/dL	0.0318	0.4–3.1 nmol/L
Female			
Follicular phase	15–70 ng/dL		0.5–2.2 nmol/L
Luteal phase	200–2500 ng/dL		6.4–79.5 nmol/L
Prolactin	Less than 20 ng/mL	1	Less than 20 mcg/L
Prostate-specific antigen (PSA)	Less than 4 ng/mL	1	Less than 4 mcg/L
Protein, total	6.0–8.0 g/dL	10	60–80 g/L
Prothrombin time (PT)	10–12 seconds		
Quinidine, therapeutic	2–5 mcg/mL or mg/L	3.08	6.2–15.4 μmol/L
Radioactive iodine uptake (RAIU)	Less than 6% in 2 hours		
Red blood cell (RBC) count (blood)			
Male	4–6.2 × 10^6/μL	10^6	4–6.2 × 10^{12}/L
Female	4–6.2 × 10^6/μL	10^6	4–6.2 × 10^{12}/L
Pregnant			
Trimester 1	4–5 × 10^6/μL	10^6	4–5 × 10^{12}/L
Trimester 2	3.2–4.5 × 10^6/μL	10^6	3.2–4.5 × 10^{12}/L
Trimester 3	3–4.9 × 10^6/μL	10^6	3–4.9 × 10^{12}/L
Post partum	3.2–5 × 10^6/μL	10^6	3.2–5 × 10^6/L
Red blood cell distribution width (RDW)	11.5–14.5%	0.01	0.115–0.145
Reticulocyte count			
Male	0.5–1.5% of total RBC count	0.01	0.005–0.015
Female	0.5–2.5% of total RBC count	0.01	0.005–0.025
Retinol-binding protein (RBP)	2.7–7.6 mg/dL	10	27–76 mg/L
Rheumatoid factor (RF) titer	Negative		
Salicylate, therapeutic	150–300 mcg/mL or mg/L	0.00724	1.09–2.17 mmol/L
	15–30 mg/dL	0.0724	
Sodium	135–145 mEq/L	1	135–145 mmol/L
Tacrolimus			
Renal transplant	6–12 ng/mL or mcg/L		
Liver transplant	4–10 ng/mL or mcg/L		
Pancreatic transplant	10–18 ng/mL or mcg/L		
Bone marrow transplant	10–20 ng/mL or mcg/L		

(Continued)

Laboratory	Conventional Units	Conversion Factor	SI Units
Testosterone (total)			
Men	300–950 ng/dL	0.0347	10.4–33.0 nmol/L
Women	20–80 ng/dL		0.7–2.8 nmol/L
Testosterone (free)			
Men	9–30 ng/dL	0.0347	0.31–1.04 nmol/L
Women	0.3–1.9 ng/dL		0.01–0.07 nmol/L
Theophylline			
Therapeutic	5–15 mcg/mL or mg/L	5.55	28–83 µmol/L
Toxic	20 or more mcg/mL or mg/L	5.55	111 or more µmol/L
Thrombin time	20–24 seconds		
Thyroglobulin	Less than 42 ng/mL	1	Less than 42 mcg/L
Thyroglobulin antibodies	Negative		
Thyroxine-binding globulin (TBG)	1.2–2.5 mg/dL	10	12–25 mcg/L
Thyroid-stimulating hormone (TSH)	0.35–6.20 microunits/ml	1	0.35–6.20 milliunits/L
TSH receptor antibodies (TSH Rab)	0–1 unit/mL		
Thyroxine (T_4)			
Total	4.5–12.0 mcg/dL	12.87	58–155 nmol/L
Free	0.7–1.9 ng/dL	12.87	9.0–24.5 pmol/L
Thyroxine index, free (FT_4I)	6.5–12.5		
TIBC See Iron-binding capacity (total)			
Tobramycin, therapeutic	4–10 mcg/mL or mg/L peak	2.14	8.6–21.4 µmol/L
	Less than or equal to 2 mcg/mL mg/L trough	2.14	Less than or equal to 4.28 µmol/L
Transferrin	200–430 mg/dL	0.01	2.0–4.3 g/L
Transferrin saturation	30–50%	0.01	0.30–0.50
Triglycerides (fasting)	Less than 160 mg/dL	0.0113	Less than 1.8 mmol/L
Triiodothyronine (T_3)	45–132 ng/dL	0.0154	0.91–2.70 nmol/L
Triiodothyronine (T_3) resin uptake	25–35%		
Troponin I	Less than 0.6 ng/mL	1	Less than 0.6 µg/L
Uric acid	3–8 mg/dL	59.48	179–476 µmol/L
Urinalysis (urine)			
pH	4.8–8.0		
Specific gravity	1.005–1.030		
Protein	Negative		
Glucose	Negative		
Ketones	Negative		
RBC	1–2 per low-power field		
WBC	3–4 per low-power field		
Valproic acid, therapeutic	50–100 mcg/mL or mg/L	6.93	346–693 µmol/L
Vancomycin, therapeutic trough	20–40 mcg/mL or mg/L peak	0.690	14–28 µmol/L peak
for CNS infections	5–20 mcg/mL or mg/L trough	0.690	3–14 µmol/L trough
	15–20 mcg/mL or mg/L trough	0.690	10–14 µmol/L trough
Vitamin A (retinol)	30–95 mcg/dL	0.0349	1.05–3.32 µmol/L
Vitamin B_{12}	180–1000 pg/mL	0.738	133–738 pmol/L
Vitamin D_3, 1, 25-dihydroxy	20–76 pg/m	2.4	48–182 pmol/L
Vitamin D_3, 25-hydroxy	10–50 ng/mL	2.496	25–125 nmol/L
Vitamin E (alpha tocopherol)	0.5–2.0 mg/dL	23.22	12–46 µmol/L
WBC count	$4–10 \times 10^3$/µL or $4–10 \times 10^3$/mm^3	10^6	$4–10 \times 10^9$/L
WBC differential (peripheral blood)			
Polymorphonuclear neutrophils (PMNs)	50–65%		
Bands	0–5%		
Eosinophils	0–3%		
Basophils	1–3%		
Lymphocytes	25–35%		
Monocytes	2–6%		

(Continued)

Laboratory	Conventional Units	Conversion Factor	SI Units
WBC differential (bone marrow)			
Polymorphonuclear neutrophils (PMNs)	3–11%		
Bands	9–15%		
Metamyelocytes	9–25%		
Myelocytes	8–16%		
Promyelocytes	1–8%		
Myeloblasts	0–5%		
Eosinophils	1–5%		
Basophils	0–1%		
Lymphocytes	11–23%		
Monocytes	0–1%		
Zinc	60–150 mcg/dL	0.153	9.2–23.0 μmol/L

This table is a modification of the Medical Algorithms Project (Chapter 40), unit conversions of the following Excel worksheets: Conversion of Conventional to SI units: Blood Chemistries; Conversion of Conventional to SI units: Urine Chemistries; Conversion of Conventional to SI units: Hematology and Coagulation; and Conversion of Conventional to SI units: Therapeutic Drug Monitoring. Available at www.medal.org/visitor/www%5CInactive% 5Cch40.aspx; accessed November 9, 2005.

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Appendix C Common Medical Abbreviations

These are abbreviations used commonly in medical practice both in verbal communication and in the medical record.

A&O	Alert and oriented
A&P	Auscultation and percussion; anterior and posterior; assessment and plans
A&W	Alive and well
AAO	Awake, alert, and oriented
AAO×3	Awake and orientated to time, place, and person
ABC	Absolute band counts; absolute basophil count; apnea, bradycardia, and cytology; aspiration, biopsy, and cytology; artificial beta cells
Abd	Abdomen
ABG	Arterial blood gases
ABO	Blood group system (A, AB, B, and O)
ABP	Arterial blood pressure
ABW	Actual body weight
ABx	Antibiotics
AC	Before meals (*ante cibos*)
ACE	Angiotensin-converting enzyme
ACE-I	Angiotensin-converting enzyme inhibitor
ACLS	Advanced cardiac life support
ACS	Acute coronary syndromes
ACTH	Adrenocorticotropic hormone
AD	Alzheimer's disease; right ear (*auris dextra*)
ADA	American Diabetes Association, adenosine deaminase
ADE	Adverse drug effect (or event)
ADH	Antidiuretic hormone
ADHD	Attention-deficit hyperactivity disorder
ADL	Activities of daily living
ADR	Adverse drug reaction
AF	Atrial fibrillation
AFB	Acid-fast bacillus; aortofemoral bypass; aspirated foreign body
AFEB	Afebrile
AIDS	Acquired immune-deficiency syndrome
AKA	Above-knee amputation; alcoholic ketoacidosis; all known allergies; also known as
ALFT	Abnormal liver function test
ALL	Acute lymphoblastic leukemia; acute lymphocytic leukemia
ALP	Alkaline phosphatase
ALT	Alanine transaminase (SGPT); alanine aminotransferase
AMA	Against medical advice; American Medical Association; antimitochondrial antibody
AMI	Acute myocardial infarction
AML	Acute myelogenous leukemia
Amp	Ampule
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
ANLL	Acute nonlymphocytic leukemia
AODM	Adult-onset diabetes mellitus
A&O×3	Awake and oriented to person, place, and time
A&O×4	Awake and oriented to person, place, time, and situation
AP	Anteroposterior
A&P	Active and present; anterior and posterior; assessment and plans; ausculatation and percussion
APAP	Acetaminophen (acetyl-*p*-aminophenol)
aPTT	Activated partial thromboplastin time
ARC	AIDS-related complex
ARD	Acute respiratory disease; adult respiratory disease; antibiotic removal device; aphakic retinal detachment
ARDS	Adult respiratory distress syndrome
ARF	Acute renal failure; acute respiratory failure; acute rheumatic fever
AROM	Active range of motion
AS	Left ear (*auris sinistra*)
ASA	Aspirin (acetylsalicylic acid)
ASCVD	Arteriosclerotic cardiovascular disease
ASHD	Arteriosclerotic heart disease
AST	Aspartate transaminase (SGOT); aspartate aminotransferase
ATG	Antithymocyte globulin
ATN	Acute tubular necrosis
AU	Each ear (*auris uterque*)
AV	Arteriovenous; atrioventricular; auditory visual
AVR	Aortic valve replacement
BBB	Bundle-branch block, blood-brain barrier
BC	Blood culture
BCOP	Board Certified Oncology Pharmacist
BCP	Birth control pill
BCPP	Board Certified Psychiatric Pharmacist
BCPS	Board Certified Pharmacotherapy Specialist
BE	Barium enema
BID	Twice daily (*bis in die*)
BKA	Below-knee amputation
BM	Bone marrow, bowel movement; an isoenzyme of creatine phospokinase
BMC	Bone marrow cells
BMD	Bone mineral density
BMR	Basal metabolic rate
BMT	Bone marrow transplantation
BP	Blood pressure
BPH	Benign prostatic hyperplasia
bpm	Beats per minute
BR	Bed rest

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BS	Bowel sounds; breath sounds; blood sugar
BSA	Body surface area
BUN	Blood urea nitrogen
Bx	Biopsy
C&S	Culture and sensitivity
CA	Cancer; calcium
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CAH	Chronic active hepatitis
CAM	Complementary and alternative medicine
CAPD	Continuous ambulatory peritoneal dialysis
CBC	Complete blood count
CBD	Common bile duct
CBG	Capillary blood gas; corticosteroid-binding globulin
CC	Chief complaint
CCA	Calcium channel antagonist
CCB	Calcium channel blocker
CCE	Clubbing, cyanosis, edema
CCK	Cholecystokinin
CCU	Coronary care unit
CF	Cystic fibrosis
CFS	Chronic fatigue syndrome
CFU	Colony-forming unit
CHD	Coronary heart disease
CHF	Congestive heart failure; chronic heart failure
CHO	Carbohydrate
CI	Cardiac index
CK	Creatine kinase
CKD	Chronic kidney disease
CLL	Chronic lymphocytic leukemia
CM	Costal margin
CMG	Cystometrogram
CML	Chronic myelogenous leukemia
CMV	Cytomegalovirus
CN	Cranial nerve
CNS	Central nervous system
C/O	Complains of
CO	Cardiac output; carbon monoxide
COLD	Chronic obstructive lung disease
COPD	Chronic obstructive pulmonary disease
CP	Chest pain; cerebral palsy
CPAP	Continuous positive airway pressure
CPK	Creatine phosphokinase (BB, MB, and MM are isoenzymes)
CPP	Cerebral perfusion pressure
CPR	Cardiopulmonary resuscitation
CrCL	Creatinine clearance
CRF	Chronic renal failure; corticotropin-releasing factor
CRH	Corticotropin-releasing hormone
CRI	Chronic renal insufficiency; catheter-related infection
CRNA	Certified Registered Nurse Anesthetist
CRNP	Certified Registered Nurse Practitioner
CRTT	Certified Respiratory Therapy Technician
CSF	Cerebrospinal fluid; colony-stimulating factor
CT	Computed tomography; chest tube
cTnI	Cardiac troponin I
CTZ	Chemoreceptor trigger zone
CV	Cardiovascular
CVA	Cerebrovascular accident
CVC	Central venous catheter
CVP	Central venous pressure
Cx	Culture; cervix
CXR	Chest x-ray
D&C	Dilatation and curettage
D_5W	5% Dextrose in water
DBP	Diastolic blood pressure
D/C	Discontinue; discharge
DCC	Direct-current cardioversion
DI	Diabetes insipidus
DIC	Disseminated intravascular coagulation
Diff	Differential
DJD	Degenerative joint disease
DKA	Diabetic ketoacidosis
dL	Deciliter
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
DNR	Do not resuscitate
DO	Doctor of Osteopathy
DOA	Dead on arrival; date of admission; duration of action
DOB	Date of birth
DOE	Dyspnea on exertion
DOT	Directly observed therapy
DPGN	Diffuse proliferative glomerulonephritis
DRE	Digital rectal examination
DRG	Diagnosis-related group
DS	Double strength
DTP	Diphtheria-tetanus-pertussis
DTR	Deep-tendon reflex
DVT	Deep-vein thrombosis
Dx	Diagnosis
EBV	Epstein-Barr virus
EC	Enteric-coated
ECG	Electrocardiogram
ECHO	Echocardiogram
ECT	Electroconvulsive therapy
ED	Emergency Department
EEG	Electroencephalogram
EENT	Eyes, ears, nose, throat
EF	Ejection fraction
EGD	Esophagogastroduodenoscopy
EIA	Enzyme immunoassay
EKG	Electrocardiogram
EMG	Electromyogram
EMT	Emergency Medical Technician
Endo	Endotracheal, endoscopy
EOMI	Extraocular movements (or muscles) intact
EPO	Erythropoietin
EPS	Extrapyramidal symptoms
ER	Emergency room
ERCP	Endoscopic retrograde cholangiopancreatography
ERT	Estrogen-replacement therapy
ESLD	End-stage liver disease
ESR	Erythrocyte sedimentation rate
ESRD	End-stage renal disease
ET	Endotracheal
EtOH	Ethanol
FB	Finger-breadth; foreign body

FBS	Fasting blood sugar
FDA	Food and Drug Administration
FEF	Forced expiratory flow rate
FEV_1	Forced expiratory volume in 1 second
FFP	Fresh-frozen plasma
FH	Family history
FiO_2	Fraction of inspired oxygen
FOBT	Fecal occult blood test
FPG	Fasting plasma glucose
FPIA	Fluorescence polarization immunoassay
FSH	Follicle-stimulating hormone
FTA	Fluorescent treponemal antibody
F/U	Follow-up
FUO	Fever of unknown origin
Fx	Fracture
G-CSF	Granulocyte colony-stimulating factor
G6PD	Glucose-6-phosphate dehydrogenase
GB	Gall bladder
GBS	Group B *Streptococcus*; Guillain-Barré syndrome
GC	Gonococcus
GDM	Gestational diabetes mellitus
GE	Gastroesophageal; gastroenterology
GERD	Gastroesophageal reflux disease
GFR	Glomerular filtration rate
GGT	γ-Glutamyl transferase
GGTP	γ-Glutamyl transpeptidase
GI	Gastrointestinal
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GN	Glomerulonephritis; graduate nurse
gr	Grain
GT	Gastrostomy tube
gtt	Drops (*guttae*)
GTT	Glucose tolerance test
GU	Genitourinary
GVHD	Graft-versus-host disease
GVL	Graft-versus-leukemia
Gyn	Gynecology
H&H	Hemoglobin and hematocrit
H&P	History and physical examination
H/A	Headache
HAART	Highly-active antiretroviral therapy
HAMD	Hamilton Rating Scale for Depression
HAV	Hepatitis A virus
Hb, hgb	Hemoglobin
HbA_{1c}	Glycosylated hemoglobin (hemoglobin A_{1c})
HBIG	Hepatitis B immune globulin
HBP	High blood pressure
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HC	Hydrocortisone, home care
HCG	Human chorionic gonadotropin
HCO_3	Bicarbonate
Hct	Hematocrit
HCTZ	Hydrochlorothiazide
HCV	Hepatitis C virus
HD	Hodgkin's disease; hemodialysis
HDL	High-density lipoprotein
HEENT	Head, eyes, ears, nose, and throat
HF	Heart failure
H flu	*Hemophilus influenzae*
HGH	Human growth hormone
HH	Hiatal hernia
Hib	*Hemophilus influenzae* type b
HIV	Human immunodeficiency virus
HJR	Hepatojugular reflux
HLA	Human leukocyte antigen; human lymphocyte antigen
HMG-CoA	Hydroxy-methylglutaryl coenzyme A
H/O	History of
HOB	Head of bed
HPA	Hypothalamic-pituitary axis
HPI	History of present illness
HR	Heart rate
HRSD	Hamilton Rating Scale for Depression
HRT	Hormone-replacement therapy
HS	At bedtime (*hora somni*)
HSV	Herpes simplex virus
HTN	Hypertension
Hx	History
I&D	Incision and drainage
I&O	Intake and output
IBD	Inflammatory bowel disease
IBW	Ideal body weight
ICD	Implantable cardioverter defibrillator
ICP	Intracranial pressure
ICS	Intercostal space
ICU	Intensive-care unit
ID	Identification; infectious disease
IDDM	Insulin-dependent diabetes mellitus
IFN	Interferon
Ig	Immunoglobulin
IgA	Immunoglobulin A
IgD	Immunoglobulin D
IHD	Ischemic heart disease
IJ	Internal jugular
IM	Intramuscular; infectious mononucleosis
INH	Isoniazid
INR	International normalized ratio
IOP	Intraocular pressure
IP	Intraperitoneal
IPG	Impedance plethysmography
IPN	Interstitial pneumonia
IRB	Institutional Review Board
ISA	Intrinsic sympathomimetic activity
ISH	Isolated systolic hypertension
IT	Intrathecal
ITP	Idiopathic thrombocytopenic purpura
IU	International unit (this can be a dangerous abbreviation because it may be read as 'IV' for "intravenous")
IUD	Intrauterine device
IV	Intravenous; Roman numeral four; symbol for class 4 controlled substances
IVC	Inferior vena cava; intravenous cholangiogram
IVDA	Intravenous drug abuse
IVF	Intravenous fluids
IVIG	Intravenous immunoglobulin
IVP	Intravenous pyelogram; intravenous push
JODM	Juvenile-onset diabetes mellitus

JRA	Juvenile rheumatoid arthritis
JVD	Jugular venous distension
JVP	Jugular venous pressure
K	Potassium
kcal	Kilocalorie
KCL	Potassium chloride
KOH	Potassium hydroxide
KUB	Kidney, ureter, and bladder
KVO	Keep vein open
L	Liter
LAD	Left anterior descending; left axis deviation
LAO	Left anterior oblique
LBP	Low-back pain
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LE	Lower extremity
LES	Lower esophageal sphincter
LFT	Liver function test
LHRH	Luteinizing hormone–releasing hormone
LLE	Left lower extremity
LLL	Left lower lobe
LLQ	Left lower quadrant (abdomen)
LMP	Last menstrual period
LMWH	Low-molecular-weight heparin
LOS	Length of stay
LP	Lumbar puncture
LPN	Licensed Practical Nurse
LPT	Licensed Physical Therapist
LR	Lactated Ringer's
LS	Lumbosacral
LUE	Left upper extremity
LUL	Left upper lobe
LUQ	Left upper quadrant
LVH	Left ventricular hypertrophy
MAP	Mean arterial pressure
MAR	Medication administration record
MB-CK	A creatine kinase isoenzyme
mcg	Microgram
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MD	Medical Doctor
MDI	Metered-dose inhaler
mEq	Milliequivalent
mg	Milligram
MHC	Major histocompatibility complex
MI	Myocardial infarction; mitral insufficiency
MIC	Minimum inhibitory concentration
mL	Milliliter
MM	An isoenzyme of creatine phosphokinase
MMR	Measles-mumps-rubella; midline malignant reticulosis
MOM	Milk of magnesia
MPV	Mean platelet volume
m/r/g	Murmur/rub/gallop
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRSE	Methicillin-resistant *Staphylococcus epidermitis*
MS	Mental status; mitral stenosis; musculoskeletal; multiple sclerosis; morphine sulfate
MSE	Mental status exam
MSW	Master of Social Work
MTD	Maximum tolerated dose
MTX	Methotrexate
MVA	Motor vehicle accident
MVI	Multivitamin
MVR	Mitral valve replacement; mitral valve regurgitation
MVS	mitral valve stenosis; motor, vascular, and sensory
N&V	Nausea and vomiting
NAD	No acute (or apparent) distress
N/C	Noncontributory; nasal cannula
NG	Nasogastric
NGT	Nasogastric tube; normal glucose tolerance
NIDDM	Non-insulin-dependent diabetes mellitus
NIH	National Institutes of Health
NKA	No known allergies
NKDA	No known drug allergies
NHDA	Nonketotic hyperosmolar acidosis
NL	Normal
NOS	Not otherwise specified
NPN	Nonprotein nitrogen
NPO	Nothing by mouth (*nil per os*)
NS	Normal saline solution (0.9% sodium chloride solution); neurosurgery
NSAID	Nonsteroidal anti-inflammatory drug
NSR	Normal sinus rhythm
NSS	Normal saline solution
NTG	Nitroglycerin
NT/ND	Nontender, nondistended
NVD	Nausea/vomiting/diarrhea; neck vein distension; neovascularization of the disk; neurovesicle dysfunction; no venereal disease; nonvalvular disease
N&V	Nausea and vomiting
O&P	Ova and parasites
OA	Osteoarthritis
OB	Obstetrics
OCD	Obsessive-compulsive disorder
OD	Right eye (*oculus dexter*)
OGT	Oral glucose tolerance test
OPV	Oral poliovirus vaccine
OR	Operating room
OR×1	Oriented to time
OR×2	Oriented to time and place
OR×3	Oriented to time, place, and person
OS	Left eye (*oculus sinister*)
OT	Occupational therapy
OTC	Over the counter
OU	*Oculus uterque* (each eye)
P	Pulse; plan; percussion; pressure
P&A	Percussion and auscultation
P&T	Peak and trough
PA	Physician Assistant; posteroanterior; pulmonary artery
PAC	Premature atrial contraction
$Paco_2$	Arterial carbon dioxide tension
Pao_2	Arterial oxygen tension
PAOP	Pulmonary artery occlusion pressure

PC	After meals (*post cibum*)
PCA	Patient-controlled analgesia
PCI	Percutaneous coronary intervention
PCKD	Polycystic kidney disease
PCN	Penicillin
PCP	*Pneumocystis carinii* pneumonia; phencyclidine
PCWP	Pulmonary capillary wedge pressure
PDE	Paroxysmal dyspnea on exertion
PE	Physical examination; pulmonary embolism
PEEP	Positive end-expiratory pressure
PEFR	Peak expiratory flow rate
PEG	Percutaneous endoscopic gastrostomy; polyethylene glycol
PEARLA	Pupils equal and react to light and accommodation
PERL	Pupils equal, react to light
PERRLA	Pupils equal, round, and reactive to light and accommodation
PERRRLA	Pupils equal, round, regular, and react to light and accommodation
PET	Positron-emission tomography
PFT	Pulmonary function test
pH	Hydrogen ion concentration
PH	Past history; personal history; pinhole; poor health; pubic hair; public health
PHx	Past history
PharmD	Doctor of Pharmacy
PID	Pelvic inflammatory disease
PKU	Phenylketonuria
PMH	Past medical history
PMI	Past medical illness; point of maximal impulse
PMN	Polymorphonuclear leukocyte
PMS	Premenstrual syndrome
PND	Paroxysmal nocturnal dyspnea
PO	By mouth (*per os*)
P_{O_2}	Partial pressure of oxygen
POAG	Primary open-angle glaucoma
POD	Postoperative day
PPBG	Postprandial blood glucose
ppd	Packs per day
PPN	Peripheral parenteral nutrition
pr	Per rectum
PRBC	Packed red blood cells
PRERLA	Pupils round, equal, react to light and accommodation
PRN	When necessary, as needed (*pro re nata*)
PSA	Prostate-specific antigen
PSH	Past surgical history
PST	Paroxysmal supraventricular tachycardia
PSVT	Paroxysmal supraventricular tachycardia
PT	Prothrombin time; physical therapy; patient
PTA	Prior to admission; percutaneous transluminal angioplasty
PTCA	Percutaneous transluminal coronary angioplasty
PTE	Pulmonary thromboembolism
PTH	Parathyroid hormone
PTSD	Posttraumatic stress disorder
PTT	Partial thromboplastin time
PUD	Peptic ulcer disease
PVC	Premature ventricular contraction
PVD	Peripheral vascular disease
PVR	Peripheral vascular resistance
PVT	Paroxysmal ventricular tachycardia
q	Every (*quaque*)
QA	Quality assurance
qd	Every day (*quaque die*)
QI	Quality improvement
qid	Four times daily (*quater in die*)
QNS	Quantity not sufficient
qod	Every other day
QOL	Quality of life
QS	Quantity sufficient
R&M	Routine and microscopic
RA	Rheumatoid arthritis; right atrium
RBC	Red blood cell
RCA	Right coronary artery
RCM	Right costal margin
RDA	Recommended daily allowance
RDS	Respiratory distress syndrome
RDW	Red cell distribution width
REM	Rapid eye movement; recent event memory
RES	Reticuloendothelial system
RF	Rheumatoid factor; renal failure; rheumatic fever
Rh	Rhesus factor in blood
RHD	Rheumatic heart disease
RLE	Right lower extremity
RLL	Right lower lobe
RLQ	Right lower quadrant
RML	Right middle lobe
RN	Registered Nurse
RNA	Ribonucleic acid
R/O	Rule out
ROM	Range of motion
ROS	Review of systems
RPh	Registered Pharmacist
R&R	Rate and rhythm
RR	Respiratory rate; recovery room
RRR	Regular rate and rhythm
RRT	Registered Respiratory Therapist
RSV	Respiratory syncytial virus
RT	Radiation therapy
RUE	Right upper extremity
RUL	Right upper lobe
RUQ	Right upper quadrant
RVH	Right ventricular hypertrophy
S_1	First heart sound
S_2	Second heart sound
S_3	Third heart sound (ventricular gallop)
S_4	Fourth heart sound (atrial gallop)
SA	Sinoatrial
SAD	Seasonal affective disorder
SAH	Subarachnoid hemorrhage
Sa_{O_2}	Arterial oxygen percent saturation
SBE	Subacute bacterial endocarditis
SBFT	Small bowel follow-through
SBGM	Self blood glucose monitoring
SBO	Small bowel obstruction
SBP	Systolic blood pressure
SC	Subcutaneous; subclavian
SCr	Serum creatinine

SEM	Systolic ejection murmur
SG	Specific gravity
SGOT (AST)	Serum glutamic oxaloacetic transaminase (aspartate transaminase)
SGPT (ALT)	Serum glutamic pyruvic transaminase (alanine transaminase)
SH	Social history
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
SIDS	Sudden infant death syndrome
SJS	Stevens-Johnson syndrome
SL	Sublingual
SLE	Systemic lupus erythematosus
SMA-6	Sequential multipler analyzer for sodium, potassium, CO_2, chloride, glucose, and BUN
SMA-7	Sodium, potassium, CO_2, chloride, glucose, BUN, and creatinine
SMA-12	Glucose, BUN, uric acid, calcium, phosporous, total protein, albumin, cholesterol, total bilirubin, alkaline phosphatase, SGOT, and LDH
SMA-23	Includes the entire SMA-12 plus sodium, potassium, CO_2, chloride, direct bilirubin, triglyceride, SGPT, indirect bilirubin, R fraction, and BUN/creatinine ratio
SMBG	Self-monitoring of blood glucose
SNF	Skilled nursing facility
SNS	Sympathetic nervous system
SOB	Shortness of breath; see order book; side of bed
S/P	Status post
SPF	Sun protection factor
SQ	Subcutaneous
SSKI	Saturated solution of potassium iodide
SSRI	Selective serotonin reuptake inhibitor
STAT	Immediately, at once
STD	Sexually transmitted disease
SV	Stroke volume
SVC	Superior vena cava
SVRI	Systemic vascular resistance index
SVR	Supraventricular rhythm; systemic vascular resistance
SVT	Supraventricular tachycardia
SW	Social worker
Sx	Signs
T	Temperature
T&A	Tonsillectomy and adenoidectomy
T&C	Type and crossmatch
TB	Tuberculosis
TBG	Thyroid-binding globulin
TBI	Total-body irradiation, traumatic brain injury
T bili	Total bilirubin
TCA	Tricyclic antidepressant
TCN	Tetracycline
TFT	Thyroid function test
TG	Triglyceride
TIA	Transient ischemic attack
TIBC	Total iron-binding capacity
TID	Three times daily (*ter in die*)
TLC	Therapeutic lifestyle changes
TMJ	Temporomandibular joint
TMP-SMX	Trimethoprim-sulfamethoxazole
TNTC	Too numerous to count
TOD	Target-organ damage
TPN	Total parenteral nutrition
TPR	Temperature, pulse, respiration
T PROT	Total protein
TSH	Thyroid-stimulating hormone
TURP	Transurethral resection of the prostate
Tx	Treat, treatment
UA	Urinalysis, uric acid
UC	Ulcerative colitis
UE	Upper extremity
UGI	Upper gastrointestinal
UOQ	Upper outer quadrant
UPT	Urine pregnancy test
URI	Upper respiratory infection
USP	United States Pharmacopeia
UTI	Urinary tract infection
UV	Ultraviolet
VF	Ventricular fibrillation
VLDL	Very low-density lipoprotein
VO	Verbal order
VOD	Veno-occlusive disease
V_A/Q	Ventilation-perfusion
VRE	Vancomycin-resistant *Enterococcus*
VS	Vital signs
VSS	Vital signs stable
VT	Ventricular tachycardia
VTE	Venous thromboembolism
WA	While awake
WBC	White blood cell (count)
W/C	Wheelchair
WDWN	Well-developed, well-nourished
WHO	World Health Organization
WNL	Within normal limits
W/U	Work-up
yo	Year-old
yr	Year

APPENDIX D GLOSSARY

2,3-Diphosphoglycerate: A compound in red blood cells that affects oxygen binding to and release from hemoglobin.

24-Hour ambulatory pH monitoring: A test that quantifies the amount of acid that refluxes into the esophagus over 24 hours under ambulatory (outpatient) conditions.

β-Lactam allergy: Refers to patients who experience allergic reactions to the β-lactam class of antimicrobials.

β_2 Microglobulin: A low-molecular-weight protein that may be elevated in multiple myeloma.

γ-Aminobutyric acid: An inhibitory amino acid found in the central nervous system.

Ablation: Destruction of part or all of an organ or structure.

Abscess: A purulent (i.e., containing, discharging, or causing the production of pus) collection of fluid separated from surrounding tissue by a wall comprised of inflammatory cells and adjacent organs. It usually contains necrotic debris, bacteria, and inflammatory cells.

Acanthosis: Increased thickness of the prickle cell layer of the skin.

Acanthosis nigricans: A skin condition characterized by dark, thickened velvety patches, especially in the folds of skin in the armpits, groin, and back of the neck that is often associated with insulin resistance. Also may be associated with internal malignancy, endocrine disorders, and obesity.

Acetaldehyde: A by-product of alcohol metabolism.

Acetylcholinesterase: An enzyme responsible for the degradation of acetylcholine.

Achlorhydria: Absence of gastric acid in the stomach.

Acidemia: An increase in the hydrogen ion concentration of the blood or a fall below normal in blood pH.

Acid-fast bacillus: General term for mycobacteria based on staining technique.

Acidosis: A pathologic state that leads to acidemia.

Acromegaly: A pathologic condition characterized by excessive production of growth hormone during adulthood after epiphyseal (long bone) fusions have completed.

Action potential: A rapid change in the polarity of the voltage of a cell membrane from negative to positive and back to negative; a wave of electrical discharge that travels across a cell membrane.

Acute chest syndrome: An acute respiratory complication of sickle-cell disease characterized by chest pain, fever, and pulmonary infiltrates.

Acute coronary syndromes: Ischemic chest discomfort at rest, most often accompanied by ST-segment elevation, ST-segment depression, or T-wave inversion on the 12-lead electrocardiogram. Furthermore, it is caused by plaque rupture and partial or complete occlusion of the coronary artery by thrombus. Acute coronary syndromes include myocardial infarction and unstable angina. Former terms used to describe types of acute coronary syndromes include Q-wave myocardial infarction, non–Q-wave myocardial infarction, and unstable angina.

Acute otitis media: Inflammation of the middle ear accompanied by fluid in the middle ear space and signs or symptoms of an acute ear infection.

Acute renal failure: Sudden loss of the kidney's ability to excrete wastes, concentrate urine, and remove electrolytes.

Acute tubular necrosis: A form of acute renal failure that results from toxic or ischemic (insufficient oxygen) injury to the cells in the proximal tubule of the kidney.

Adenocarcinoma: Malignant tumor originating in glandular tissue.

Adenoma: A nonmalignant tumor of epithelial tissue characterized by glandular structures.

Adenomatous polyposis coli (*APC*) gene: A tumor suppressor gene, acting as a "gatekeeper" to prevent development of tumors. A familial cancer syndrome called FAP, or familial adenomatous polyposis, is caused by mutations in *APC*. Mutation of *APC* also occurs commonly in sporadic cases of colorectal carcinoma.

Adjuvant chemotherapy: Chemotherapy given after the primary cancer treatment, designed to eliminate any remaining cancer cells that are undetectable with the goal of improving survival.

Adjuvant therapy: Therapy that supplements or follows primary therapy to prevent the risk of disease recurrence or manage associated symptoms.

Adrenalectomy: Surgical removal of one or both adrenal glands.

Adrenocorticotropic hormone: A hormone secreted by the anterior pituitary that controls secretion of cortisol from the adrenal glands; also referred to as corticotropin.

Afterload: The force against which a ventricle contracts that is contributed to by the vascular resistance, especially of the arteries, and by the physical characteristics (mass and viscosity) of the blood. Afterload is the overall resistance to blood flow leaving the heart.

Air embolus: An obstruction in a small blood vessel caused by air that is introduced into a blood vessel and carried through the circulation until it lodges in a smaller vessel.

Akathisia: Motor or subjective feelings of restlessness.

Akinesia: Lack of movement.

Alcohol dehydrogenase: An enzyme that degrades ethanol in the gut and liver.

Aldosterone: A hormone produced in and secreted by the zona glomerulosa of the adrenal cortex. Aldosterone acts on the kidneys to reabsorb sodium and excrete potassium. It is also a part of the renin–angiotensin–aldosterone system, which regulates blood pressure and blood volume.

Alkalemia: A decrease in the hydrogen ion concentration of the blood or a rise above normal in blood pH.

Alkalosis: A pathologic state that leads to alkalemia.

Allergen immunotherapy: Treatment for IgE-mediated conditions in which specific allergen extracts are sequentially administered in order to modify or eliminate allergic symptoms.

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Allergic rhinitis: A highly prevalent, allergen-induced, upper airway inflammatory disease characterized by chronic hyperreactive airway mucosa with periods of acute exacerbations.

Allodynia: A condition in which pain results from a stimulus that does not normally cause pain.

Allogeneic hematopoietic cell transplantation: A transplantation of hematopoietic (blood-forming) bone marrow, peripheral blood, or umbilical cord blood involving one person as a donor and another person as a recipient.

Allograft survival: After an organ transplant procedure, when the transplanted organ continues to have some degree of function, from excellent to poor.

Allograft: Tissue or organ transplanted from a donor of the same species but different genetic makeup; the recipient's immune system must be suppressed to prevent rejection of the allograft (graft).

Allorecognition: Recognition of the foreign antigens present on the transplanted organ or the donor's antigen-presenting cells.

Alopecia: Hair absence or loss.

Alport's syndrome: A hereditary disease that affects kidney function and can also cause hearing and vision disorders.

Amenorrhea: The absence or discontinuation of regular menstrual periods.

Amotivation: Apathy, loss of effectiveness, and diminished capacity or willingness to carry out complex, long-term plans, endure frustration, concentrate for long periods, follow routines, or successfully master new material.

Amylase: A pancreatic enzyme that cleaves starches.

Amyloid: Any of a group of chemically diverse proteins that are composed of linear non-branching aggregated fibrils.

Anaphylactic/anaphylaxis: Immediate, severe, potentially fatal hypersensitivity reaction induced by an antigen.

Anaphylactoid: An anaphylactic-like reaction, similar in signs and symptoms, but not mediated by IgE. A drug causing this reaction produces direct release of inflammatory mediators by a pharmacologic effect.

Anaphylaxis: The immediate, transient kind of immunologic (allergic) reaction characterized by contraction of smooth muscle and dilation of capillaries due to release of pharmacologically active substances (histamine, bradykinin, serotonin, and slow-reacting substance), classically initiated by the combination of antigen (allergen) with mast cell–fixed, cytophilic antibody (chiefly IgE). The reaction can also be initiated by relatively large quantities of serum aggregates (antigen–antibody complexes and others) that seemingly activate complement leading to production of anaphylatoxin.

Anemia: A reduction below normal in the concentration of hemoglobin in the body that results in a decrease of the oxygen-carrying capacity of the blood.

Anemia of chronic kidney disease: A decline in red blood cell production caused by a decrease in erythropoietin production by the progenitor cells of the kidney. As kidney function declines in chronic kidney disease, erythropoietin production also declines, resulting in decreased red blood cell production. Other contributing factors include iron deficiency and decreased red blood cell lifespan, caused by uremia.

Anergy: A reduction or lack of an immune response to a specific antigen.

Aneuploidy: Abnormal number of chromosomes.

Angina pectoris: Severe constricting pain in the chest, often radiating from the precordium to a shoulder (usually left) and down the arm, due to ischemia of heart muscle usually caused by coronary artery disease.

Angioedema: Swelling similar to urticaria (hives), but the swelling occurs beneath the skin instead of on the surface. Angioedema is characterized by deep swelling around the eyes and lips, and sometimes of the hands and feet. If it proceeds rapidly, it can lead to airway obstruction and suffocation, and it should therefore be treated as a medical emergency.

Angiogenesis: The formation of new blood vessels.

Anhedonia: Loss of interest or pleasure in activities previously enjoyed.

Anorexia: Loss of appetite.

Antenatal: Prior to birth.

Anterograde amnesia: A condition in which events that occurred after the onset of amnesia cannot be recalled and new memories cannot be formed.

Antiangiogenic: A substance that prevents the formation of new blood vessels.

Anticoagulant: Any substance that inhibits, suppresses, or delays the formation of blood clots. These substances occur naturally and regulate the clotting cascade. Several anticoagulants have been identified in a variety of animal tissues and have been commercially developed for therapeutic use.

Antimicrobial prophylaxis: Antibiotics given to prevent an infection.

Antiproteinase: A substance that inhibits the enzymatic activity of a proteinase.

Antrectomy: Surgical excision of the wall of the antrum, the region of the stomach that produces the hormone gastrin.

APACHE II: Acute Physiology and Chronic Health Evaluation II; a severity of disease classification system using a point score based on initial values of 12 routine physiologic measurements, age, and previous health status; used to provide a general measure of disease severity.

Aphakic: Absence of a lens in the eye.

Aphasia: Impairment of language affecting the ability to speak and understand speech.

Aphthous ulcer: A small superficial area of ulceration within the gastrointestinal mucosa, typically found in the oral cavity.

Apoptosis: Programmed cell death, a normal process in which cells perish in an orderly, highly controlled manner to control an organism's development.

Arcuate scotoma: An arc-shaped area of blindness in the field of vision.

Arterial hypotension: Systolic blood pressure less than 90 mm Hg or an acute fall of greater than 40 mm Hg from baseline.

Arthrocentesis: Puncture and aspiration of fluid from a joint.

Arthroconidia: A specialized spore-like form found in soil that is the propagating infectious form of coccidioidomycoses.

Arthus reaction: Local inflammatory response due to deposition of immune complexes in tissues.

Articular: Related to a joint or joints.

Ascites: Abnormal accumulation of serous fluid in the spaces between tissues and organs in the peritoneal cavity of the abdomen.

Asterixis: Abnormal posture and movements that may occur in advanced liver disease and a few other circumstances.

Asymptomatic bacteriuria: Bacteria present in the urine in a patient without signs or symptoms of a urinary tract infection.

Atelectasis: Decreased or absent air in a partial or entire lung, with resulting loss of lung volume.
Atherosclerosis: A disease process of the arteries involving fatty plaque formation and inflammation in the vascular wall.
Atopic: Related to a genetically determined hypersensitivity to environmental allergens; allergic.
Atopy: A genetic predisposition to develop type I hypersensitivity reactions against common environmental antigens; commonly seen in patients with allergic rhinitis, asthma, and atopic dermatitis.
Atresia: Congenital absence of a normal opening or normally patent lumen.
Atrial natriuretic peptide: A type of peptide, 28 amino acids in length, secreted by the atria of the heart when atrial pressure and stretch are increased.
Attenuate: To render less virulent; to reduce or diminish.
Autograft: A tissue or organ grafted into a new position in or on the body of the same individual.
Autologous hematopoietic cell transplantation: Infusion of a patient's own hematopoietic (blood-forming) cells that rescue the recipient from otherwise dose-limiting hematopoietic toxicity of chemotherapy and radiotherapy.
Autologous: Transplantation using one's own tissues or cells.
Automaticity: Ability of a cardiac fiber or tissue to spontaneously initiate depolarizations.
Autonomic nervous system: Parasympathetic and sympathetic nerves that control involuntary actions in the body.
Azoospermic: Having no living spermatozoa in the semen, or failure of spermatogenesis.
Azotemia: An excess of urea and other nitrogenous wastes in the blood as a result of kidney insufficiency.

Bacille Calmette-Guérin (BCG): A vaccine prepared from a living attenuated strain of tubercle bacilli and used to vaccinate human beings against tuberculosis or treat some types of cancer.
Bacteriuria: Bacteria in the urine evidenced either by urine culture or wet prep evaluation of gross urine under high powered field.
Barium enema: A diagnostic test using x-ray examination to view the lower gastrointestinal tract (colon and rectum) after oral ingestion of barium sulfate, a chalky liquid contrast medium.
Basal ganglia: Clusters of nerve cells deep in the brain that coordinate normal movement.
Bence Jones proteins: Light chain immunoglobulins found in the urine.
Benign prostatic hyperplasia: A benign condition wherein the overgrowth of prostate tissue may impede the flow of urine.
Bilateral: On both sides of the body.
Bilateral salpingo-oophorectomy: Surgical excision (removal) of both ovaries.
Bile acids: The organic acids in bile; contains sodium glycocholate and sodium taurocholate, cholesterol, biliverdin and bilirubin, mucus, fat, lecithin, and cells and cellular debris.
Bile: The yellowish-brown or green fluid secreted by the liver and discharged into the duodenum where it aids in the emulsification of fats, increases peristalsis, and retards putrefaction.
Biliary sludge: A deposit of tiny stones or crystals made up of cholesterol, calcium bilirubinate, and other calcium salts. The cholesterol and calcium bilirubinate crystals in biliary sludge can lead to gallstone formation.
Biopsy: Removal and pathologic examination of specimens in the form of small pieces of tissue from the living body.
Blastospore: A fungal spore produced by budding.
Blood dyscrasias: Any abnormality in blood or bone marrow cellular components such as low white blood cells, red blood cells, or platelets.
Blood urea nitrogen (BUN): A waste product in the blood produced from the breakdown of dietary proteins. The kidneys filter blood to remove urea and maintain homeostasis. A decline in kidney function results in an increase in BUN.
Body mass index: A calculation used to correct weight changes for height and is a direct calculation regardless of gender. It is the result of the weight in kilograms divided by the height in meters squared.
Bone remodeling: The constant process of bone turnover involving bone resorption followed by bone formation.
Bouchard's nodes: Bony outgrowths on the proximal interphalangeal joints due to osteoarthritis.
Brachial plexus: The collection of nerves that arises from the spine at the base of the neck from nerves that supply parts of the shoulder, arm, forearm, and hand.
Brachytherapy: A procedure in which radioactive material, sealed in needles, seeds, wires, or catheters, is placed directly into or near a tumor. Also called internal radiation, implant radiation, or interstitial radiation therapy.
Bradykinesia: Slow movement.
Brain abscess: A localized collection of pus inside the brain.
Bronchiectasis: Chronic dilation of bronchi or bronchioles as a result of inflammatory disease or obstruction associated with heavy sputum; or a chronic condition of one or more bronchi or bronchioles marked by irreversible dilatation and destruction of the bronchial walls.
Bronchoalveolar lavage: Washing out of the lungs with saline or mucolytic agents for diagnostic or therapeutic purposes.
Bronchoscopy: An examination used for inspection of the interior of the tracheobronchial tree.
Brudzinski's sign: A physical sign associated with meningitis, in which flexion of the hips and knees occurs when the neck is flexed by bringing the chin to the chest.
Bullectomy: Surgical removal of one or more bullae (air spaces in the lung measuring more than 1 cm in diameter in the distended state).
Bursa: The fluid-filled sac near the joint where tendons and muscles pass over bone.
Bursitis: An inflammation of the bursa.

Cachectic: Relating to or having the symptoms of cachexia.
Cachexia: Weight loss, wasting of muscle, loss of appetite, and general debility.
Capillary leak: Abnormally high permeability of the capillaries that allows fluid to flow excessively from the capillaries to the interstitial space.
Carcinoembryonic antigen: A protein normally seen during fetal development. When carcinoembryonic antigen is elevated in adults it suggests the presence of colorectal and other cancers. The normal level in nonsmokers is about less than 2.5 ng/mL, but it can be elevated in smokers and other nonmalignant conditions such as pancreatitis.
Carcinogenesis: The process that leads to development of cancer. Carcinogenesis may be a matter of induction by chemical, physical, or biological agents, of neoplasms that are usually not observed, an earlier induction of neoplasms that are usually observed, and/or the induction of more neoplasms than are usually found.

Carcinoma: A malignant growth that arises from epithelium, found in skin or the lining of body organs. Carcinomas tend to infiltrate into adjacent tissue and spread to distant organs; or a cancerous tumor of the epithelial tissue of an organ.

Carcinoma in situ: The earliest stage of a cancer; also referred to as "noninvasive cancer." The cancer has not yet grown through the membranes surrounding the affected organ or invaded other tissues and organs.

Carcinomatosis: Condition of having widespread dissemination of carcinoma (cancer) in the body.

Cardiac cachexia: Physical wasting with loss of weight and muscle mass caused by cardiac disease; a wasting syndrome that causes weakness and a loss of weight, fat, and muscle.

Cardiac index: Cardiac output (see below) normalized for body surface area (cardiac index = cardiac output/body surface area).

Cardiac output: The volume of blood ejected from the left side of the heart per unit of time [cardiac output (L/minute) = stroke volume × heart rate].

Cardiac remodeling: Genome expression resulting in molecular, cellular, and interstitial changes and manifested clinically as changes in size, shape, and function of the heart resulting from cardiac load or injury.

Carotid: The two main arteries in the neck.

Caseating granulomas: A mass or nodule of chronically inflamed tissue with granulations, usually associated with an infective process.

Cataplexy: A sudden attack of muscle weakness with retention of clear consciousness that follows a strong emotional stimulus (e.g., elation, surprise, or anger); a characteristic symptom of narcolepsy.

Causalgia: Persistent burning pain, allodynia, and hyperpathia following a traumatic nerve lesion.

Cavitary lesions: The formation of cavities in an organ or tissue especially in disease.

Central pain: Pain that results from a lesion or dysfunction in the central nervous system.

Cephalgia: Head pain; headache.

Cervicitis: Inflammation of the cervix.

Chemoprevention: The use of drugs, vitamins, or other agents to reduce the risk of or delay the development or recurrence of cancer.

Chemoreceptor trigger zone: Located in the area postrema of the fourth ventricle of the brain, it is exposed to cerebrospinal fluid and blood and is easily stimulated by circulating toxins to induce nausea and vomiting.

Chemosis: Edema of the bulbar conjunctiva, forming a swelling around the cornea.

Cheyne-Stokes respiration: Pattern of breathing with gradual increase in depth and sometimes in rate to a maximum, followed by a decrease resulting in apnea. The cycles ordinarily are 30 seconds to 2 minutes in duration, with 5 to 30 seconds of apnea.

Chimeric: Composed of parts from different origins.

Chloasma: Melasma characterized by irregularly shaped brown patches on the face and other areas of the skin, often seen during pregnancy or associated with use of oral contraceptives.

Chlorpromazine equivalents: Approximate dose equivalent of a first-generation antipsychotic to 100 mg of chlorpromazine (relative potency).

Cholecystitis: Inflammation or infection of the gallbladder; chronic cholecystitis is associated with gallstones.

Cholelithiasis: Formation of stones in the gallbladder (gallstones).

Cholestasis: Reduced or lack of flow of bile, or obstruction of bile flow.

Cholesteatoma: A mass of keratinized epithelial cells and cholesterol resembling a tumor that forms in the middle ear or mastoid region.

Chorea: A type of dyskinesia with rhythmic dance-like movement. The increase in motor activity may be associated with fidgeting, twitching, or flinging movements.

Choroidal neovascular membranes: Development of abnormal blood vessels in and under the retina.

Chronic kidney disease: A progressive, irreversible decline in kidney function that occurs over a period of several months to years.

Chronotropic: Affecting pulse rate, or referring to changes in heart rate.

Churg-Strauss syndrome: A systemic necrotizing vasculitis with prominent lung involvement including severe asthma and eosinophilia.

Chvostek's sign: The physical sign noted when a tap on the patient's facial nerve adjacent to the ear produces a brief contraction of the upper lip, nose, or side of the face.

Chylothorax: The presence of lymphatic fluid (chyle) in the pleural cavity.

Circadian: Pertaining to events that occur with a cycle of about 24 hours.

Circadian rhythm: 24-Hour cycles of behavior and physiology that are generated by endogenous biological clocks (pacemakers).

Circulatory shock: A life-threatening condition wherein the circulatory system is unable to deliver enough oxygen and metabolic substrates to meet the demands of tissues and adequately clear metabolic waste products from those tissues.

Cirrhosis: Widespread disruption of normal liver structure by fibrosis and the formation of regenerative nodules that is caused by any of various chronic progressive conditions affecting the liver.

Class switching: Change in the isotype of antibody produced after a B cell has encountered an antigen.

Clinical cure: Resolution of signs and symptoms of a disease.

Closed comedo: A plugged follicle of sebum, keratinocytes, and bacteria that remains beneath the surface of the skin; also referred to as a "whitehead."

Clotting cascade: A series of enzymatic reactions by clotting factors leading to the formation of a blood clot. The clotting cascade is initiated by several thrombogenic substances. Each reaction in the cascade is triggered by the preceding one, and the effect is amplified by positive feedback loops.

Clotting factor: Plasma proteins found in the blood that are essential to the formation of blood clots; clotting factors circulate in inactive forms, but are activated by their predecessor in the clotting cascade or a thrombogenic substance. Each clotting factor is designated by a Roman numeral (e.g., factor VII) and by the letter "a" when activated (e.g., factor VIIa).

Clubbing: Proliferation of soft tissues, especially in the nail bed, which results in thickening and widening of finger and toe extremities.

Clue cells: Vaginal epithelial cells that, when coated with bacteria, appear with fuzzy, irregular borders under microscopic examination.

Coalescence: Fusion of smaller lipid emulsion particles forming larger particles, resulting in destabilization of the emulsion.

Cognitive function: Executive function and mental processing such as understanding, perception, reasoning, language, and awareness. Executive function involves a long list of skills, but they can

be divided into four categories: organization, self-regulation, attention, and problem solving. For example, a patient may have trouble thinking quickly, making decisions, and planning and prioritizing tasks. These functions can be evaluated by various neuropsychological tests.

Coitus: Sexual intercourse.

Coliforms: Gram-negative organisms that commonly inhabit the intestines of humans and other vertebrates (e.g., *Escherichia coli*).

Colloids: Resuscitation fluids that restore and/or increase the intravascular oncotic pressure.

Colon cancer: A disease in which cells in the lining of the colon become malignant and proliferate without control. Often referred to as colorectal cancer to include cells of the rectum.

Colonoscopy: Visual examination of the colon using a lighted, lens-equipped, flexible tube (colonoscope) inserted into the rectum.

Colony-forming units: The number of microorganisms that form colonies when cultured; indicates the number of viable microorganisms in a sample.

Comedolytic: An agent that is able to break up or destroy a comedo.

Comorbidities: Multiple disease states occurring concurrently in one patient.

Complementary and alternative medicines: A group of practices and products that are not presently considered to be part of conventional medicine, including alternative medical systems (e.g., homeopathic medicine and naturopathic medicine), mind-body interventions (e.g., meditation and mental healing), biologically-based therapies (e.g., dietary supplements, vitamins, herbs, and other natural products), manipulative body-based methods (e.g., acupuncture and massage), and energy therapies (e.g., therapeutic touch and bioelectromagnetic-based therapies).

Complicated urinary tract infection (UTI): Generally used to describe a UTI in a patient who has a structural or functional abnormality or an indwelling foreign body such as a urinary catheter.

Computed tomography (CT) scan: A series of x-ray scans taken from different angles and then compiled by computer to show a cross-section of a body part of interest; a method of body imaging that uses x-ray technology to create cross-sectional images of a person's body.

Computed tomography: Radiographic imaging of anatomic information from a cross-sectional plane of the body.

Concreteness: Inability to think in abstract terms. It may be a primary developmental defect or secondary to organic mental disorder or schizophrenia.

Congenital adrenal hyperplasia: A rare inherited condition resulting from a deficiency in cortisol and aldosterone synthesis with resulting excess androgen production. The clinical presentation depends on the variant of the condition, but it typically manifests as abnormalities in sexual development and/or adrenal insufficiency.

Conidia: Propagating form (spores) of filamentous fungi that are released into soil and air currents. Inhalation of spores is the most common route of infections for endemic fungi and invasive molds.

Conjunctival injection: Erythema of the conjunctiva.

Conjunctivitis medicamentosa: A contact allergy to a topical medication.

Conjunctivitis: Inflammation of the conjunctiva.

Contiguous: Describes two structures that are in close contact, or located next to each other.

Continuous positive airway pressure: Therapy delivered using a nasal mask to improve the patency of the upper airway by maintaining sufficient air pressure to alleviate sleep-disordered breathing.

Contralateral: Pertaining to the opposite side of the body.

Copulation: Sexual union of male and female; coitus; sexual intercourse; also, conjugation between two cells that do not fuse but separate after mutual fertilization.

Cor pulmonale: Right-sided heart failure, usually due to structural lung disease (e.g., pulmonary fibrosis or emphysema).

Corneal arcus: Accumulation of lipid on the cornea.

Coronary artery bypass graft surgery: Thoracic surgery whereby parts of a saphenous vein from a leg or internal mammary artery from the arm are placed as conduits to restore blood flow between the aorta and one or more coronary arteries to "bypass" the coronary artery stenosis (occlusion).

Corpus luteum: The small yellow endocrine structure that develops within a ruptured ovarian follicle and secretes progesterone and estrogen.

Corticotropin-releasing hormone: A hormone released by the hypothalamus that stimulates release of adrenocorticotropic hormone by the anterior pituitary gland.

Cortisol: An adrenal gland hormone responsible for maintaining homeostasis of carbohydrate, protein, and fat metabolism.

Cosyntropin: A synthetic version of adrenocorticotropic hormone.

C-reactive protein: A nonspecific inflammatory marker that may be elevated in osteomyelitis as well as other infections and inflammatory diseases; represents a specific protein produced by the liver during times of inflammation.

Creaming: Aggregation of lipid emulsion particles that then migrate to the surface of the emulsion that can be reversed with mild agitation.

Creatine kinase, creatine kinase myocardial band: Creatine kinase (CK) enzymes are found in many isoforms, with varying concentrations depending on the type of tissue. Creatine kinase is a general term used to describe the nonspecific total release of all types of CK, including that found in skeletal muscle (MM), brain (BB) and heart (MB). CK MB is released into the blood from necrotic myocytes in response to infarction and is a useful laboratory test for diagnosing myocardial infarction. If the total CK is elevated, then the relative index (RI), or fraction of the total that is composed of CK MB, is calculated as follows: RI = (CK MB/CK total) × 100. An RI greater than 2 is typically diagnostic of infarction.

Creatinine: A waste product in the blood produced from the breakdown of protein by-products generated by muscle in the body or ingested in the diet. The kidneys filter blood to remove creatinine and maintain homeostasis. A decline in kidney function results in an increase in creatinine.

Creatinine clearance: The rate at which creatinine is filtered across the glomerulus; an estimate of glomerular filtration rate.

Crescendo: Rapidly increasing symptoms.

Cretinism: Obsolete term for congenital hypothyroidism.

Cross allergenicity: Sensitivity to one drug that results in reaction to a different drug with a similar chemical structure.

Crossover design: A clinical trial design in which patients receive, in sequence, the treatment (or the control), and then after a specified time, receive the opposite arm of the trial. This allows patients to serve as their own controls. Randomization should be

used to determine the order in which a patient receives the treatment and control.

Cryoprecipitate: Component of blood obtained by freezing and thawing plasma that is rich in clotting factors. One unit of cryoprecipitate derived from a unit of whole blood contains a volume of 10 to 20 mL, 80 to 100 units of factor VIII which consists of both the procoagulant activity and the von Willebrand factor, 150 to 250 mg of fibrinogen, 50 to 100 units of factor XIII, and 50 to 60 mg of fibronectin.

Crypt abscess: Neutrophilic infiltration of the intestinal glands (crypts of Lieberkühn); a characteristic finding in patients with ulcerative colitis.

Crystalloids: Resuscitation fluids that are composed of dissolved electrolytes.

Cyanosis: A dark blue or purple discoloration of the skin and mucous membranes due to deficient oxygenation of the blood.

Cyclic citrullinated peptide: A circular peptide (a ring of amino acids) containing the amino acid citrulline. Autoantibodies directed against cyclic citrullinated peptide provide the basis for a test of importance in rheumatoid arthritis.

Cyclooxygenase: Enzymes responsible for metabolizing arachidonic acid to prostaglandins.

Cyst: An abnormal membranous sac within the body that contains liquid or partially solid material.

Cystitis: Cystitis refers to the syndrome associated with a urinary tract infection involving dysuria, frequency, urgency, and occasional suprapubic tenderness.

Cystocele: Hernial protrusion of the bladder, usually through the vaginal wall.

Cytogenetic analysis: Laboratory identification of chromosomes to detect mutational defects.

Cytokines: Regulatory proteins, such as interleukins and lymphokines, that are released by cells of the immune system and act as intercellular mediators in the generation of an immune response.

Cytomegalovirus (CMV) disease: The term used when patients who are already infected with CMV present with classic symptoms that resemble a viral infection and may include fever, malaise, arthralgias, and others.

Cytomegalovirus (CMV) infection: The term used when a patient has anti-CMV antibodies in the blood, when CMV antigens are detected in infected cells, or when the virus is isolated from a culture.

Dactylitis ("hand-foot syndrome"): Diffuse swelling of the hands and/or feet often associated with pain and tenderness.

Deep vein thrombosis: A disorder of thrombus (blood clot) formation causing obstruction of a deep vein in the leg, pelvis, or abdomen.

Dementia: An organic mental disorder characterized by a general loss of intellectual abilities involving impairment in memory, judgment, and abstract thinking, as well as changes in personality.

Denervation: Loss of nerve impulse input, such as by severing a nerve during surgery or nerve impulse blockade farther up the nerve chain.

Dermatophyte: Any microscopic fungus that grows on the skin, scalp, and nails; a microscopic fungus that grows on the skin or mucosa but does not invade deeper tissues.

Desensitization: A method to reduce or eliminate an individual's negative reaction to a substance or stimulus.

Desquamation: Peeling or shedding of the epidermis (superficial layer of the skin) in scales or flakes.

Detrusor muscle: Smooth muscle of the bladder body. When the detrusor muscle contracts, the bladder is emptied of urine.

Detumescence: Reduction or lessening of a swelling, especially the restoration of a swollen organ or body part to normal size; the return of the penis to a flaccid state after an erection.

Diabetes insipidus: Polyuria due to the failure of renal tubules to reabsorb water in response to antidiuretic hormone.

Diabetes mellitus: A group of chronic metabolic disorders characterized by hyperglycemia and associated with long-term microvascular, macrovascular, and neuropathic complications.

Diabetic ketoacidosis: A reversible but life-threatening short-term complication primarily seen in patients with type 1 diabetes caused by the relative or absolute lack of insulin that results in marked ketosis and acidosis.

Diarrhea: Excessive and frequent evacuation of watery feces.

Diarthrodial joint: A joint in which the opposing bony surfaces are covered with a layer of hyaline cartilage and in which some degree of free movement is possible.

Diastolic dysfunction: Abnormal filling of the ventricles during diastole.

Digital rectal examination: Procedure in which the health care professional inserts a gloved finger into the rectum to examine the rectum and the prostate gland for signs of cancer.

Direct current cardioversion: The process of administering a synchronized electrical shock to the chest to simultaneously depolarize all of the myocardial cells, resulting in restoration of normal sinus rhythm.

Directly observed therapy: A treatment method in which patients are under direct observation when they take their medication or receive their treatment. This method is designed to reduce the risk of treatment interruption and to ensure patient adherence.

Disease-free survival: Length of time after treatment during which no disease is found.

Disseminated idiopathic skeletal hyperostosis: Excessive bone formation at skeletal sites subject to stress, generally where tendons and ligaments attach to bone.

Disulfiram-like reaction: Adverse reaction associated with alcohol use manifested by severe nausea, vomiting, and abdominal pain.

DNA mismatch repair genes: Genes that identify and correct errors in DNA base pairs during DNA replication. Mutations in the mismatch repair genes can lead to cancer by allowing abnormal cells to continue to grow.

Dose intensity: Delivery of a predetermined dose per unit of time (e.g., $mg/m^2/wk$).

Down-regulation: The process of reducing or suppressing a response to a stimulus.

Drug of choice: The optimal drug for any given disease state.

Drusen: Tiny yellow or white deposits in the retina.

Ductus arteriosus: The structure that shunts fetal blood flow away from the undeveloped fetal lungs.

Duodenum: The beginning portion of the small intestine, starting at the lower end of the stomach and extending to the jejunum.

Dysarthria: A speech disorder due to weakness or incoordination of speech muscles; speech is slow, weak, and imprecise.

Dysentery: An illness involving severe diarrhea that is often associated with blood in the stool.

Dysesthesias: An unpleasant abnormal sensation.

Dysgeusia: Unpleasant taste in the mouth.
Dyskinesia: Abnormal involuntary movements, which include dystonia, chorea, and akathisia.
Dysmenorrhea: Crampy pelvic pain occurring with or just prior to menses. Primary dysmenorrhea implies pain in the setting of normal pelvic anatomy, whereas secondary dysmenorrhea is due to underlying pelvic pathology.
Dyspareunia: Painful or difficult sexual intercourse.
Dysphagia: Painful or difficult swallowing, accompanied by a sensation of food being stuck in passage.
Dysphonia: Impairment of the voice or difficulty speaking.
Dysphoria: A feeling of general unwellness and discontent.
Dysplasia: Abnormal change in size, shape, or organization of cells in a tissue.
Dyspnea: Difficulty in breathing, often associated with lung or heart disease, and resulting in shortness of breath.
Dyssynergic defecation: A lack of coordination between the pelvic floor muscles and the anal sphincter.
Dystonia: A type of dyskinesia. The movement is slow and twisting. It may be associated with painful muscle contractions or spasms.
Dysuria: Painful urination.

Eburnation: Degeneration of bone into a hard, dense mass with a smooth surface; may occur at articular surfaces of bones in osteoarthritis.
Ecchymoses: Passage of blood from ruptured blood vessels into subcutaneous tissue, causing purple discoloration of the skin.
Ectopic pregnancy: Presence of a fertilized ovum outside the uterine cavity.
Effector cells: Cells that become active in response to initiation of the immune response.
Eisenmenger's syndrome: A congenital heart defect with an abnormal connection between systemic circulation and lung circulation.
Ejection fraction: The fraction of the volume present at the end of diastole that is pushed into the aorta during systole.
Electrocardiogram: A noninvasive method of recording the electrical activity of the heart.
Electroconvulsive therapy: Administration of electric current to the brain through electrodes placed on the head in order to induce seizure activity in the brain, used in the treatment of certain mental disorders.
Electroencephalography: The recording of brain waves via electrodes placed on the scalp or cortex.
Embolism: The sudden blockage of a vessel caused by a blood clot or foreign material that has been brought to the site by the flow of blood.
Embolization: The process by which a blood clot or foreign material dislodges from its site of origin, flows in the blood, and blocks a distant vessel.
Emesis: Vomiting.
Empiric antimicrobial therapy: Antimicrobial therapy given prior to the availability of microbiologic culture results.
Empyema: Pus in the pleural cavity, usually secondary to infection in the lung.
Encephalitis: Acute inflammation of the brain tissue.
Endarterectomy: Excision of the inner lining of an artery occluded by atherosclerotic plaque.
Endogenous: Originating from or produced by metabolic synthesis in the body.
Endometritis: Inflammation of the membrane lining the uterus.
Endoscopic retrograde cholangiopancreatography: A procedure that combines the use of an endoscope with x-rays to examine the ducts that drain the liver, gallbladder, and pancreas.
Endoscopy: A procedure used to evaluate the interior surfaces of an organ by inserting a small scope into the body; through it, one can directly examine almost any part of the intestinal tract. Biopsies can be obtained, polyps removed, and clear images obtained.
Endothelial cells: A single layer of cells surrounding the lumen of arteries.
End-stage liver disease: Liver failure that is usually accompanied by complications such as ascites or hepatic encephalopathy.
Enteral nutrition: Delivery of nutrients via the gastrointestinal tract, either by mouth or by feeding tube.
Enterobacteriaceae: A family of enteric gram-negative bacilli (e.g., *Escherichia coli* or *Klebsiella pneumoniae*).
Enterocytes: Cells lining the small intestine.
Enuresis: Involuntary urination, usually occurring at night or during sleep.
Enzyme-linked immunosorbent assay (ELISA): A biochemical technique used to detect the presence of an antibody or antigen in a sample. The technique uses two antibodies. The first is specific to the antigen and the second is coupled to an enzyme. The second antibody will cause a chromogenic or fluorogenic substrate to produce a signal. Because the ELISA can be used to evaluate the presence of either an antibody or an antigen in a sample, it is useful for both determining serum antibody concentrations (e.g., with human immunodeficiency virus or West Nile virus) and detecting the presence of an antigen.
Epilepsy: A neurologic disorder characterized by recurring motor, sensory, or psychic malfunction with or without loss of consciousness or convulsive seizures.
Erectile dysfunction: The inability to achieve or maintain an erection sufficient for sexual intercourse.
Erythema multiforme: A rash characterized by papular (small raised bumps) or vesicular lesions (blisters), and reddening or discoloration of the skin, often in concentric zones around the lesion.
Erythematous: Flushing of the skin caused by dilation of the capillaries. It is often a sign of inflammation and infection.
Erythrocyte sedimentation rate (ESR): A nonspecific inflammatory marker that may be elevated in some infections and inflammatory diseases; specifically, the ESR is obtained from a blood sample by measuring the distance that red blood cells precipitate after 1 hour.
Erythropoiesis-stimulating agents: Agents developed by recombinant DNA technology that have the same biologic activity as endogenous erythropoietin to stimulate erythropoiesis (red blood cell production) in the bone marrow.
Erythropoietin: A hormone primarily produced by the progenitor cells of the kidney that stimulates red blood cell production in the bone marrow. Lack of this hormone leads to anemia.
Esophageal stricture: Narrowing of the esophageal lumen. Esophageal strictures are usually benign and caused by acid refluxing into the lower esophagus.
Esophageal varices: Dilated blood vessels in the esophagus.
Esophagitis: Inflammation of the esophagus caused by frequent regurgitation of acid and peptic juices from the stomach. The main symptoms are heartburn, regurgitation of bitter fluid, and sometimes difficulty in swallowing. Complications of esophagitis

include narrowing (stricture) of the esophageal lumen, ulcerations, and hemorrhage.

Essential fatty acid deficiency: Deficiency of linoleic acid, linolenic acid, and/or arachidonic acid, characterized by hair loss, thinning of skin, and skin desquamation. Long-chain fatty acids include trienes (containing three double-bonds [e.g., 5,8,11-eicosatrienoic acid, or Mead acid; trienoic acids) and tetraenes (containing four double-bonds [e.g., arachidonic acid]). Biochemical evidence of essential fatty acid deficiency includes a triene:tetraene ratio greater than 0.4 and low linoleic or arachidonic acid plasma concentrations.

Euthymia: Normal mood.

Euthyroid: State of normal thyroid function or hormone activity.

Event-free survival: The length of time after treatment that a person remains free of certain negative events.

Evoked potential testing: A procedure in which sensory nerve pathways are stimulated and the time lapse to electrical response in the corresponding area of the brain is measured.

Exanthem: Eruption of the skin.

Exfoliative dermatitis: Widespread dermatitis characterized by scaling and shedding of the skin and usually accompanied by redness. Also called pityriasis rubra.

Exogenous: Originating outside a body organ or part of the body.

Exophthalmos: Abnormal protrusion of the eyeball; seen in Graves' disease.

Exploratory laparotomy: Surgical incision into the abdominal cavity, performed to examine the abdominal organs and cavity in search of an abnormality and diagnosis.

External beam radiotherapy: Treatment by radiation emitted from a source located at a distance from the body; also called beam therapy and external beam therapy.

Extra-abdominal: Refers to operations taking place outside the abdominal cavity.

Extrapyramidal symptoms (EPS): Adverse effects of medications such as antipsychotics. EPS include dystonia (involuntary muscle contractions), tardive dyskinesia (repetitive, involuntary movements), parkinsonian symptoms (akinesia and tremors), and akathisia (motor restlessness or anxiety).

Extravasation: Movement of fluid from inside a blood vessel into the surrounding tissues; for example, leakage or infiltration of a vesicant chemotherapy agent into local tissue.

Fabry's disease: An x-linked recessive lipid storage disease with an accumulation of the glycosphingolipid.

Facultative anaerobe: An organism that makes adenosine triphosphate by aerobic respiration if oxygen is present, but switches to fermentation under anaerobic conditions.

Facultative: Biologically capable but not restricted to a particular function or mode of life (e.g., survival within macrophages).

Failure to thrive: Below-average growth due to a medical condition. A pronounced lack of growth in a child because of inadequate absorption of nutrients or a serious heart or kidney condition, resulting in below-average height and weight.

Familial adenomatous polyposis: An inherited condition in which numerous polyps form, mainly in the epithelium of the large intestine. While these polyps start out benign, malignant transformation into colon cancer occurs 100% of the time when not treated.

Felty's syndrome: An extra-articular manifestation of rheumatoid arthritis associated with splenomegaly and neutropenia.

Festination: Walking with short, rapid, shuffling steps.

Fetal growth restriction: Diminished fetal growth that often leads to low birth weight.

Fibrin: An insoluble protein that is one of the principal ingredients of a blood clot. Fibrin strands bind to one another to form a fibrin mesh. The fibrin mesh often traps platelets and other blood cells.

Fibrinolysis: A normal ongoing process that dissolves fibrin and results in the removal of small blood clots; hydrolysis of fibrin.

Fibroadenoma: A benign neoplasm derived from glandular epithelium that commonly occurs in breast tissue.

Fistula: Abnormal connection between two internal organs (e.g., arteriovenous fistula, which is a connection between an artery and a vein), or between an internal organ and the exterior or skin (e.g., enterocutaneous fistula, which is a connection between the intestine and the skin).

Flame hemorrhage: Bleeding into the sclera in a pattern similar to a fork or flame. May be associated with bacterial endocarditis.

Flank pain: Pain in the side of the trunk between the right or left upper abdomen and the back (costovertebral angle).

Flight of ideas: A nearly continuous flow of rapid speech and thought that jumps from topic to topic, usually with topics loosely connected.

Flow cytometry: A method of measuring the number of cells in a sample, the percentage of live cells in a sample, and certain characteristics of cells, such as size, shape, and the presence of tumor markers on the cell surface. The cells are stained with a light-sensitive dye, placed in a fluid, and passed in a stream before a laser or other type of light. The measurements are based on how the light-sensitive dye reacts to the light.

Foam cell: Lipid-laden white blood cells.

Fragility fracture: A fracture resulting from a fall from standing height or lesser trauma.

Frank-Starling mechanism: The ability of the heart to change its force of contraction and therefore stroke volume in response to changes in venous return.

Fremitus: A sensation felt by a hand placed on a part of the body (as the chest) that vibrates during speech.

Fresh frozen plasma: Plasma that is frozen within hours after donation to preserve clotting factors.

Friable: Easily crumbled, pulverized, or reduced to powder.

Frontotemporal: Located to the front or side of the head.

Fructooligosaccharides: Polymers of fructose that reach the colon undigested and are broken down there to short-chain fatty acids by bacterial enzymes.

Functional bowel disease: A condition characterized by gastrointestinal symptoms in the absence of a demonstrated pathologic condition.

Galactorrhea: Inappropriate breast milk production.

Gallstone (cholelithiasis): A solid formation in the gallbladder or bile duct composed of cholesterol and bile salts.

Gamma knife: A device that uses multiple converging beams of gamma radiation from cobalt-60 to highly focus radiation on small tumors within the brain.

Gastric bypass: A surgical procedure for weight loss that elicits its effectiveness through malabsorption and volume limitation. The procedure involves full partitioning of the proximal gastric segment into a jejunal loop.

Gastritis: Acute or chronic inflammation of the lining of the stomach.

Gastroenteritis: Inflammation of the gastrointestinal tract causing nausea, vomiting, diarrhea, and fever.

Gastroesophageal reflux disease: Symptoms or mucosal damage that result from abnormal reflux of gastric contents into the esophagus.

Gastroparesis: Partial or mild paralysis of the stomach.

Gastroplasty: A surgical procedure for weight loss that elicits its effectiveness through gastric volume limitation. The procedure involves partial partitioning at the proximal gastric segment with the placement of a gastric outlet stoma of fixed diameter.

Gastroschisis: Rare congenital fissure of the abdominal wall.

Gastrostomy: Operative placement of a new opening into the stomach, usually associated with feeding tube placement.

Geniculate nucleus: The portion of the brain that processes visual information from the optic nerve and relays it to the cerebral cortex.

Genotype: The genetic constitution of an individual.

Gigantism: A condition of abnormal size or overgrowth of the entire body or of any of its parts.

Glasgow Coma Scale (GCS): A scale for evaluating level of consciousness after central nervous system injury (evaluates eye opening and verbal and motor responsiveness).

Glomerular filtration rate (GFR): The volume of plasma that is filtered by the glomerulus per unit time, usually expressed as mL/minute or mL/minute/1.73 m^2, which adjusts the value for body surface area. GFR is the primary index used to describe overall renal function.

Glomerulonephritis: Glomerular lesions that are characterized by inflammation of the capillary loops of the glomerulus. These lesions are generally caused by immunologic, vascular, or other idiopathic diseases. Glomerulonephritis can lead to high blood pressure and loss of kidney function.

Gluconeogenesis: Formation of glucose from precursors other than carbohydrates (especially by the liver and kidney) using amino acids from proteins, glycerol from fats, or lactate produced by muscle during anaerobic glycolysis.

Glutamate: An excitatory amino acid found in the central nervous system.

Glycogenolysis: The process by which glycogen is broken down to glucose in body tissues.

Glycosuria: The presence of abnormal amounts of glucose in the urine.

Goiter: A nonmalignant enlargement of the thyroid gland, visible as a swelling at the front of the neck, that is often associated with iodine deficiency.

Gonioscopy: Examination of the anterior chamber angle of the eye. A gonioprism or Goldman lens is used to perform gonioscopic evaluation.

Goodpasture's syndrome: A rare autoimmune disease that can affect the lungs and kidneys.

Gout: A group of disorders of purine metabolism, manifested by various combinations of hyperuricemia; recurrent acute inflammatory arthritis induced by crystals of monosodium urate monohydrate; tophaceous deposits of monosodium urate monohydrate crystals in and around the joints of the extremities, which may lead to crippling destruction of joints; and uric acid urolithiasis.

Graft-versus-host disease: Failure of a recipient's body to accept a transplanted tissue or organ as the result of immunologic incompatibility; immunologic resistance to foreign tissue.

Graft-versus-tumor effect: Cytotoxic T lymphocytes in the donor stem cells have anti-cancer activity.

Grandiosity: Exaggerated sense of self-importance, ideas, plans, or abilities.

Granuloma: A small nodular delimited aggregation of mononuclear inflammatory cells, or such a collection of modified macrophages usually surrounded by a rim of lymphocytes. Generally denotes a chronic, cell-mediated immune response.

Gummatous: A tumor of rubbery consistency that is characteristic of the tertiary stage of syphilis.

Gut-associated lymphoid tissue (GALT): Lymphoid tissue, including Peyer's patches, found in the gut that is important for providing localized immunity against pathogens.

Haptenation: The process by which a drug, usually of low molecular weight, is bound to a carrier protein or cell and becomes immunogenic.

Heberden's nodes: Small bony growths found on the terminal phalanges of the fingers in patients with osteoarthritis.

Hematochezia: The presence of visible bright red blood in the stool.

Hematogenous: Spread through the blood.

Hematopoietic cell transplantation: Infusion of hematopoietic cells from a donor after administration of a combination of chemotherapy and/or radiation.

Hematuria: Blood in the urine.

Hemiballismus: A rare movement disorder that can be life-threatening. Patients with hemiballismus have a dismal prognosis, with physical exhaustion, injuries, and medical complications often leading to death.

Hemiparesis: Weakness or slight paralysis involving one side of the body.

Hemisensory deficit: Loss of sensation on one side of the body.

Hemithorax: One side of the chest.

Hemolytic uremic syndrome: A syndrome characterized by microangiopathic hemolytic anemia, acute renal failure, and a low platelet count (thrombocytopenia).

Hemoptysis: The expectoration of blood or blood-tinged sputum from the larynx, trachea, bronchi, or lungs.

Hemorrhagic conversion: Conversion of an ischemic stroke into a hemorrhagic stroke.

Hemostasis: Cessation of bleeding through natural (clot formation or constriction of blood vessels), artificial (compression or ligation), or surgical means.

Heparin-induced thrombocytopenia: A clinical syndrome of IgG antibody production against the heparin-platelet factor 4 complex occurring in approximately 1% to 5% of patients exposed to either heparin or low-molecular-weight heparin. Heparin-induced thrombocytopenia results in excess production of thrombin, platelet aggregation, and thrombocytopenia (due to platelet clumping), often leading to venous and arterial thrombosis, amputation of extremities, and death.

Hepatic encephalopathy: Change in mental or neurologic status secondary to progressive liver disease; or confusion and disorientation that a patient with advanced liver disease experiences due to accumulation of ammonia.

Hepatic steatosis: Fatty infiltration of the liver.

Hepatocytes: The basic functional cells of the liver.

Hepatojugular reflex: A physical sign evidenced by distention of the jugular vein with application of pressure on the abdomen over the liver.

Hepatosplenomegaly: Enlargement of the liver and spleen.

Hepatotoxicity: Toxicity to the liver causing damage to liver cells.
Herniation: A protrusion through an abnormal bodily opening.
Heterozygous: Having different alleles at a gene locus.
Hirschsprung's disease: A disease of the small intestine that causes constipation (bowel movements are difficult).
Hirsutism: Excess body hair.
HIV genotype: A type of resistance testing for human immunodeficiency virus (HIV) in which a patient's blood sample is obtained, their HIV RNA is sequenced, and mutations that have developed that may confer resistance to antiretrovirals are reported.
HIV phenotype: A type of resistance testing for human immunodeficiency virus (HIV) in which a patient's blood sample is obtained, and the patient's HIV genes that encode for reverse transcriptase and protease are removed and placed in an HIV viral vector. This viral vector is replicated in a cell culture system with varying concentrations of antiretrovirals. A drug concentration–viral inhibition curve is developed and the concentration needed to inhibit 50% of the patient's virus is reported. This is used to predict resistance versus susceptibility.
HIV virtual phenotype: A database of matching human immunodeficiency virus (HIV) genotypes and phenotypes is developed. When an HIV genotype for a patient is obtained, the database is used to predict the patient's phenotype based on their actual genotype using matches that occur in the database.
Homozygous: Having identical alleles at a gene locus.
Hot flashes: A feeling of warmth that is commonly accompanied by skin flushing and mild to severe perspiration.
Hypothalamic–pituitary–adrenal (HPA) axis: A neuroendocrine feedback loop that controls response to stress.
Human chorionic gonadotropin: A hormone secreted by the placenta that is used to aid in the determination of pregnancy.
Human leukocyte antigens (HLA): Groups of genes found on the major histocompatibility complex, which contain cell-surface antigen-presenting proteins. The body uses HLA to distinguish between self-cells and non–self-cells.
Humoral: Relating to products secreted into the blood or body fluids.
Hydramnios: Excess amniotic fluid.
Hydronephrosis: Distention of the pelvis and kidney with urine resulting from obstruction of the ureter.
Hyperalgesia: An increased pain response to a stimulus that normally causes pain.
Hyperbilirubinemia: Abnormally high concentrations of the bile pigment bilirubin in the bloodstream. Hyperbilirubinemia is defined as a total serum bilirubin level greater than 5 mg/dL.
Hypercalcemia: Excessive calcium concentration in the blood.
Hypercalciuria: Excessive amount of calcium in the urine.
Hypercapnia: Abnormally high concentration of carbon dioxide in the blood.
Hypercoagulable state: A disorder or state of excessive or frequent thrombus formation; also known as thrombophilia.
Hyperemesis gravidarum: A rare disorder of severe and persistent nausea and vomiting during pregnancy that can result in dehydration, malnutrition, weight loss, and hospitalization.
Hyperemic: Denotes an increased amount of blood in a part of the body.
Hyperglycemia: Abnormally high blood glucose concentration.
Hyperglycemic hyperosmolar nonketotic syndrome: Severe increase in serum glucose concentration without the production of ketones, leading to an increase in serum osmolality and symptoms such as increased thirst, urination, weakness, fatigue, confusion, and in severe cases convulsions and/or coma.
Hyperinsulinemia: High concentration of insulin in the blood.
Hyperopia: Farsightedness.
Hyperosmolar hyperglycemic state: A potentially fatal short-term complication most commonly seen in older patients with type 2 diabetes caused by an insufficiency of insulin action that leads to alterations of osmolality and hyperglycemia, but without the ketosis and acidosis seen in diabetic ketoacidosis.
Hyperpathia: A painful syndrome characterized by increased reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold.
Hyperpigmentation: A common darkening of the skin which occurs when an excess of melanin forms deposits in the skin.
Hyperplasia: An increase in the number of cells within a tissue leading to an increase in tissue or organ size.
Hyperprolactinemia: Elevated serum prolactin characterized by prolactin serum concentrations greater than 20 ng/mL (20 mcg/L) in men or 25 ng/mL (25 mcg/L) in women.
Hyperthyroidism: State caused by excess production of thyroid hormone.
Hypertrichosis: Excessive growth of hair.
Hyperuricemia: Elevated serum uric acid concentration, defined as a level greater than 7.0 mg/dL.
Hypochlorhydria: Hypoacidity; decreased hydrochloric acid secretion by the stomach.
Hypocretin: A wakefulness-promoting hypothalamic neuropeptide, a deficiency of which is involved in the pathophysiology of narcolepsy.
Hypogammaglobulinemia: Reduced levels of antibodies.
Hypoglycemia: Abnormal decrease in blood glucose below the normal range.
Hypogonadism: A condition resulting from or characterized by abnormally decreased functional activity of the gonads, with retardation of growth and sexual development; or reduced or absent secretion of hormones from the sex glands resulting in low testosterone levels in men.
Hypomania: Abnormal mood elevation that does not meet the criteria for mania.
Hypopituitarism: A clinical disorder characterized by complete or partial deficiency in pituitary hormone production.
Hypothyroidism: State caused by inadequate production of thyroid hormone.
Hypovolemic shock: A shock state characterized by an inadequate intravascular volume to meet the oxygen and metabolic needs of the body.
Hypoxemia: Deficient oxygenation of the blood.
Hypoxia: A pathologic condition in which the body (generalized hypoxia) or region of the body (tissue hypoxia) is deprived of adequate oxygen supply (partial arterial oxygen pressure less than 80 mm Hg). Hypoxia in which there is complete deprivation of the oxygen supply is referred to as anoxia.
Hysterectomy: Excision of the uterus.

Immune reconstitution syndrome: A syndrome characterized by fever and worsening of clinical symptoms of opportunistic infections or new symptoms occurring within weeks after starting antiretroviral therapy. This has been described for mycobacterial infections (*Mycobacterium avium* complex and *Mycobacterium tuberculosis*), *Pneumocystis jiroveci* pneumonia, toxoplasmosis,

hepatitis B and C viruses, cytomegalovirus infection, varicella-zoster virus infection, cryptococcal infection, and progressive multifocal leukoencephalopathy.

Immunocompromised: A condition in which the immune system is not functioning normally. This condition is seen in the very young, the very old, human immunodeficiency virus–infected individuals, and in transplant patients. An immunocompromised person is susceptible to opportunistic infections.

Immunogenicity: The property that gives a substance the ability to provoke an immune response.

Immunoglobulin G index: The ratio of immunoglobulin G to protein in the serum or cerebrospinal fluid.

Immunophenotype: The process of identification and quantitation of cellular antigens through fluorochrome-labeled monoclonal antibodies.

Implantable cardioverter-defibrillator (ICD): A device implanted into the heart transvenously with a generator implanted subcutaneously in the pectoral area that provides internal electrical cardioversion of ventricular tachycardia or defibrillation of ventricular fibrillation.

Index patient: The patient originally diagnosed with a disease.

Indirect immunofluorescence assay (IFA): A laboratory test used to detect antibodies in serum or other body fluid. The specific antibodies are labeled with a compound that will make them glow a fluorescent green color when observed microscopically under ultraviolet light.

Induration: An increase in the fibrous elements in tissue commonly associated with inflammation and marked by loss of elasticity.

Infarction: The formation of an infarct, an area of tissue death due to a local lack of oxygen.

Infective endocarditis: Historically referred to as bacterial endocarditis, this is an infection, either acute or subacute, that primarily affects the heart valves, but may extend into other surrounding areas of the heart.

Inotropic: Relating to or influencing the force of muscular contractions, usually referring to changes in the contractile state of the heart.

Insensate: Devoid of sensation or feeling.

Insulin-like growth factor-I: An anabolic peptide that acts as a direct stimulator of cell proliferation and growth in all body cells.

Insulin secretagogue: A substance or medication that stimulates insulin secretion from the pancreas.

Insulin sensitizer: A substance that increases the action of insulin in peripheral tissues by reducing the effects of insulin resistance.

International Normalized Ratio (INR): The ratio of the patient's clotting time to the clinical laboratory's mean reference value; normalized by raising it to the International Sensitivity Index (ISI) power to account for differences in thromboplastin reagents. Therefore, INR = (patient's prothrombin time/laboratory's mean normal prothrombin time)$_{ISI}$.

Intima: The inner layer of the wall of an artery or vein.

Intra-abdominal: Within the abdominal cavity.

Intra-articular: In the hollow space within joints.

Intrapartum: During labor and delivery.

Intraperitoneal: Within the peritoneal cavity.

Intrathecal: Drug administration into the cerebrospinal fluid of the spinal cord.

Intravenous pyelogram: Radiograph of the urinary tract, including the kidney, ureters, urinary bladder, and urethra; radiographic contrast media that is filtered 100% by the glomerulus is given intravenously. Timed x-rays are taken after administration of the contrast media to assess anatomy and function of the organs in the urinary tract.

Intussusception: The folding of one part of the intestine into the lumen of an immediately adjoining part; or the enfolding of one segment of the intestine within another.

Iontophoresis: Introduction of a medication into tissue through use of an electric current.

Ipsilateral: Pertaining to the same side of the body.

Iron hematoxylin: Stain or dye to identify cell nuclei or identifiable characteristics of an organism.

Janeway lesion: A finding of endocarditis wherein there are nonraised and nonpainful linear lines on the palms of the hands or soles of the feet.

Jarisch-Herxheimer reaction: A reaction to antibiotic therapy commonly seen in secondary syphilis wherein the patient develops a skin rash and temperature.

Jejunum: The section of the small intestine between the duodenum and the ileum.

Jejunostomy: Operative placement of a new opening into the jejunum, usually associated with feeding tube placement.

Karyotypic: Number, size, and structure of cell chromosomes.

Kegel exercises: Specific exercises that strengthen the pelvic floor muscles and help to prevent and treat stress incontinence.

Keratinocyte: The epidermal cell that synthesizes keratin, making up 95% of all epidermal cells; commonly called "skin cells."

Keratitis: Infection of the cornea.

Keratoconjunctivitis sicca: Dryness of conjunctiva and cornea; a component of Sjögren's syndrome.

Keratotic: Pertaining to any horny growth such as a wart or callus.

Kernig's sign: Sign associated with meningitis, in which reflex contraction or spasm of the hamstring muscle occurs when extending the lower leg at an angle greater than 90° to the body.

Ketosis: An abnormal increase of ketone bodies present in conditions of reduced or disturbed carbohydrate metabolism.

Koebner phenomenon: The occurrence of psoriatic lesions due to skin trauma.

Korotkoff sounds: The noise heard over an artery by auscultation when pressure over the artery is reduced below the systolic arterial pressure.

Kyphosis: Abnormal curvature of the spine resulting in protrusion of the upper back; hunchback.

Lactic acidosis: A condition caused by build-up of lactic acid in the body. It leads to acidification of the blood (acidosis), and is a form of metabolic acidosis.

Lactose intolerance: Inability of the body to digest lactose.

Lagophthalmos: Poor closure of the upper eyelid.

Lamina cribrosa: A series of perforated sheets of connective tissue that the optic nerve passes through as it exits the eye.

Laminectomy: Excision of the posterior arch of a vertebra to relieve pressure on the spinal cord.

Laparoscopy: A type of surgical procedure in which a small incision is made, usually in the navel. A viewing tube (laparoscope) which has a small camera on the eyepiece is inserted, allowing examination of the abdominal and pelvic organs using a video

monitor connected to the tube. Other small incisions can be made to insert instruments to perform procedures. This procedure is less invasive than regular open abdominal surgery (laparotomy).

Laparotomy: Surgical opening of the abdominal cavity.

Lentigines: Plural of lentigo, which is a small, flat, tan to dark brown or black, macular melanosis on the skin that looks like a freckle but is histologically distinct. Lentigines do not darken on exposure to sunlight, freckles do.

Leukemoid reaction: An elevated white blood cell count that is a physiologic response to stress or infection (as opposed to a primary blood malignancy, such as leukemia).

Leukocytoclastic: The breaking up of white blood cells.

Leukocytosis: Elevation of the white blood cell count above the normal range.

Leukopenia: A reduction in the circulating white blood cell count; also a condition in which the number of circulating white blood cells is abnormally low due to decreased production of new cells, possibly in conjunction with medication toxicities.

Leukostasis: Abnormal intravascular leukocyte aggregation and clumping seen in leukemia patients. The brain and the lungs are the two most frequent organs involved.

Lewy bodies: Abnormal masses inside some nerve cells. They occur in a variety of locations, and their structure and composition vary depending on location.

Lhermitte's sign: Paresthesias radiating down the back of the extremities with neck flexion; also tingling or shock-like sensation passing down the trunk when the neck is flexed.

Libido: Conscious or unconscious sexual desire.

Ligament of Treitz: Suspensory muscle of the duodenum; the tissue that connects the duodenum to the diaphragm.

Linea nigra: Common physical finding during pregnancy, which manifests as a dark line on the skin running from the navel to the pubis.

Linear accelerator: A device that uses microwave technology to accelerate electrons in a highly focused beam to deliver targeted radiation to tumor sites.

Lipase: A pancreatic enzyme that cleaves lipids.

Lipolysis: The splitting up (hydrolysis) or chemical decomposition of fat.

Lipophilic: Having an affinity for fatty substances.

Lipoprotein lipase: Enzyme located in the capillary endothelium involved in the breakdown of intravenous lipid emulsion particles.

Locus ceruleus: Nucleus of norepinephrine-containing neurons located in the brain stem that are responsible for physiologic response to stress and panic.

Lower urinary tract infection (UTI): Includes infections of the bladder, urethra, and (in men) prostate and epididymis.

Luteolysis: The structural and functional degradation of the corpus luteum that occurs at the end of the luteal phase in the absence of pregnancy; caused by the hormones prostaglandin-2α and oxytocin. Communication between the corpus luteum and uterine endometrium is necessary for luteolysis.

Lymphadenectomy: Surgical excision of lymph nodes.

Lymphadenitis: Inflammation of the lymph nodes, which become swollen, painful, and tender.

Lymphatic system: The tissues and organs that produce, store, and carry white blood cells that fight infection and disease. This system includes the bone marrow, spleen, thymus, and lymph nodes and a network of thin tubes that carry lymph and white blood cells.

Lymphoproliferative: Of or related to the growth of lymphoid tissue.

Maceration: The softening or breaking down of a solid by leaving it immersed in a liquid.

Macrophages: Large scavenger cells present in connective tissue and many major organs that remove bacteria.

Macula: An oval, yellow-pigmented area on the central retina containing color-sensitive rods and the central point of sharpest vision.

Maculopapular: Describes a rash that contains both macules and papules. A macule is a flat discolored area of the skin, and a papule is a small raised bump. A maculopapular rash is usually a large area that is red and has small, confluent bumps.

Magnetic resonance imaging (MRI): Method of body imaging that uses a magnetic field and radio waves to create cross-sectional images of one's body, which provides detailed pictures of organs and tissues.

Manometry: Measurement of pressures within organs of the body. Manometry is often used to indicate muscular activity in motile tubes such as the esophagus.

Mastalgia: Tenderness of the breast.

Matrix metalloproteinases: Zinc-dependent enzymes capable of degrading extracellular matrix proteins, including connective tissue.

Mean arterial blood pressure: A calculated measure of arterial blood pressure; mean arterial blood pressure = (2 × diastolic blood pressure + systolic blood pressure)/3.

Meatal stenosis: Narrowing of the urethral opening at the tip of the penis.

Meconium: The first intestinal discharge or "stool" of a newborn infant, usually green in color and consisting of epithelial cells, mucus, and bile.

Media: The middle layer of the wall of an artery or vein.

Mediastinitis: Inflammation of the midline partition of the chest cavity.

Mediastinum: The space in the thoracic cavity between the pleural sacs and behind the sternum.

Medullary cystic disease: A hereditary kidney disorder characterized by gradual and progressive loss of kidney function because of cysts in the kidney medulla.

Melanosis: Excessive pigmentation of the skin due to a disturbance in melanin pigmentation; also called melanism.

Melasma: Facial pigmentation found across the upper cheeks, nose, and forehead.

Menarche: The onset of menstrual periods, usually occurring between the ages of 10 and 17.

Meninges: Group of three membranes (dura mater, pia mater, arachnoid) surrounding the brain and spinal cord.

Meningitis: An acute inflammation of the membranes surrounding the brain or spinal cord (meninges) and the cerebrospinal fluid in contact with these membranes.

Menopause: Permanent cessation of menstruation following the loss of ovarian follicular activity.

Menorrhagia: Menstrual blood loss of greater than 80 mL per cycle; a more practical definition is heavy menstrual flow associated with problems of containment of flow, unpredictably heavy flow days, or other associated symptoms.

Mesocortical: A neural pathway that connects the ventral tegmentum to the cortex, particularly the frontal lobes. It is one of the major dopamine pathways in the brain.

Mesothelioma: A rare benign or malignant tumor affecting the lining of the chest or abdomen. Exposure to asbestos fibers is the most common risk factor for mesothelioma.

Metabolic acidosis: An acid-base disorder caused by overproduction or accumulation of acid (often lactic acid; see lactic acidosis) or a deficit of base (i.e., bicarbonate).

Metabolic alkalosis: Increased alkalinity of body fluids caused by excessive alkali (usually bicarbonate) intake or excessive acid loss (e.g., from vomiting).

Metalloproteinase: A family of protein-hydrolyzing endopeptidases that contain zinc ions as part of the active structure.

Metastasis: The migration of cancer cells from the original tumor site through the blood and lymph vessels to produce cancers in other tissues.

Micelle: A microscopic particle of digested fat and cholesterol.

Microalbuminuria: Presence of small quantities of urine albumin (a urine albumin test measures the amount of protein in urine); the presence of a small amount of albumin (30 to 300 mg/day) in the urine, which is an early sign of chronic kidney disease.

Micrographia: Small handwriting, often seen in patients with Parkinson's disease.

Microvascular pulmonary emboli: An obstruction in the small blood vessels in the lung caused by material (e.g., blood clot, fat, air, and foreign body) that is carried through the circulation until it lodges in another small vessel.

Micturition: Voiding; urination.

Migraineur: A person who suffers from migraine headaches.

Minimum bactericidal concentration: The lowest concentration of antibiotic that will eliminate 3 logs or 99.9% of bacteria.

Minimum inhibitory concentration: The lowest concentration of a drug that will visually inhibit the growth of a microorganism.

Miosis: Pupillary constriction.

Mixed acid-base disorder: More than one of the following disorders occurring simultaneously: acidosis (metabolic or respiratory) and alkalosis (metabolic or respiratory).

Mixed mood episodes: Symptoms of mania and depression occurring simultaneously or in close juxtaposition.

Molds: Multicellular filamentous fungi that asexually reproduce by formation of reproductive hyphae that release conidia into the environment.

Monocytes: A leukocyte that protects against blood-borne pathogens which rapidly moves to sites of infection in tissues. Monocytes consist of 3% to 8% of the leukocytes in the blood. In tissues, monocytes mature into different types of macrophages at different anatomic locations. Their main function is phagocytosis of foreign material, cellular debris, and pathogens that are not effectively controlled by neutrophils.

Monoparesis: Slight or incomplete paralysis affecting a single extremity or part of one.

Monosodium urate: A crystallized form of uric acid that can deposit in joints leading to an inflammatory reaction and the symptoms of gout.

Morphology: The science of structure and form of cells without regard to function.

Motor tics: Sudden, involuntary muscle movements (e.g., spasms).

Mucositis: Inflammation of mucous membranes, typically within the oral and esophageal mucosa. Mucositis is usually associated with certain chemotherapy agents and radiation therapy involving mucosal areas.

Mucous colitis: A condition of the mucous membrane of the colon characterized by pain, constipation, or diarrhea (sometimes alternating), and passage of mucus or mucous shreds.

Multidrug resistant tuberculosis (TB): The presence of at least 1% of *Mycobacterium* strains in a bacterial population or culture that are resistant to at least isoniazid and rifampin.

Multiparity: Condition of having given birth to multiple children.

Multiple organ dysfunction syndrome: Relatively simultaneous failure of more than one organ, regardless of etiology.

Mydriasis: Pupillary dilation.

Myelin: A protein and phospholipid sheath that surrounds the axons of certain neurons. Myelinated nerves conduct impulses more rapidly than nonmyelinated nerves.

Myelodysplastic syndrome: A diverse collection of hematologic conditions united by ineffective production of some or all of the blood cells.

Myeloproliferative disorder: A group of diseases of the bone marrow in which excess cells, usually lymphocytes, are produced.

Myelosuppression: A condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets. Myelosuppression is a side effect of some cancer treatments.

Myocardial contractility: The force of contraction of the heart during systole.

Myocarditis: Inflammation of the muscular wall of the heart.

Myoclonus: A sudden, involuntary jerking of a muscle or group of muscles.

Myoglobinuria: The presence of myoglobin in urine.

Myopathy: Any disease of the muscle causing weakness, pain, and tenderness.

Myringotomy: A surgical incision in the tympanic membrane to relieve pressure and drain fluid from the middle ear.

Myxedema: Advanced hypothyroidism characterized by a relatively firm edema of subcutaneous tissue, subnormal body temperature, dryness and loss of hair, hoarseness, and muscle weakness.

Nasal polyposis: Presence of several polyps (benign growths) in the nasal cavity.

Nasal scotoma: An area of blindness in the nasal portion of peripheral vision.

Nascent: Immature; beginning.

Nasolacrimal occlusion: The closing of the tear duct by application of manual pressure to decrease systemic absorption of a drug.

Nausea: A feeling of sickness or discomfort in the stomach that may come with an urge to vomit.

Necrotizing fasciitis: A severe soft-tissue infection involving the superficial fascia.

Nelson's syndrome: A condition characterized by the aggressive growth of a pituitary tumor and hyperpigmentation of the skin.

Neoadjuvant therapy: Therapy given prior to the primary treatment. In cancer, it is usually given prior to surgery to make the surgical procedure easier to perform.

Neovascularization: New blood vessel formation (vascularization) especially in abnormal quantity (as in some conditions of the retina) or in abnormal tissue (as a tumor).

Nephrolithiasis: A condition marked by the presence of renal calculi (stones) in the kidney or urinary system.

Nephron: The working unit of the kidney that filters blood to remove fluid, toxins, and drugs. Each kidney contains approximately 1 million nephrons.

Nephrostomy: Insertion of a catheter through the skin into the renal pelvis to bypass ureteral obstruction and facilitate urine drainage.

Neuralgia: Pain that extends along the course of one or more nerves.
Neural tube defects: Birth defect resulting from improper development of the central nervous system.
Neuritic (senile) plaques: Microscopic lesions composed of fragmented axon terminals and dendrites surrounding a core of amyloid seen in the cerebral cortex in Alzheimer's disease.
Neuritis: Inflammation of a nerve.
Neurofibrillary tangles: Intracellular knots or clumps of neurofibrils seen in the cerebral cortex in Alzheimer's disease.
Neuroimaging: Radiologic studies of the brain, usually referring to computed tomography (CT) or magnetic resonance imaging (MRI).
Neurologic focality: Symptomatic sensory or motor deficits that point to specific lesions or dysfunction in the brain.
Neuropathic pain: Pain resulting from a lesion or dysfunction of the nervous system.
Neuropathy: An abnormal and usually degenerative state of the nervous system or nerves.
Neurotransmitter: Chemical intermediary in the nervous system that facilitates transmission of impulses across synapses.
Neutralizing antibodies: Antibodies that develop in response to a therapeutic agent that decrease the efficacy of the agent.
Nuclear factor-κB: Nuclear factor-kappa B (NF-κB) is a transcription factor that regulates cytokine production.
Nociceptors: Receptors for pain caused by injury from physical stimuli (mechanical, electrical, or thermal) or chemical stimuli (toxins). Nociceptors are located in the skin, muscles, and in the walls of the viscera.
Nocturia: Urination at night, especially if excessive.
Nocturnal polysomnography: Visual and electrophysiologic assessment of human sleep minimally composed of electroencephalogram, electrooculogram, and electromyogram that allows determination of sleep stage, breathing events, and muscle movements.
Nodules: Subcutaneous knobby tissue mass over bony prominences or extensor surfaces.
Nonbacterial thrombotic endocarditis: Endocarditis caused by noninfectious vegetations.
Nonnucleoside reverse transcriptase inhibitor (NNRTI): A noncompetitive inhibitor of the viral reverse transcriptase enzyme that binds to the active site of the enzyme itself, rather than by terminating the enzymatic product. NNRTIs are only active against human immunodeficiency virus-1.
Nonpolyposis: Absence of polyps.
Nonprotein kcal:nitrogen ratio: Ratio of carbohydrate plus fat calories in a volume compared to the grams of nitrogen (calculated as number of grams of protein divided by 6.25).
Non-REM sleep: A state of usually dreamless sleep that occurs regularly during a normal period of sleep with intervening periods of rapid eye movement (REM) sleep and that consists of four distinct substages and low levels of autonomic physiologic activity.
Non–ST-segment elevation: A type of myocardial infarction (MI) that is limited to the subendocardial myocardium and is smaller and less extensive than an ST-segment MI. There is usually no pathologic Q-wave on the electrocardiogram in non–ST-segment elevation.
Normal flora: Normal colonizing bacteria of a human host.
Normochromic: Being normal in color; referring especially to red blood cells.
Normocytic: Normal size, especially referring to red blood cells.
Nosocomial infection: An infection acquired within the health care system. Generally, symptoms of infection must occur after at least 48 hours of care to be considered nosocomial.
Nuchal rigidity: Severe neck stiffness usually associated with meningitis; inability to touch chin to chest.
Nuclear medicine scans: Method of body imaging that uses a radioactive tracer material (e.g., technetium and gallium) to produce body images. For example, bone scans detect uptake and cellular activity in areas of inflammation.
Nucleoside reverse transcriptase inhibitor (NRTI)/nucleotide reverse transcriptase inhibitor (NtRI): A modified version of a naturally-occurring nucleoside or nucleotide that prevents human immunodeficiency virus (HIV) replication by interfering with the function of the viral reverse transcriptase enzyme. The nucleoside/nucleotide analog causes early termination of the proviral DNA chain. For activity, an NRTI requires three phosphorylation steps once inside the cell, whereas an NtRI has a phosphate group attached and needs only two phosphorylation steps inside the cell for activity.
Nucleus: A group of specialized nerve cells or a localized mass of gray matter in the brain or spinal cord.
Nulliparity: The condition of not having borne children.
Nystagmus: Rapid, involuntary eye movements.

Obliterative bronchiolitis: Inflammation of the bronchioles (the small elements of the tracheobronchial tree) characterized by obliteration and/or permanent narrowing of the airways.
Odynophagia: Sensation of pain behind the sternum when swallowing food or fluids.
Oiling out: Continued coalescence of lipid emulsion particles, resulting in irreversible separation of the emulsion (or "breaking" of the emulsion).
Oligoanovulation: The condition of having few or no ovulatory menstrual cycles.
Oligoclonal bands: Two to five bands of immunoglobulins on protein electrophoresis of cerebrospinal fluid.
Oligomenorrhea: Reduced frequency of menses with a time interval between periods more than 40 days but less than 6 months.
Oliguria: Reduced urine output; usually defined as less than 400 mL in 24 hours or less than 0.5 mL/kg/hour.
Omentumectomy: Excision of the double fold of peritoneum attached to the stomach and connecting it with abdominal viscera (omentum).
Oncogene: Family of genes that encodes for proteins involved with cell growth or regulation; Genes that cause transformation of normal cells into cancer cells by promoting uncontrolled cell growth and multiplication leading to tumor formation.
Onychomycosis: Fungal infection of fingernails or toenails.
Oophorectomy: Surgery to remove the ovaries.
Open comedo: A plugged follicle of sebum, keratinocytes, and bacteria that protrudes from the surface of the skin and appears black or brown in color. Also referred to as a "blackhead."
Opsonization: The process by which an antigen is altered so as to become more readily and more efficiently engulfed by phagocytes.
Optic neuritis: Usually monocular central visual acuity loss and ocular/periorbital pain caused by demyelination of the optic nerve.
Orbital and supraorbital: Pertaining to the eye socket and the area directly above it.
Orchiectomy: Surgical removal of the testicles.

Organification: Binding of iodine to tyrosine residues of thyroglobulin.
Orthopnea: Difficulty in breathing that occurs when lying down and is relieved upon changing to an upright position.
Orthostasis: A drop in blood pressure when standing up from sitting or lying down, often causing lightheadedness and dizziness.
Orthotopic: Placing a transplanted organ into the normal anatomic location.
Osler's node: Raised, painful, red lesions found on the finger pulps and soles of the feet; indicative of subacute bacterial endocarditis. Osler's nodes are caused by immune complex deposition.
Osmolality: A measure of the number of osmotically active particles per unit solution, independent of the weight or nature of the particle.
Osmolar gap: The difference between the measured serum osmolality and the calculated serum osmolality.
Osmophobia: A fear of strong odors and unpleasant smells; also called olfactophobia.
Osteoblasts: Cells involved in bone formation during the remodeling process.
Osteoclasts: Cells responsible for bone resorption during the remodeling process.
Osteomalacia: A disease characterized by softening of bones.
Osteonecrosis: Death of bone tissue.
Osteopenia: Reduced bone density or mass.
Osteophytes: Pathologic bony outgrowths, often seen in osteoarthritis.
Osteoporosis: Disease of the bones characterized by a loss of bone density or mass, resulting in brittle, weak bones that are susceptible to fracture (porous bones).
Ostomy: A surgical operation whereby part of the abdominal wall is opened and part of the intestine is connected to the opening for intestinal draining (e.g., colostomy and ileostomy).
Otitis media with effusion: Fluid in the middle ear space with no signs or symptoms of an acute infection.
Ovulation: Periodic ripening and rupture of a mature follicle and the discharge of an ovum from the cortex of the ovary.

Pacemaker: A mass of fibers that possess actual or potential automaticity, which initiates and determines the rate of spontaneous depolarizations.
Pancolitis: Inflammation involving the majority of the colon in patients with inflammatory bowel disease.
Pancreatitis: Inflammation of the pancreas.
Panhypopituitarism: A state in which the secretion of all anterior pituitary hormones is inadequate or absent.
Pannus: Inflamed synovial tissue that invades and destroys articular structures.
Papilledema: Edema of the optic disc typically associated with increased intracranial pressure.
Paracentral scotoma: A blind spot near the center of the visual field.
Parasomnia: Undesirable physical or behavioral phenomena that occur predominantly during sleep (e.g., sleep walking, bruxism, enuresis, sleep talking, and rapid eye movement behavior disorder).
Parenchyma: The essential and distinctive cells or tissue of an organ (as distinguished from its supporting framework).
Parenteral nutrition: Delivery of nutrients via the intravenous route.
Paresthesia: An abnormal touch sensation, such as burning, tingling, or prickling, often in the absence of external stimuli.
Parietooccipital: Located to the top and back of the head.
Paroxysmal: An intermittent occurrence initiating suddenly and spontaneously; may last minutes to hours; terminates suddenly and spontaneously.
Patent ductus arteriosus: Failure of the ductus arteriosus to close, resulting in neonatal hypoxemia.
Peak expiratory flow: The maximum flow rate of air leaving the lungs upon forced exhalation.
Pelvic inflammatory disease (PID): Inflammation of the endometrium, uterine tubes, and pelvic peritoneum. PID is often due to a sexually transmitted infection.
Percutaneous coronary intervention: A minimally invasive procedure whereby access to the coronary arteries is obtained through the femoral artery up the aorta to the coronary os. Contrast media is used to visualize the coronary artery stenosis using a coronary angiogram. A guidewire is used to cross the stenosis and a small balloon is inflated and/or stent is deployed to break up atherosclerotic plaque and restore coronary artery blood flow. The stent is left in place to prevent acute closure and restenosis of the coronary artery. Newer stents are coated with antiproliferative drugs, such as paclitaxel and sirolimus, which further reduce the risk of restenosis of the coronary artery.
Percutaneous endoscopic gastrostomy: Gastric feeding tube placed via endoscopic technique.
Percutaneous endoscopic jejunostomy: Jejunal feeding tube placed via endoscopic technique.
Performance status: A clinical staging of the patient's ability to perform activities of daily life. Oncologists use it in evaluation of a patient's ability to tolerate a contemplated chemotherapy regimen.
Perihilar: The area surrounding the depression in the medial surface of a lung that forms the opening through which the bronchus, blood vessels, and nerves pass.
Perimenopause: The period of time prior to menopause when hormonal and biological changes and physical symptoms begin to occur and usually lasts for 1 year after the last menstrual period. The perimenopausal period may last for an average of 3 to 5 years. Perimenopause is also known as the climacteric.
Perimetry: Measurement of the field of vision.
Peripheral resistance: The sum of resistance to blood flow offered by systemic blood vessels.
Peritonitis: An acute inflammatory reaction of the peritoneal lining to microorganisms or chemical irritation.
Perseveration: Continued involuntary repetition of a response to varied stimuli.
Petechiae: Tiny localized hemorrhages from the small blood vessels just beneath the surface of the skin.
Phagocyte: A cell that engulfs and digests foreign material (e.g., microorganisms) and debris.
Phagocytosis: The process of ingesting and destroying foreign material and debris by phagocytes.
Pharmacogenomics: The science of understanding the correlation between an individual patient's genetic make-up (genotype) and their response to drug treatment.
Pharyngitis: Inflammation and/or infection of the pharynx that causes throat pain.
Phenotype: The expression of the genes present in an individual. This may be directly observable (e.g., eye color) or apparent only

with specific tests (e.g., blood type). Some phenotypes such as the blood groups are completely determined by heredity, while others are readily altered by environmental agents.

Pheochromocytoma: A tumor arising from chromaffin cells, most commonly found in the adrenal medulla. The tumor causes the adrenal medulla to hypersecrete epinephrine and norepinephrine, resulting in hypertension and other signs and symptoms of excessive sympathetic nervous system activity. The tumor is usually benign but may occasionally be cancerous.

Phlebitis: Inflammation of a blood vessel (e.g., vein).

Phonophobia: A fear of or intolerance to sounds, loud noises, and even one's own voice.

Photophobia: An abnormal sensitivity to or intolerance of light.

Phototherapy: The use of ultraviolet light applied to the skin, for example in treating psoriasis or neonatal hyperbilirubinemia.

Plasma cell: A lymphocyte that is a mature antibody-secreting B cell.

Plasmapheresis: A process of separating blood cells from plasma. This process is used to remove monoclonal antibodies from the blood.

Platelet-activating factor: A mediator of platelet aggregation and inflammation that is produced in response to stimuli, such as white blood cells.

Pleocytosis: A transient increase in the number of leukocytes in a body fluid.

Pleuritis: Inflammation of the lining around the lungs.

Plication: A folding or putting together in pleats. Plication is an operation for reducing the size of a hollow organ by taking folds or tucks in its wall.

Pneumatic otoscopy: A diagnostic technique involving visualization of the tympanic membrane for transparency, position, and color, and its response to positive and negative air pressure to assess mobility.

Pneumothorax: The presence of air in the pleural cavity, often causing part of the lung to collapse.

Polycystic kidney disease: A disorder in which clusters of cysts develop within the kidneys.

Polycythemia: A condition in which there is a net increase in the total circulating erythrocyte (red blood cell) mass of the body.

Polydipsia: Excessive thirst.

Polymerase chain reaction (PCR): Laboratory technique involving amplification of small amounts of DNA or RNA. PCR is commonly used in medical and biological research labs for a variety of tasks, such as the detection of hereditary diseases, the identification of genetic fingerprints, the diagnosis of infectious diseases, the cloning of genes, and paternity testing.

Polymorphic metabolism: Genetically determined rates of metabolism (fast vs. slow) by selected isozymes of cytochrome P-450 drug-metabolizing enzymes.

Polyp: A growth from a mucous membrane commonly found in organs such as the colon, rectum, and nose.

Polyphagia: Eating excessively large amounts of food at a meal.

Polyradiculitis: Refers to inflammation of multiple spinal nerve roots.

Polyradiculopathy: Disease or injury involving multiple spinal nerve roots.

Polyuria: Excessive excretion of urine.

Portal hypertension: Increased blood pressure within the portal vein that supplies the liver.

Positron emission tomography (PET) scan: A scan that produces images of the body after the injection of a radioactive form of glucose. The scan is often used to detect cancer since tumors use more sugar than normal cells. PET scans may also be used to see how well the tumor is responding to treatment.

Postpyloric feeding: Delivery of nutrients via a tube placed with its tip past the pyloric sphincter separating the stomach from the duodenum.

Postvoid residual urine volume: Amount of urine left in the urinary bladder after the patient has been asked to empty the bladder. Assessed by urethral catheterization or ultrasonography. Normal postvoid residual urine volume should be less than 50 mL. An increased postvoid residual urine volume is consistent with incomplete bladder emptying.

Prediabetes: An asymptomatic but abnormal state that precedes the development of clinically evident diabetes.

Preload: The stretched condition of the heart muscle at the end of diastole just before contraction; volume in the left ventricle at the end of diastole estimated by the pulmonary artery occlusion pressure (also known as the pulmonary artery wedge pressure or pulmonary capillary wedge pressure).

Premenstrual dysphoric disorder: Severe psychiatric mood disorder with marked affective symptoms causing significant interference in work or relationships that is temporally associated with the luteal phase and not caused by an underlying psychiatric disturbance.

Premenstrual syndrome: A constellation of symptoms including mild mood disturbance, and physical symptoms that occur prior to menses, and resolve with initiation of menses.

Preparative regimen: The combination of chemotherapy and/or radiation used immediately prior to allogeneic hematopoietic cell transplantation; also referred to as the conditioning regimen.

Priapism: A prolonged, often painful erection of the penis.

Primary amenorrhea: Absence of menses by age 16 in the presence of normal secondary sexual development; or absence of menses by age 14 in the absence of normal secondary sexual development.

Primary prevention: The removal or reduction of risk factors before the development of disease.

Probiotics: Dietary supplements containing potentially beneficial bacteria that promote health by stimulating optimal mucosal immune responses.

Proctitis: Inflammation confined to the rectum in patients with inflammatory bowel disease.

Prodrome: Early symptom(s) indicating the onset of an attack or a disease.

Progenitor cell: An immature or precursor cell that can divide and give rise to a differentiated cell.

Prolapse: Protrusion of an organ or part of an organ through an opening (e.g., uterine prolapse occurs when the uterus is displaced downward such that the cervix is within the vaginal opening [first-degree], the cervix is outside the opening [second-degree], or the entire uterus is outside the opening [third-degree]).

Proptosis: Forward displacement of the eyeball.

Prostaglandin: Any of a large group of biologically active, carbon-20, unsaturated fatty acids that are produced by the metabolism of arachidonic acid through the cyclooxygenase pathway.

Prostate: An organ in the urogenital tract that surrounds the urethra at the base of the urinary bladder. Prostatic secretions are secreted into the urethra and become part of the ejaculate in males.

Prostatectomy: Removal of all or part of the prostate gland.
Prostate-specific antigen (PSA): a substance secreted by the prostate and normally carried by ducts to the urethra during ejaculation; PSA is used as a screening test for prostate cancer.
Prosthetic-valve endocarditis: Endocarditis that occurs in patients with bioprosthetic or synthetic implanted heart valves.
Protease: Any one of numerous enzymes that hydrolyze proteins.
Protease inhibitor: A drug that acts by inhibiting the viral protease enzyme, which prevents long strands of protein from being cleaved into the smaller proteins the virus requires for assembly.
Proteinase: Any one of numerous enzymes that catalyze the breakdown of proteins; also called protease.
Proteinuria: Abnormally high amount of protein in the urine. Proteinuria is defined as urinary protein excretion of greater than 150 mg per day.
Proteoglycans: Glycosaminoglycans (mucopolysaccharides) bound to protein chains in covalent complexes. Proteoglycans are present in the extracellular matrix of connective tissue.
Proteolysis: The hydrolysis of proteins, usually by enzyme action, into simpler substances.
Proteosome: An enzyme complex that degrades intracellular proteins.
Prothrombin: A clotting factor that is converted to thrombin; also known as factor II.
Prothrombin time (PT): A measure of coagulation representing the amount of time required to form a blood clot after the addition of thromboplastin to the blood sample; PT is also known as Quick's test.
Prothrombotic state: A state of high coagulation of the blood.
Pruritus: Localized or generalized itching due to irritation of sensory nerve endings.
Pseudohyphae: Elongated forms created by replicating yeast that form buds but do not detach from one another.
Pseudophakic: Refers to presence of a lens after cataract extraction.
Pseudopolyp: An area of hypertrophied gastrointestinal mucosa that resembles a polyp and contains nonmalignant cells.
Pulmonary artery catheter: An invasive device used to measure hemodynamic parameters directly, including cardiac output and pulmonary artery occlusion pressure; calculated parameters include stroke volume and systemic vascular resistance.
Pulmonary embolism: A disorder of thrombus formation causing obstruction of a pulmonary artery or one of its branches; may result in pulmonary infarction.
Pulsus paradoxus: Exaggeration of normal variation in the pulse during respiration—the pulse becomes weaker during inhalation and stronger during exhalation; characteristic of constrictive pericarditis or pericardial effusion.
Purified protein derivative (PPD): Material used in the tuberculin skin test, the most common test for exposure to *Mycobacterium tuberculosis.*
Purkinje fibers: Specialized myocardial fibers that conduct impulses from the atrioventricular node to the ventricles.
Purpura: A small hemorrhage in the skin, mucous membrane, or serosal surface.
Purulent: Containing, consisting of, or being pus.
Pyloroplasty: A surgical procedure for enlarging the opening of the stomach to the duodenum.
Pyuria: The presence of white blood cells in the urine, a known marker of inflammatory response to bacterial infection.
Quality of life: Measured by validated scales and patient interviews to determine the effect of therapy on a patient's lifestyle. An improvement in quality of life may be an endpoint in clinical trials.

Radiation nephritis: Kidney injury and impairment of function caused by ionizing radiation.
Radical prostatectomy: Surgical removal of the entire prostate and the seminal vesicles.
Radiofrequency catheter ablation: Procedure during which radiofrequency energy is delivered through a catheter positioned at the atrioventricular node of the heart for the purpose of destroying one pathway of a reentrant circuit.
Raphe nuclei: A bed of serotonin-containing neurons that extends to the hypothalamus, septum, hippocampus, and cingulate gyrus.
Rebound effect: Symptoms reoccur after treatment has been stopped or is no longer effective. In some cases, symptoms can be more pronounced than when symptoms were initially identified.
Rectal prolapse: Sinking of the rectum through the anal sphincter so that it is visible externally.
Recurrence: The occurrence of another episode of illness once recovery has been made from the previous episode.
Reentry: Circular movement of electrical impulses; a mechanism of many arrhythmias.
Refractory periods: The period of time after an impulse is initiated and conducted during which cells cannot be depolarized again.
Regurgitation: A passive process without involvement of the abdominal wall and the diaphragm wherein gastric or esophageal contents move into the mouth.
Relapse: Regression after partial or full recovery from an illness.
Rapid eye movement (REM) sleep: A state of sleep that recurs cyclically several times during a normal period of sleep and is characterized by increased neuronal activity of the forebrain and midbrain, by depressed muscle tone, and especially in humans by dreaming, rapid eye movements, and vascular congestion of the sex organs.
Remission: The resolution or abatement of symptoms of a disease state.
Renal osteodystrophy: Altered bone turnover that results from sustained metabolic conditions that occur in chronic kidney disease, including secondary hyperparathyroidism, hyperphosphatemia, hypocalcemia, and vitamin D deficiency.
Renin–angiotensin–aldosterone system (RAAS): The hormonal system controlled mainly by the kidneys and adrenal glands that regulates blood pressure, blood volume, and electrolyte balance.
Resorption of bone: The process of bone breakdown by osteoclasts.
Respiratory acidosis: Acidosis caused by retention of carbon dioxide due to a respiratory abnormality (e.g., chronic obstructive lung disease).
Respiratory alkalosis: Alkalosis caused by excessive loss of carbon dioxide due to a respiratory abnormality (e.g., hyperventilation).
Respiratory disturbance index: A summary measure that quantifies the number of apneas, hypopneas, and respiratory effort–related arousals per hour of sleep.
Response: Refers to a predefined reduction of symptoms from baseline that generally results in significant functional improvement.
Retching: A process that follows nausea and consists of diaphragm, abdominal wall, and chest wall contractions and spasmodic breathing against a closed glottis.
Reticulocytes: Immature blood cells that mature into erythrocytes.
Reticuloendothelial system: Cells located throughout the body that can phagocytose particulate matter.

Retroperitoneal fibrosis: An accumulation of fibrotic tissues in the retroperitoneum (the anatomic space behind the abdominal cavity). Structures that lie behind the peritoneum are thus termed "retroperitoneal." These structures include kidneys, the bladder, portions of the duodenum, portions of the colon, and the inferior vena cava.

Reye's syndrome: A sudden, sometimes fatal, syndrome characterized by encephalopathy and liver degeneration; it occurs in children after viral infection and may be associated with aspirin use.

Rhabdomyolysis: Destruction of skeletal muscle.

Rheumatic fever: An acute inflammatory disease involving the joints, heart, skin, and other tissues caused by an immune response to streptococcal infection, particularly seen in children.

Rheumatoid factors: Antibodies reactive with the Fc region of immunoglobulin G.

Rhinitis medicamentosa: Inflammation of nasal mucous membranes due to excessive use of topical medication.

Rhinorrhea: Nasal secretions; a runny nose.

Rhinosinusitis: Inflammation of the mucous membranes in the nose and sinuses.

Rhonchi: Abnormal rumbling sounds heard on auscultation of an obstructed airway. They are more prominent during expiration and may clear somewhat on coughing.

Risk factor: Refers to any characteristic of a patient or procedure that increases the chance of a patient experiencing a negative endpoint.

Roth spot: Possible sign of endocarditis where there is localized capillary retinal bleeding.

Rubefacient: An agent applied to the skin that causes local irritation and redness; used to relieve pain by a counterirritant mechanism.

Sarcoidosis: An inflammatory disease characterized by granulomas (masses of chronically inflamed tissues with granulations) that can produce many different symptoms.

Scarlatiniform rash: Bright, scarlet-colored skin eruption that occurs in patches over the entire body with eventual peeling as a result of streptococcal infection.

Scleritis: Inflammation of the outer layer of the eyeball.

Scoliosis: Lateral curvature of the spine.

Secondary amenorrhea: Absence of menses for three cycles or 6 months in a previously menstruating woman.

Secondary hyperparathyroidism: Increased secretion of parathyroid hormone from the parathyroid glands caused by hyperphosphatemia, hypocalcemia, and vitamin D deficiency that result from decreased kidney function. It can lead to bone disease (renal osteodystrophy).

Secondary transmission: Transferring a disease from the primary source to another person.

Sepsis: A syndrome characterized by a systemic inflammatory response (abnormal increases in body temperature, heart rate, respiratory rate, and/or white blood cell concentration) caused by infection.

Serosal: An enclosing serous membrane of the pericardial, pleural, and peritoneal cavities.

Serum ferritin: A complex protein formed in the intestine, containing about 23% iron, the amount of ferritin found in serum is directly related to iron storage in the body.

Serum bactericidal titer: The lowest titer of serum and antibiotic obtained from the patient, usually at the peak or trough of antibiotic administration, that results in a 99.9% kill of bacteria.

Serum inhibitory titer: The lowest titer of serum and antibiotic obtained from the patient, usually at the peak or trough of antibiotic administration, that inhibits bacterial growth.

Serum sickness: A group of symptoms that can be caused by a delayed immune response to certain medications. Arthralgias, fever, malaise, and urticaria may develop, usually 7 to 14 days after exposure to the causative antigen.

Shear stress: A risk factor for pressure ulcers that is generated when the head of a patient's bed is elevated, causing deeper blood vessels to crimp, which leads to ischemia.

Shock: A condition wherein the principal function of the circulatory system to supply oxygen and vital metabolic substrates to cells throughout the body as well as removal of metabolic waste products is compromised. The four major shock types are hypovolemic, obstructive, cardiogenic, and distributive.

Sialorrhea: Drooling.

Sickle-cell anemia: An autosomal recessive disorder in which a mutation in the gene for one of the proteins that comprises hemoglobin results in the formation of defective hemoglobin molecules known as hemoglobin S. Individuals who are homozygous for this mutation (possess two genes for hemoglobin S) have red blood cells that change from the normal discoid shape to a sickle shape when the oxygen supply is low. These sickle-shaped cells are easily trapped in capillaries and damaged, resulting in severe anemia.

Sickle-cell syndrome: A group of autosomal recessive genetic disorders characterized by the presence of at least one sickle-hemoglobin gene.

Sickle hemoglobin: A defective form of hemoglobin produced as a result of a single substitution of the amino acid valine for glutamic acid at position 6 of the β-polypeptide chain.

Sick sinus syndrome: Idiopathic sinus node dysfunction leading to symptomatic sinus bradycardia.

Sigmoidoscopy: Visual inspection of the sigmoid colon and rectum with a flexible tube called a sigmoidoscope.

Single nucleotide polymorphisms: Single base-pair changes that are inherited as mendelian traits and might associate with a trait such as susceptibility to disease.

Sjögren's syndrome: An inflammatory disorder of unknown cause that affects the mucous membranes, causing dry mouth, decreased tear production, decreased sense of taste and smell, joint pain, and swollen glands.

Sleep apnea: The temporary cessation of breathing during sleep; can be caused by airway narrowing as a result of soft tissue swelling.

Sleep latency: The amount of time it takes to fall asleep.

Slit lamp biomicroscope: An instrument that allows for the microscopic examination of the cornea, anterior chamber lens, and posterior chamber.

Somatic hypermutation: High frequency of mutation that occurs in the gene segments encoding the variable regions of antibodies during the differentiation of B lymphocytes into antibody-producing plasma cells.

Somatostatin: A growth hormone–inhibiting hormone that stops production of growth hormone from the anterior pituitary.

Somatotrope: Growth hormone producing cells in the anterior pituitary.

Source control: Removal of the primary cause of an infection such as contaminated prosthetic materials (e.g., catheters), necrotic tissue, or drainage of an abscess. Antimicrobials are unlikely to be effective if the process or source that led to the infection is not controlled.

Spasticity: A motor disorder characterized by an increase in muscle tone with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex.
Spastic colon: A synonym for irritable bowel syndrome.
Spectrum of activity: A qualitative term that describes the number of different bacterial species that are susceptible to an antimicrobial regimen. Generally, broad-spectrum activity refers to regimens that possess activity against many bacterial species, whereas narrow-spectrum therapy refers to activity against a few bacterial species.
Sphincter of Oddi: A muscular valve separating the common bile duct from the duodenum. The sphincter of Oddi is the structure through which the common bile duct empties bile and pancreatic secretions into the duodenum.
Spinal shock: Shock that occurs as a result of malfunction of the sympathetic nervous system after a spinal cord injury.
Splinter hemorrhage: Linear image under the nail beds caused by local hemorrhage as a result of hand trauma or endocarditis.
Spirometry: Measurement of inhaled and exhaled volumes and flow rates of gas from the lungs. Pulmonary function tests obtained from spirometry are used to aid in the diagnosis of obstructive and restrictive airway diseases.
Splenomegaly: An enlarged spleen.
Spontaneous bacterial peritonitis: Bacterial infection of the peritoneal fluid without an abdominal source.
Sprain: An overstretching of supporting ligaments that results in a partial or complete tear of the ligament.
Sputum cultures: The process of growing living material obtained from sputum (as bacteria or viruses) in prepared nutrient media.
Sputum smears: Lower respiratory tract smear on a microscope slide to determine the presence of organisms.
Status epilepticus: Any seizure lasting more than 30 minutes, with or without a loss of consciousness; having recurrent seizures without regaining consciousness between seizure episodes.
Steatohepatitis: A severe form of liver disease caused by fat deposition in the liver, characterized by hepatic inflammation that may rapidly progress to liver fibrosis and cirrhosis.
Steatorrhea: Excessive loss of fat in stool.
Steatosis: A process of tissue degeneration characterized by deposition of fat globules in cells; also known fatty degeneration.
Stenosis: Narrowing or constriction of the diameter of a bodily passage or orifice.
Stenting: Placement of a stent (a short metal or plastic tube) to allow blood flow through an artery.
Stevens-Johnson syndrome: A severe expression of erythema multiforme (also known as erythema multiforme major). It typically involves the skin and the mucous membranes with the potential for severe morbidity and even death.
Stimulants: Medications that increase physiologic activity in the body by augmenting dopamine and/or norepinephrine.
Stomatitis: Inflammation of mucous membranes in the mouth.
Strain: Damage to the muscle fibers or muscle sheath without tearing of the ligament.
Striae: Linear, atrophic, pinkish or purplish, scar-like lesions that later become white (striae albicantes or lineae albicantes); may occur on the abdomen, breasts, buttocks, and thighs; they are due to weakening of the elastic tissues; commonly called stretch marks.
Stricture: An area of narrowing or constriction of a tubular structure. Strictures may result from long-standing inflammation.
Stroke volume: The amount of blood ejected from the heart during systole.
ST-segment elevation: A type of myocardial infarction (MI) that typically results in an injury that transects the thickness of the myocardial wall. Following an ST-elevation MI, pathologic Q waves are frequently seen on the electrocardiogram, indicating transmural myocardial infarction.
Subchondral: Beneath or below the cartilage.
Substantia nigra: The area in the brain stem that makes dopamine.
Surgical site infection: Refers to an infection resulting from a surgical procedure. May involve the incision or associated tissue and organs.
Synechia: Adhesions or the abnormal attachment of the iris to another structure. Peripheral anterior synechia refers to occurrence of synechia with the trabecular meshwork.
Synovitis: Inflammation of the synovial membrane, especially when a joint is involved.
Synovium: The membrane lining the internal surfaces of the joint.
Systemic vascular resistance: The portion of resistance to blood flow leaving the heart that is determined by vascular tone (constriction or relaxation). Systemic vascular resistance = mean arterial blood pressure/cardiac output.
Systolic dysfunction: An abnormal contraction of the ventricles during systole.

T2-weighted magnetic resonance imaging: A setting of the magnetic resonance imaging machine that shows water as a bright signal.
Tachycardia: An abnormally rapid beating of the heart, defined as a resting heart rate over 100 beats per minute in an average adult.
Tachyphylaxis: Rapidly decreasing response to a drug or other physiologically active agent after a few doses.
Tachypnea: Abnormally rapid respiratory rate.
Tangentiality: Abandoning one's ideational objective in pursuit of thoughts peripheral to the original goal. Used to describe a thought and speech pattern wherein the individual never gets to the point or answers the question.
Tardive dyskinesia: A chronic disorder of the nervous system characterized by involuntary jerky or writhing movements of the face, tongue, jaws, trunk, and limbs, usually developing as a late side effect of prolonged treatment with antipsychotic drugs.
Telangiectasia: Permanent dilation of preexisting small blood vessels (capillaries, arterioles, and venules), usually in the skin or mucous membranes, which presents as a coarse or fine red mark.
Tendinitis: Inflammation of a tendon.
Tenesmus: Straining, especially painful, or ineffectual straining with a bowel movement or straining on defecation.
Tenosynovitis: Inflammation of the tendon sheath.
Teratogen: Any substance that leads to structural or functional abnormality in the fetus, including death.
Teratogenic: Causing malformations in a fetus.
Teratogenicity: The property of causing malformations in the developing fetus.
Teratogenic potential: The ability of an agent to cause harm or malformations to a fetus or embryo. Medications are assigned pregnancy categories based on their teratogenic potential.
Tetany: Hyperexcitability of nerves and muscles characterized by muscular twitching and cramps, laryngospasm with inspiratory stridor, and hyperreflexia.

Therapeutic drug monitoring: The process of using drug concentrations, pharmacokinetic principles, and pharmacodynamic criteria to optimize drug therapy in individual patients.
Thoracentesis: Removal of fluid present in the pleural space; a common procedure to determine the cause of fluid accumulation.
Thought blocking: Speech is halted, often in mid-sentence, and then picked up later, usually at another point in the thought process.
Thrombin: The enzyme formed from prothrombin, which converts fibrinogen to fibrin. It is the principal driving force in the clotting cascade.
Thrombocytopenia: Persistent decrease in the number of blood platelets.
Thrombocytosis: Increased number of platelets in the blood.
Thrombogenesis: The process of forming a blood clot.
Thrombogenic: Relating to thrombogen; causing thrombosis or coagulation of the blood.
Thrombolysis: The process of enzymatically dissolving or breaking apart a blood clot.
Thrombolytic: Breaking up a clot.
Thrombophlebitis: Inflammation of a blood vessel (e.g., vein) associated with the stimulation of clotting and formation of a thrombus (or blood clot).
Thromboplastin: A substance that triggers the coagulation cascade. Tissue factor is a naturally-occurring thromboplastin and is used in the prothrombin time test.
Thrombosis: A condition in which blood changes from a liquid to a solid state and produces a blood clot (thrombus).
Thrombotic thrombocytopenic purpura: Condition characterized by formation of small clots within the circulation resulting in the consumption of platelets and a low platelet count.
Thrombus: An aggregation of fibrin and platelets within a blood vessel. A thrombus often causes vessel obstruction, inflammation, and injury.
Thymoma: A tumor derived from the epithelial or lymphoid elements of the thymus.
Thyroglobulin: A thyroid hormone–containing protein, usually stored in the colloid within the thyroid follicles.
Thyroiditis: Inflammation of the thyroid gland.
Thyroid peroxidase: An enzyme that catalyzes the organification and coupling steps of thyroid hormone synthesis.
Thyrotoxicosis: A state caused by an excess of thyroid hormone.
Tocolytic agents: Medications that can stop labor by slowing down or halting the contractions.
Tonometry: A method of measuring the pressure of the eye by measuring the tone or firmness of its surface.
Tophi: Chalky deposits of sodium urate occurring in gout. Tophi form most often around joints in cartilage, bone, bursae, and subcutaneous tissue and in the external ear, producing a chronic, foreign-body inflammatory response. If untreated, tophi can lead to joint deformity or destruction.
Topoisomerase: An enzyme that uncoils DNA during replication by cutting the DNA. Topoisomerase inhibitors prevent DNA from sealing the cut, which causes DNA strand breakage.
Toxic epidermal necrolysis: A life-threatening skin disorder characterized by blistering and peeling of the top layer of skin.
Toxoid: A toxin of a pathogenic organism treated to destroy its toxicity but leave it capable of inducing antibody formation upon injection.
Tracheal aspiration: Suctioning of secretions from the trachea.
Transaminases: Hepatocellular enzymes that are released into the bloodstream after hepatic damage.
Transesophageal echocardiogram: A procedure used to generate an image of the heart using sound waves, via a probe introduced into the esophagus (rather than the traditional transthoracic view) in order to obtain a better image of the left atrium.
Transferrin saturation: A laboratory test that indicates the amount of transferrin that is bound with iron.
Transient ischemic attack: A focal neurologic deficit lasting less than 24 hours in which symptoms resolve completely.
Transit time: The time it takes for food to travel from mouth to anus.
Translocation: Movement of bacteria and endotoxin from the intestinal lumen through the gut mucosa and into the lymphatic and systemic circulation.
Transmural: Across the wall of an organ or structure.
Transsphenoidal pituitary microsurgery: Surgery through the nasal cavity to access the pituitary gland through the sphenoid bone.
Transvenous pacing: Insertion of a pacemaker into the heart via venous access for the purpose of pacing.
Travelers' diarrhea: An acute infectious diarrhea that afflicts travelers. The disease is characterized by the presence of at least three loose stools within 24 hours that is associated with nausea, vomiting, abdominal pain, fecal urgency, or dysentery.
Treatment-resistant depression: Depression characterized by multiple failed trials of antidepressants and/or electroconvulsive therapy.
Trigeminal nerve: The fifth cranial nerve responsible for pain perception in the head and face.
Trigeminal neuralgia: A disorder of the fifth cranial (trigeminal) nerve characterized by excruciating paroxysms of pain in the face.
Trigeminovascular: Referring to the cranial nerve and its vascular supply responsible for the generation of headache pain.
Troponins T or I: Proteins found predominantly in cardiac muscle that regulate calcium-mediated interaction of actin and myosin; troponins I and T are released into the blood from myocytes at the time of myocardial cell necrosis after infarction. These biochemical markers become elevated and are used in the diagnosis of myocardial infarction.
Trousseau's sign: An indication of latent tetany in which carpal spasm occurs when the upper arm is compressed, as by a tourniquet or a blood pressure cuff.
Trypsin: A proteolytic enzyme formed in the small intestine from trypsinogen.
Tuberoeruptive xanthomas: Small yellow-red raised papules usually presenting on the elbows, knees, back, and buttocks.
Tubulointerstitial: Pertaining to the renal tubules and interstitial tissue.
Tumor suppressor genes: Genes that normally restrain cell growth, but when missing or inactivated by mutation, allow cells to grow uncontrolled and tumors to form.
Turbinate: Any of the scrolled spongy bones of the nasal passage.
Tympanocentesis: Puncture of the tympanic membrane with a needle to aspirate middle ear fluid.
Tympanostomy tube: A small plastic or metal tube inserted in the eardrum to keep the middle ear aerated and improve hearing in patients with chronic middle ear effusion.

Uhthoff's phenomenon: Acute worsening of multiple sclerosis symptoms on exposure to heat because high body temperatures may exceed the capacitance of the demyelinated nerve and conduction may fail.

Ulceration: A suppurative or non-healing lesion on a surface such as skin, cornea, or mucous membrane.
Ultrasound: Noninvasive imaging of organ or tissue to detect fluid, masses, or cyst.
Uncomplicated urinary tract infection (UTI): Generally used to describe a UTI in a patient without structural or functional abnormalities of the urinary tract.
Unilateral: Pertaining to one side.
Upper respiratory tract infection: Sinusitis, bronchitis, or otitis caused by viral or bacterial infections.
Upper urinary tract infection: Typically used to describe infection involving the upper urinary tract, particularly the kidneys.
Uremia: A condition that results from accumulation of metabolic waste products and endogenous toxins in the body resulting from impaired kidney function. Symptoms of uremia include nausea, vomiting, weakness, loss of appetite, and mental confusion.
Urethral stricture: Fibrosis and scarring of the urethra that results in narrowing of the urethral lumen.
Uric acid: A by-product of purine metabolism in mammals, including humans. A high serum uric acid concentration is a major risk factor for gout.
Uricosuric: Pertaining to, characterized by, or promoting renal secretion of uric acid.
Urosepsis: The sepsis syndrome that may be seen in patients with a urinary tract infection.
Urticaria: Itchy, raised, swollen areas on the skin; also known as hives.
Uveitis: An inflammation of the uvea in the eye. Uveal structures include the iris, the ciliary body, and the choroid.

Vagal maneuvers: Maneuvers that stimulate the activity of the parasympathetic nervous system and thereby inhibit atrioventricular nodal conduction. Examples of vagal maneuvers include cough, carotid sinus massage, and Valsalva maneuver.
Vagotomy: A surgical procedure that blocks vagal (cholinergic) stimulation to the stomach.
Valsalva maneuver: A vagal maneuver in which the patient bears down against a closed glottis, as if having a bowel movement.
Variceal bleeding: Gastric or esophageal bleeding from collateral vessels (varices).
Vasculitis: Inflammation of the walls of blood vessels.
Vasopressors: Medications that cause constriction of blood vessels, increase in vascular resistance, and increase in blood pressure.
Ventilation-perfusion ratio (V_A/Q): A comparison of the proportion of lung tissue being ventilated by inhaled air to the rate of oxygenation of pulmonary blood.
Ventricular depolarization: Change in the membrane potential of a ventricular myocyte, resulting in loss of polarization. Under normal conditions, depolarization of ventricular myocytes is followed by ventricular contraction.
Vertigo: Sensation of spinning or feeling out of balance.
Vesicant: A drug that causes significant tissue damage (e.g., necrosis) upon infiltration into soft tissue after intravenous administration.
Virilization: Production or acquisition of virilism, which is a masculine characteristic.
Vital signs: Major physical parameters, including heart rate, blood pressure, respiratory rate, and body temperature.
Volvulus: Abnormal twisting of the intestine causing obstruction.
Vomiting: A reflexive rapid and forceful oral expulsion of upper gastrointestinal contents due to powerful and sustained contractions in the abdominal and thoracic musculature.

Western blot: A method to detect protein in a given sample of tissue homogenate or extract. It uses gel electrophoresis to separate denatured proteins by mass. Some diagnostic applications for the Western blot include Lyme disease, bovine spongiform encephalopathy, and human immunodeficiency virus (HIV) (it is considered the gold standard for HIV diagnostic testing).
Wheeze: A high-pitched whistling sound caused by air moving through narrowed airways. Wheezes are usually heard at the end of expiration, but may be heard during inspiration and expiration in severe acute asthma.
White coat hypertension: A persistently elevated average office blood pressure greater than 140/90 mm Hg (stage 1) in the presence of a health care worker, whereas the patient otherwise has an average daytime ambulatory reading less than 135/85 mm Hg.
Wilms' tumor: A kidney cancer that primarily affects children.
Wilson's disease: A disorder of copper metabolism characterized by cirrhosis of the liver and neurologic manifestations; a potentially fatal genetic disorder that causes the body to retain copper.

Xanthoma: Firm, raised nodules composed of lipid-containing histiocytes.
Xerostomia: Dryness of the mouth resulting from diminished or arrested salivary secretion.

Yeast: Single-celled fungi that reproduce by budding.

ZAP-70 expression: An intracellular tyrosine kinase found in B cells in chronic lymphocytic leukemia.
Zymogen: A proenzyme; the inactive or nearly inactive precursor of an enzyme that is converted into an active enzyme by proteolysis.

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